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SYNTHESIS OF "O-TRANSMETHYLATED" CATECHOLAMINES AND PSYCHODYSLEPTIC β-PHENYLISOPROPYLAMINES

by

JOHN ROBERT BUTTERICK

B. S., Manhattan College, 1967
M. S., University of California, Berkeley, 1969

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Synthesis of "O-Transmethylated" Catecholamines and Psychodysleptic β-Phenylisopropylamines

Author: John R. Butterick

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March 11, 1975

(date)

Abstract

Speculations from many disciplines over the last twenty-five years concerning the nature of the diffusive clinical syndrome, schizophrenia, have given rise to twelve distinct biochemical theories of its aetiology and symptomology. The "transmethylation hypothesis" of Osmond/Smythies/Harley-Mason (1952) suggested synthesis of four O-methylated analogs of catecholamine neuro-transmitters as well as their metabolic precursor, DOPA, (3,4-dihydroxy-phenylalanine).

From the outset, facile chemical incorporation of ^{14}C-label from available sources dictated specific synthetic routes in the elaboration of ring-substituted β-phenylisopropyl amines and optimized yields of such are reported. Preliminary tolerance/cross tolerance studies in mice of mescaline (7) and 1-(3,4-dimethoxy-phenyl)-2-aminoethane (2) were performed. Results from these studies are like-wise reported.

Synthesis in the psychodysleptic β-phenylisopropylamine series was initiated because of projected application in detection of "excess in vivo methylation" under the terms of Osmond/Smythies/Harley-Mason hypothesis. On its own merit, five hithertofore unreported compounds of this series were synthesized. A synthetic route for ^{14}C-side chain labelling in the series was explored. Optimization of yields, facile condensation conditions, utilization of a new reducing agent, and possible syntheses of general application are described. As a new class

of psychodysleptics, this series of β-phenylisopropylamines is finding application in psychotherapy.

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Chapter 1

Introduction

At the present time, "schizophrenia" is a word whose definition is a matter of contention amongst the psychological and psychiatrical professions. For this reason, the World Health Organization has recently initiated a pilot study program for the purpose of standardizing a definition of "schizophrenia" (1).

In classical descriptive psychiatry, "schizophrenia" is distinguished from "schizoid". The latter syndrome is defined as the state of affairs when one possesses two or more distinctive personalities. The former syndrome is tentatively described in terms of a functional psychoses (as opposed to an organic psychoses) in which the symptoms are withdrawal and poverty of affect, delusions, hallucinations (frequently in the auditory mode), confusion, flight of ideas, autism, and disturbances in the sense of identity.

Bleuler (2) coined the term "schizophrenia" in 1911 which in effect supplanted Kraepelin's (3) term, "dementia praecox". Bleuler divided his "schizophrenia" into four subgroups:

(a) simple schizophrenia, characterized by "withdrawal from reality".

(b) hebephrenic schizophrenia, characterized by "mistaken cosmic identity" -- of being omnipotent or omniscient.

(c) catatonic schizophrenia, characterized by blunting of emotions, mutism, and catalepsy.

(d) paranoid schizophrenia, characterized by a persecutory trend.

Hallucinations are generally characteristic of all forms of schizophrenia except the simple type. In England and on the European continent, simple schizophrenia is considered a character disorder rather than a "true schizophrenia". For the other schizophrenic syndromes, the nature of the hallucinosis varies with the course of the disorder. In the relatively "hot" patient, the hallucinations are usually accompanied by much stress and anxiety. Alternatively, subjecting an acute patient to emotional stress and anxiety produces an hallucinatory exacerbation, and medication with tranquilizers, such as the phenothiazines, the butyrophenones, or the diphenylbutapiperidines often modulates or at best abolishes the intensity and frequency of the hallucinations (4). In contrast, many chronic patients hallucinate with little apparent stress. Even under heavy medication, hallucinations seem to constitute a "way of life" for such patients.

Over the past fifteen years, evidence has been presented to support the hypothesis that schizophrenia is a genetic morphism (5, 6, 7, 8). This is based partially on the observations that children of schizophrenic twin pairs show a concordance rate of 76 - 91%, whereas in dizygotic pairs the rate is only 10 - 17%. Occurence of "schizophrenia" in the global population is reported to be at a fixed rate of 1%, transcending ethnic, racial, and cultural origin (8). Based upon such evidence, biochemical hypotheses of this disease have been advanced.

Caution should, however, be exercised in entertaining

hypotheses based on evidence which is diffusive at best. Szasz and Laing have noted the resistance of schizophrenia to current chemotherapeutic and psychotherapeutic practices and have individually expressed their respective disagreements with the epistemological assumptions of traditional psychiatric theory. Szasz (9) has developed a case for schizophrenia as a social myth. Laing (10, 11) has attempted to reduce the question of "madness" to deviance from a social norm and has as well called into question the role that the observor plays in such an evaluation. To Laing, "madness is in the eye of the beholder" (to paraphrase the Bard of Avon). Indeed, Mandell reports a recent freshman medical school class reacting negatively to a film (circa 1956) of an adolescent with "borderline schizophrenia" because "they could not see his 'hippy-like' strangeness as pathological" (12). Laing (11) has developed a "therapy" based upon a half-way house concept. He has allowed 12 groups of unmedicated schizophrenics in London houses to interact with the stresses and commitments of the "outside world" in inverse proportion to the severity of their individual maladies.

A review of the literature on the biochemical investigations of schizophrenia is next presented and the roots of present day hypotheses and model systems are described.

Chapter 2

Biochemical Theories of Schizophrenia.

Literature Survey.

TABLE 1. BIOCHEMICAL THEORIES OF SCHIZOPHRENIA

1. TRANSMETHYLATION
   - (a) 1-(3,4-dimethoxyphenyl)-2-aminoethane
   - (b) N,N-dimethyltryptamine-bufotenine
2. SEROTONIN-MELATONIN
3. HARMALINE
4. KRYPTOPYROLLE
5. NORADRENERGIC DEFICIT
6. TOXIC PROTEIN
   - (a) taraxein
   - (b) S - anti S
7. HISTAMINE
8. ADRENOCHROME-ADRENOLUTIN
9. DOPAMINERGIC-CHOLINERGIC
10. MOLECULAR COMPLEXES OF NEUROTRANSMITTERS

2-1 Review (1892 - 1950)

A biochemical basis for some kinds of chronic/acute mental disease such as schizophrenia was suggested as early as 1892 by Kraepelin (3). Credit for the first model system must go to Moreau (13) for his comparison of hashish intoxication newly introduced into French artistic society and insanity as seen at his clinic. A review of the literature in Chemical Abstracts reveals the roots of several present day biochemical hypotheses in the work of Buscaino in 1924 (14). It was his contention that he could demonstrate the existence of "abnormal" amines in the urine of schizophrenics and that these amines (of unspecified structure), originating from microorganisms in the intestine, caused intoxication of brain cells.

Noteboom (15 - 17) and DeJong (18) in the years 1932 - 1945 demonstrated the peculiar "catatonizing" of test animals by injections of synthetic derivatives of mescaline (7) and adrenalin. To them must go the credit for the second model system.

Concurrently, a school of theorists published a number of works on cerebral metabolism and electrolyte balance as a function of general neurological activity. Katzenelbogen and Snyder (19) reported that sodium, calcium and magnesium in the blood cells and serum of 29 schizophrenics were within normal limits. In 5 persons, potassium was slightly elevated, as was phosphorus and chloride levels of the cells in one case. Further, these authors tested the glucose level, and the oxygen and carbon dioxide contents of arterial and venous blood from

the cranial cavity. "In some schizophrenic cases, a lower blood sugar content relative to that reported for normals was found while in others a great difference was observed between arterial and venous sugar content. In some patients, a lower intracranial oxygen metabolism was found than in normal subjects" (20). This last finding is at variance with work by Looney and Freeman (21) whose test group of 112 schizophrenics showed no essential difference in levels of oxygen and carbon dioxide in the venous blood and carbon dioxide in the arterial blood with that found in 67 normal subjects.

Chloride content of blood cells was investigated by Muyle(22), Chatagnon (23) and Gross and Wortis (24). Levels of chloride were found to be the same in normals and schizophrenics and therefore of little interest. Carbohydrate metabolism investigations were performed by Lafvendahl and Valatin(25,26). In a study of 13 schizophrenics (catatonics and "acute restless" cases), an increased "bisulfite-binding substance" was found. In approximately 50% of the cases studies, pyruvic acid levels were elevated while elevated lactic acid levels were found in 33%.

Cholesterol levels in the blood were investigated by Stenberg (27) who found that in a test group of 21 cases of "strong emotional disturbance" high cholesterol levels were observed. When insulin treatment was successful, cholesterol levels tended to be decreased. In six cases of schizophrenia "without emotional disturbance", insulin treatment had no therapeutic value and cholesterol in the blood was found to be slightly higher after such treatment. Jellinek

and Looney (28) noted a seasonal variation in cholesterol levels in the blood, namely a lower level in the winter and a peak in late summer.

The body's cholinergic system, meanwhile, became a target for research. Choline levels in cerebrospinal fluid were found by Yuki (29) to be elevated in 21 or 31 cases of "general paralysis of the insane." Moreover, elevated choline levels were also observed in 6 of 9 epileptics, in 11 or 23 manic-depressives, in 9 or 20 schizophrenics, and only in 1 of 8 neurosyphilitics or cases of tabes dorsalis. A rise in cholinesterase activity in blood serum of "anxious neurotics" and a fall in that activity in catatonics and epileptics was observed by Tod and Jones (30). Cholinesterase activity was found by Birkhäuser (31) to be increased in cases of meningococcal and tuberculin meningitis and only slightly in cases of schizophrenia.

Creatine levels in the urine of 50 cases of schizophrenia were normal (32) as were acetone levels. β-Hydroxybutyric acid was, however, elevated in 16 cases. Stora and Tcherneakofsky (33) had previously studied 20 patients (8 catatonics) and found that 14 subjects showed hypercreatinuria with no correlation to catatonic states or endocrine functions.

In 1938, Quastel and Wales (34) published an article which must be credited with initiating the first metabolic-experimental artifact debate in schizophrenia research. They claimed that catatonic patients showed a loss in ability to excrete hippuric acid at a normal rate after oral administration of sodium benzoate (test group of 18 catatonics). Ström-Olsen, et al. (35)

claimed that a metabolic disturbance in the liver detoxification of benzoic acid did not appear to be characteristic of catatonia; in only 5 of 28 of their catatonics and in only 6 of 34 undifferentiated schizophrenics were excretion rates below normal. Quastel and Wales (36) then published results of an intravenous study to support their argument. They attempted to rule out differential rates of absorption from the gut, and demonstrated an improved ability to detoxify benzoic acid after mental improvement as a result of metrazole treatment. Davies and Hughes (37) reported delayed excretion of hippuric acid in 40 of 75 patients with undifferentiated mental disorders and in 15 of 17 catatonics. However, they claim "while faulty detoxification is more readily demonstrated in catatonia than in any other mental condition, it does not seem to be specific for this disorder." Finkelman, et al. (38) found faulty detoxification in 50% of his cases of catatonia and "deteriorated epilepsy". A reinvestigation in 1944 by Michael, Looney, and Boricovic (39) found that hippuric acid excretion in normal control subjects and schizophrenics were similar.

Porphyria research spawned two papers in schizophrenia research. Scheid (40) observed marked hemolysis during febrile episodes in schizophrenia. Just before the psychotic episode, an erythrocytosis occurred with low color index and with small erythrocyte cells. A blood sample taken several days later showed a color index of 1.0 or higher with normal-sized erythrocytes. The osmotic resistance, which was normal before the attack,

increased during the episode. Blood bilirubin was elevated slightly and excretion of coproporphyrin I was increased. The ratio of urobilinogen to hemoglobin excretion was abnormal, although the ratio of urinary to fecal urobilinogen was normal. Porphyrins of series III and uroporphyrin were absent (41).

Blood histamine levels were found to be unelevated (42). Bromide levels of blood were lower in one study (43) with iodide elevated. A further study of 172 patients failed, however, to manifest such a bromide diminution (44).

Studies on the pharmacological activities of the cerebral spinal fluid of schizophrenics commenced during this period. Le Grande and Année (45) produced a "catatonic stupor" by injecting cerebral spinal fluid from a schizophrenic into rats. Heating the fluid 30 minutes at 44° C destroyed the active principle. Cerebral spinal fluid from normals produced no significant effect. Claude, et al. (46) demonstrated an inhibiting action or no action at all on the development of the genital tract in the immature male mouse. Stimulatory action in this system was not observed by these authors.

An interesting model system was that of Hermann and Barbour (47). Introduction of 0.1 - 0.3 cc ^2H_2O over the parietal cortex of rats through a previously prepared trephinated hole induced a cataleptic state within minutes. The effect lasted many hours, occasionally being evident on the next day. Ultimately, complete recovery was observed.

2-2 1950 - 1974

Hofmann's (48) accidental intoxification with d-lysergic acid diethylamide tartrate in 1943 had an indirect stimulatory effect on biochemical theorists in schizophrenia research. The first hypothesis to emerge was the Transmethylation Hypothesis of Harley-Mason, Osmond, and Smythies (1952) (49). The suggestion was made at that time that mescaline (7) or some related compound might be easily synthesized in the body from normal precursors if a biochemical lesion developed in the body in the trans-methylation function of the adrenal medulla. (The more recent locale for this lesion has been cerebral catechol-O-methyl transferase (COMT)). The original paper suggested a transmethylation of noradrenalin to O-methylated derivatives, such as 1-(3,4-dimethoxyphenyl)-2-aminoethanol(4) and 1-(3-hydroxy-4-methoxyphenyl)-2-aminoethanol (6). At this time,no data on deactivation processes of biologically active endogenous catecholamines was available (50). By virtue of the structural similarities these compounds shared with mescaline (7) it was hoped that these compounds would show psychoactive properties. They noted in passing that 1-(3,4-dimethoxyphenyl)-2-aminoethane (2), a "cataconic" in animals (as demonstrated by Noteboom and DeJong (15-18), required fairly high doses for its effect, even in animals.

During the next twenty four years, the Harley-Mason, Osmond and Smythies hypothesis was explored partly from a therapeutic

point of view. Acting on the supposition that if indeed such faulty methylation (originally applied to this hypothesis, later couched in terms of the methylated tryptamines) did occur in schizophrenia, a group of clinicians initially associated with the Saskatchewan mental hospital advocated administration of a biological "methyl acceptor" in the form of nicotinic acid or nicotinamide (51 - 57). Work of Sydenstricker and Cleckley (58), Lehman (59), and Washburn (60) had shown a benefit of nicotinic acid in treating psychotic patients showing no detectable symptoms attributable to pellagra.* Although promising results have been reported by the group proposing such therapy (51 - 57), others have failed to verify the results claimed (61 - 75). In an editorial supporting the advocates of this chemotherapeutic approach (Huxley Institute - CSF Newsletter), Hoffer (76) decried the "workers (that) have examined simple components of the megavitamin approach but have ignored the basic reports of orthomolecular psychiatrists and have made no attempt to reproduce the complete program." The complete program has been described (77) as one consisting of three steps: (1) Consultation with trained psychological personnel (testing with Hoffer-Osmond diagnostic quiz)(78), the (Inpatient Multidimensional Psychiatric Scale) I. M. P. S. (79), and the Experiential World Inventory (80); (2) Psychotherapy coupled with appropriate chemotherapy, as well as initiation of megavitamin therapy (large doses of Vitamin B_3 (Nicotinamide)) and Vitamin C, orally or by injection; (3) Elec-

* Vitamin B^3 deficiency.

troshock therapy coupled with continued chemotherapy and megavitamin therapy. Linus Pauling introduced the words "orthomolecular psychiatry" in 1968 to designate this therapeutic approach and subsequently a full book of the same title was published in 1973 (80). Parenthetically, injections of nicotinamide adenine dinucleotide of 10-100 mg kg have been shown to have a suppressive effect on response rates in rats on Sidman avoidance schedule, suggesting that this compound is a central nervous system depressant (81).

In 1955, the Protein Factor hypothesis was first articulated. Akerfeldt (82) reported that serum obtained from patients with mental disease, including schizophrenic, manic depressive, and senile psychoses, had the capacity to oxidize N,N-dimethyl-p-phenylene diamine (DPP) more rapidly than did serum from control subjects. It was postulated at that time that elevated ceruloplasmin was responsible for the rapid oxidation of DPP, and that such a diagnostic tool might be helpful in the hospitals.

Wurtman, et al. (83), however, could not duplicate Akerfeldt's findings, and found as well that the test does not in fact measure serum ceruloplasmin content. The test was found to be sensitive to levels in plasma ascorbic acid (84), dietary factors and disease, temperature and pH. Recently, Alias, et al. (85), noted a significant increase in serum ceruloplasmin in schizophrenia (acute cases, particularly catatonics) and in women utilizing oral contraceptives.

Starting in 1957, Heath, et al. (86-89) isolated the first of the protein factors from the serum of schizophrenics.

They called the protein, taraxein, and characterized it as a specific subfraction of schizophrenic gamma G immunoglobulin (90). The readministration of this factor to monkeys (90), non-psychotic human volunteers, and schizophrenic patients in remission was claimed to produce schizophrenic-like symptoms (91). Attempts to confirm Heath's taraxein work have been successful (92 - 94) in a few laboratories but unsuccessful in others (95 - 96). In any case, it is interesting to note the chameleon nature of this theory. Taraxein was originally believed to be a coenzyme or a co-factor dialyzable from a protein fraction, possibly a small molecule (possibly an indole) (92). Most recently, Heath has advanced the possibility that schizophrenia is a genetically carried (97) autoimmune reaction (90)!

In 1960, Frohman, et al. (98) found that chicken erythrocytes incubated with plasma from schizophrenics had higher lactate to pyruvate ratios than those incubated with plasma from normals. Results with rat diaphragms manifested a similar trend, with both carbohydrate metabolism and protein synthesis being inhibited (99, 100).

This factor was affected by pH and temperature and appeared to be an α-globulin or a prosthetic group attached to an α-globulin. Frohman (101) on a single blind basis demonstrated that schizophrenics could be differentiated from non-schizophrenics by the above tests. Subsequently, Frohman (102) reported that normal subjects should be moderately exercised in order to eli-

cit the differences reported. Frohman (103) also reported that the schizophrenia plasmic factor significantly increased transport of glutamic acid and histamine across membranes of chicken erythrocytes, with lysine and methionine transport unaltered.

In May, 1972, accounts of "Clues to Schizophrenia" appeared in the popular press (104). At an annual meeting of the American Psychiatric Association, Frohman announced integration of the Tryptamine Transmethylation Hypothesis (below) and his own Protein Factor(s). Indications that such an ideological mating had been envisaged occur in the literature as far back as 1968 (105). Frohman (106) reported his protein factor was a specific and homogeneous α-2 globulin factor. Among the protein samples from patients with schizophrenia, various percentages of α-helical conformation (up to 74%) were found, with all patients having their protein in this conformation on one or more occasions. Among α-2 globulin samples from healthy controls, either the β and/or random-chain conformation were found. Previously, Frohman (107) had correlated uptake of tryptophan by chicken erythrocytes with amount of α-helix in his α-2 globulin samples and reported that a "counteracting protein" isolated from chickens (108) destroys the α-helix when mixed with the schizophrenic α-2-globulin samples. He suggested that the interaction more closely resembled an enzymatic process than an antibody-antigen process (107). In 1971, Frohman, et al. (109) reviewed properties of the "S-Protein" and reported greater tryptophan uptake in subcortical (and most probably

limbic areas) of the brains of rats pretreated with "S-Protein" and that work was currently oriented toward a better definition of the "locus" of this substance using cow brains. In 1972, Gottlieb (104) reported that the presence of a second protein ("anti-S-Protein") that controlled the ability of "S-Protein" to stimulate the uptake of tryptophan. It appears from a subsequent report that Frohman and Gottlieb (110) consider "anti-S-Protein" synonymous with their "counteracting protein" isolated from chicken brains (108). In a study of the distribution and mechanism of action of the "anti-S-Protein" in human brain (110), Frohman, et al. present data to suggest that "anti-S-protein" asserts its action by changing the conformation of the "S-protein" which is incidently in contradiction to previous speculations (107). Additionally, in schizophrenia, increased sensitivity of the "S-protein" is the result of decreased activity of the "anti-S-protein" as shown by percentage inhibition of "S-Protein"-stimulated tryptophan uptake in chicken erythrocytes by extracts of various areas of human brains (normals relative to schizophrenics).

Cowen (111) maintains that Transcephalic Direct Current (TCDC) potentials may be used to diagnose schizophrenia. TCDC potentials are slowly changing voltages that can be measured over specified diploic-emissary vein loci on the intact surface of the head. Cowen (112) attempted to mate his method to the theories of Frohman, et al. (101 - 110) with data recorded (double blind) showing a high incidence of TCDC pecularities

in patients with S-Protein abnormalities.

Work on isolation and identification of protein factors from schizophrenic plasma was also stimulated by a report of Winter and Flataker (113) in 1959. Injection of human blood plasma or serum into rats previously trained to climb a rope decreased the animals' climbing speed (114). Crucially, plasma from psychotic donors slowed the animals' performance dramatically more so than did plasma from non-psychotics. A number of investigators have since made efforts to reproduce and extend these findings. Using whole plasmas, Bergen, et al. (115, 116) obtained positive results, whereas Haddad (117) and Sanders, et al. (118) could find no systematic differences between patients and control samples. Negative results with whole sera have been reported by Ghent and Freedman (119), by Haddad (117), and by Bergen, et al. (115).

Serum fractions (120) were utilized in two separate studies by a group at Buffalo (121, 122) and a group in Worcester (115, 116, 123). Both groups have reported marked retardation of rope climbing ability of rats, and significantly more retardation with schizophrenic donors than from controls. On the other hand, negative results have been found by investigators at the New Jersey Bureau of Research in Neurology and Psychiatry (124, 125). Serum fractions were assayed as a plasma globulin precipitate (PGP) in the case of the Worcester group and contained α-2, β, and γ-globulins. The Buffalo group utilized "Cohn Fraction III" which also contained α-2, β, and γ-globulins.

Axelrod, et al. (126) conducted a reinvestigation of this work and found no difference in rope-climbing time between serum fractions (normal versus schizophrenics).

In 1962, Friedhoff and Van Winkle (127, 128) reported a ninhydrin-positive "pink spot" which did not occur as often in paper chromatographic analysis of the urine of controls, and tentatively identified it as 1-(3,4-dimethoxyphenyl)-2-aminothane (2). These reports were to catalyse a reemerging interest in the Transmethylation Hypothesis of Osmond, Smythies, and Harley-Mason and spark a tremendous experimental and theoretical controversy. The original finding has been variously supported (129 - 136) and denied (137 - 150). Summaries of available data have appeared (80, 150 - 157) from time to time. As there are no valid reasons to question the laboratory competence of the many investigators reporting such contradictory results, the apparent discrepancies must lie not in the data, but in its intepretation. Various methodologies have been applied by various researchers and any meaningful statement as to the presence or absence of these substances must be accompanied by a clear exposition of the sensitivity and detection range of the methods employed. Of added impact, criticism of the original findings has cautioned investigators to be more cogniscent of dietary artifacts (136, 139, 150, 158 - 9, 163); metabolites of medication (160) and non-specificity of a component for a particular disorder (140, 159, 161 - 163).

In 1966, two papers appeared on the pharmacology of 1-(3,4-di-

methoxyphenyl)-2-aminoethane (2) in normal human subjects. 1-(3,4-Dimethoxyphenyl)-2-aminoethane (2) was found to be inactive in humans when given in oral doses comparable to mescaline(7) (164,165). Vojtechovsky (166) and Perry (167) have also administered the compound to humans without effect. Previously, Smythies and Sykes (168 - 170) had reported that this compound lacked the characteristics of hallucinogens in conditioned avoidance response (CAR) studies with rats. The lack of activity in normals of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) can possibly be explained by assuming that deamination at the blood-brain barrier is competitive with interaction with its site of action. Preliminary analysis of the urine of those participating in one oral experiment (165) indicated that of the 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) administered, 0.37% was recovered as the amine and 77.1% was recovered as the dimethoxyphenylacetic acid (77.5% total). In a similar experiment with mescaline (7), 23.9% was recovered as the free amine and 18.1% as the trimethoxyphenyl acetic acid (41.2% total). Charalampous (171, 172), using carbon-14 labelled 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and mescaline (7), indicated a half-life of 2.5 hours in the former and 6 hours in the latter. Moreover, of the 92% total activity recovered in the case of (2), 0.2% was the amine, 90% the dimethoxyphenylacetic acid and 1.4% homovanillic acid. In the case of (7), 60% free amine, 30% trimethoxyphenyl acetic acid, $<0.1\%$ N-acetyl mescaline and 5% gluconide of N-acetyl-1-(3,4-dimethoxy-5-hydroxyphenyl)-2-aminoethane were recovered (95%

total activity).

Smythies (173) reported that following pretreatment wit a monoamine oxidase inhibitor of unspecified type, 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) exhibits properties of a hallucinogen. Charalampous (172) reported potentiation of a 1.8 mg/kg i.v. injection of 1-(3,4-methoxyphenyl)-2-aminoethane (2) by pre-treatment with nialamide* (300 mg. orally daily). His subjects were drug naive and no comparison of effects were made.

Conclusions drawn from the monoamine oxidase (MAO) inhibition studies constitute an addendum to the original hypothesis as proposed by Smythies, Osmond, and Harley-Mason, since one must tacitly presume a site of generation of the "psychotogen" intracerebrally. Once postulating such a site, however, test compounds administered externally must be adequately protected from repulsion or degradation by cerebral defenses, if necessary.

Huszti and Borsy (174) showed that 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and p-tyramine are deaminated by similar enzyme systems but different from those deaminating mescaline (7). Previous work by Alles and Heegaard (175) and by Steesholt (176) suggested that with the introduction of an increasing number of methoxy residues on the phenethylamine molecule, the substrate is diverted from monoamine oxidase to a diamine oxidase. Takeo and Himwich (177) reported that a considerably larger dose of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) than of mescaline (7) was required to produce electroencephalographic arousal in the rabbit. They suggested that in the brain either 1-(3,4-dimethoxy-

* 1-Isonicotinyl-2-(2-benzylcarbamyl)ethylhydrazine

phenyl)-2-aminoethane (2) is more rapidly inactivated by monoamine oxidase or that it does not easily penetrate the blood-brain barrier. Subsequent work by Shah and Himwich (178) has indicated that monoamine oxidase inactivates 1-(3,4-dimethoxyphenyl)-2-amino ethane (2) more rapidly than it does mescaline (7). The presence of iproniazid* in these in vitro studies in the incubating medium effectively depressed the deamination of 1-(3,4-dimethoxy phenyl)-2-aminoethane (2) (178) and permitted more effective penetration of brain areas (179). Deamination of mescaline (7) in mice brain is not suppressed by pretreatment with either tranylcypromine,** iproniazid or semicarbazide (180). Along these lines phenelezine-pretreated rats showed increased response to smaller doses of 1-(3,4-dimethoxyphenyl)-2-amino-ethane (2) (181).

In the reinvestigation of animal studies by Noteboom (15 - 17) and DeJong (18), the investigators Cession-Fossion, et al. (182), Michaux and Verly (183), and Michaux (184) reconfirmed "catatonic" properties of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and established a cataleptic dose (CD_{50}) of 132 mg/kg. Such "catatonic" properties were also observed in studies of Barbeau (185), Lusvarghi (186) and Brown (187). Barbeau (185) suggested that the mode of action of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) is via interference (unspecified) with the normal metabolism of dopamine in the central nervous system. Prepas, et al. (188) have presented preliminary data indicating a direct effect of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) on the brain. This con-

* 1-Isonicotinyl-2-isopropylhydrazine
** 2-Phenylcyclopropylamine

tention is supported by Smythe and Lazarus (189) and Shah (190-1).

A formidable argument against a continuing role for active metabolites in schizophrenic states is the existence of acute and chronic mechanisms of adaption or tolerance (12). "Tolerance" has been defined as (192) "acquired insensitivity of a biological target for a substance at any dose". The observation in a behavioural test that prior exposure to a drug produces decreased responsiveness to that drug has been explained in several ways (193): 1. Metabolic Tolerance, an alteration in absorption, metabolism (autoinduction) or excretion which reduces the concentration of drug at the target tissues; 2. Cellular Tolerance, a diminished sensitivity of the target tissue; and 3. Behavioural Tolerance, changes which arise via compensatory behavioural mechanisms. A related concept, "tachyphylaxis" has been defined as "an increase in the amount of a drug required to produce a given pharmacological effect" (194).

Chronic injections of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) at doses of "more than 10 mg/kg/day over periods extending to 6 months in rats, rabbits and monkeys elicited a persistent 'akinetic syndrome'" (185). Such a lack of tolerance has also been observed by Carlini, et al. (195) in injection studies using rats over a duration of 16 days and at 80 mg/kg.

Interest in 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) as a "psychotogen" spurred interest in other derivatives of related structure and possible biological significance in schizophrenia. Little and Dill (196) noted that the intrastriatal (i. s.)

injection of 1-(3-methoxy-4-hydroxyphenyl)-2-aminoethane (8) in rats produced a sminlar pattern of what they referred to as "dykinesias", as did injections of mescaline. The similarity of effects on the striatum produced by a hallucinogen and a normal metabolite of dopamine suggested the hypothesis to these authors that pathological accumulation of 1-(3-methoxy-4-hydroxyphenyl)-2-aminoethane (8) in the striatum of man could lead to psychotic states (197).

N-Acetyl-1-(3,4-dimethoxyphenyl)-2-aminoethane (9) was shown to be a metabolite of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and to be ten-fold more potent than the parent amine in producing hypokinetic behaviour in test animals (198, 199). Doses ranging from 1.36 - 16.4 mg/kg were without hallucinogenic effect in man (200). Van Winkle, Schweitzer and Friedhoff (201) studied the metabolism of N-acetyl-1-(3,4-dimethoxyphenyl)-2-aminoethane (9) in rats. In vitro, pineal hydroxyindole-O-methyl transferase (HIOMT) catalysed formation of N-acetyl-1-(3,4-dimethoxyphenyl)-2-aminoethane from both N-acetyl 1-(4-hydroxy-3-methoxyphenyl)-2-aminoethane (10) and N-acetyl 1-(3-hydroxy-4-methoxyphenyl)-2-aminoethane (11) (202). Carbon-14 (4-methoxy)N-acetyl-1-(3,4-dimethoxyphenyl)-2-aminoethane (9) was administered to four acute schizophrenics, two chronic schizophrenics and four normal controls. Differences in demethylation were observed. Demethylation proceeded at a faster than normal rate in acute cases and at a slower than normal rate in chronic cases (203).

Research into catecholamine transmethylation has been

conducted to answer questions raised by the Transmethylation Hypothesis of Harley-Mason, Osmond, and Smythies (1952), namely whether methylation of the 4-hydroxyl is a process in "normal" and/or "abnormal" deactivation of endogenous catecholamines. In 1957, Armstrong, et al. (204) and Axelrod (205) reported that epinephrine and norepinephrine are transmethylated at the 3-hydroxyl in the course of normal human metabolism. In 1963, Friedhoff and Van Winkle (206) reported that dopamine could be converted to 3,4-dimethoxyphenylacetic acid (12), using liver obtained from autopsy samples and details of these experiments were promised at that time to be forthcoming (207). To date, full details have not been published.

In 1959, Senoh, et al. (208) showed that crude preparations of catechol-O-methyl transferase (S-Adenosylmethionine: Catechol-O-methyl transferase, E. C. 2.1.1.6) can methylate catechol derivatives in either the para or meta positions (208). This work was confirmed by other investigators using perfused rat liver preparations (209 - 212) as well as preparations of catechol-O-methyl transferase from rat liver (213 - 218). Frère and Verly (219) reported a 250-fold purification of the enzyme without separating the meta-O-methylating from the para-O-methylating activities. No dimethylation of noradrenaline could be detected. Two isoenzymes were separated by gel electrophoresis; they each individually O-methylated noradrenaline in the meta and para positions in a ratio m/p ≈ 13. Frère and Verly (220) also demonstrated absence of para-O-methylated products when

noradrenaline was incubated with whole rat blood, leading the authors to postulate preferential 4-demethylation in biological fluids. Similar observations were made by Sargent, et al. (221) in vivo with 1-(3,4-dimethoxyphenyl)-2-aminoethane (2), ^{14}C-labelled in the 3- or 4-methoxyl.

Creveling, et al. (222, 223) and Katz (224) have discussed factors that alter m/p ratio as applied to catechol O-methyl transferase in vitro. Friedhoff has examined 4-O-methylation in rat liver (225 - 227) and claimed to isolate a mammalian enzyme, guaiacol-O-methyl transferase (GOMT), capable of forming di-O-methyl catecholamine derivatives (228).

Endogenous 1-(4-methoxy-3-hydroxyphenyl)-acetic acid (13) has been detected by a number of groups in studies on humans (229-33). The presence of this 4-O-methylated product of catecholamine metabolism suggests that 4-O-methylation is a normal, albeit minor, metabolic pathway regardless of the pathological state of the human.

Studies on catechol-O-methyl transferase activity have been undertaken in humans to ascertain what correlation, if any, such activity bears upon psychologically inappropriate states. Reports by Horst, et al. (234) and Männl, et al. (235) indicating the presence of a catechol-O-methyl transferase with high activity in intact red blood cells of chicken, rat, and man, could not be reproduced by Gugler (236). Instead, these findings (236) support a very low catechol-O-methyl transferase activity in lysed red blood cells as described by Axelrod (237).

Axelrod (237) reported reduced red blood cell catechol-O-methyl transferase, elevated histamine-N-methyl transferase and unchanged methanol-forming enzyme (238) in women with primary affective disorder (depression). Matthysse and Baldessarini (239) assayed for S-adenosylmethionine concentration and catechol-O-methyl transferase activity in a group of 20 schizophrenic men (medicated with haloperidol* or thorazine**) and a control group from the same ward with various diagnoses (epilepsy, chronic alcholism, depression, senile psychosis and severe anxiety neurosis. Concentrations of blood SAMe were reported to be statistically insignificant with slight elevation in catechol-O-methyl transferase activity by the schizophrenics.

In a preliminary study of psychopharmacological response of a test group of five male schizophrenics to L-3,4-dihydroxyphenyl alanine (L-DOPA), the two "paranoids" of the group showed exacerbation of symptoms (240). Tran, et al. (241) studied decarboxylation of D, L-dihydroxyphenyl alanine-carboxyl-^{14}C by erythrocytes in samples from seven normal volunteers, four schizophrenics in remission, and five schizophrenics with hallucinations and thought disorder. Elevated $^{14}CO_2$ production was indicated for the schizophrenics with hallucinations and thought disorder were found to produce more $^{14}CO_2$ than normals and remitters. Studies of this nature are of a tantalizingly preliminary nature.

In 1961, an attempt was made to test the Transmethylation Hypothesis by feeding large oral doses of methionine (10 -- 20 g.)

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* N-[4-(4-Fluorophenylbutan-1-one)]-4-(4-chlorophenyl)-4-hydroxypiperidine HCl

** 2-Chloro-10-[3-(dimethylamino)propyl]-phenothiazine

to schizophrenic patients under conditions postulated to aggravate the abnormality. Schizophrenics given methionine and iproniazid, a monoamine oxidase inhibitor, suffered a striking exacerbation of psychoses, not produced by either agent alone, nor by any other amino acid (242). Rather similar results were obtained in a repeat study of the phenomenon (1963) by Park, et al (243). Since that time a plethora of reports have confirmed the initial observations (244-49). Antun, et al (247) reported that excretion of 1-(3-methoxy-4-hydroxyphenyl)ethyleneglycol (14) and 1-(3-methoxy-4-hydroxyphenyl)acetic acid (15) was not elevated during L-methionine administration. However, a preliminary comparison (247) of levels of 1-(3-methoxy-4-hydroxyphenyl)ethyleneglycol (14) excretion in schizophrenics versus normals revealed an elevation, in general, of the former over the latter. Coper, et al (248) reported 10 of 20 male and 1 of 6 female patients with increased 1-(3-methoxy-4-hydroxyphenyl)acetic acid excretion over 16 normal volunteers. After administering methionine (10 g) only 4 patients eliminated an increased quantity of 1-(3-methoxy-4-hydroxyphenyl)acetic acid; these were 4 of 5 alcoholics.

Israelstam, et al. (249) reported prolonged excretion of $^{14}CO_2$ in the breath of acute schizophrenics following administration of ^{14}C-S-methylmethionine to a group of five normals, five schizophrenics in remission, three acute schizophrenics and three depressives. The depressives excreted $^{14}CO_2$ most rapidly, while the excretion in schizophrenics was delayed. Cohn, Vesell, and Axelrod (250) report isolation of

a methionine-activating enzyme in human erythrocytes and other species.

Sprince (251) has advanced some mechanisms for the action of methionine other than in the transmethylation of catecholamine "psychotogens". Rats fed on various diets with excess methionine, homocysteine, or cysteine manifested a marked fall in the excretion of N-methyl nicotinamide. He suggested that methionine or its metabolites exerted an inhibitory effect at some point in the tryptophan → kynurenine → N-methyl nicotinamide pathway. Concomittant with this decrease was an increase in the excretion of indoleacetic acid, particularly when the diet contained an excess of methionine. Sprince (251) suggested that such an effect on tryptophan metabolism could be accounted for in four ways:

(a) Inhibition of the oxidative enzymes in the kynurenine pathway;

(b) Liberation of free tryptophan from bound tryptophan;

(c) Formation of N-methylated derivatives of tryptamine;

(d) Formation of O-methylated derivatives of tryptophan metabolites.

The last two possibilities of Sprince supplied impetus for a second Transmethylation Hypothesis, The Serotonin/Bufotenine/Dimethyl Tryptamine Hypothesis, which was articulated for the first time in 1961 (252), although its roots go back to Bumpus and Page (253). The close structural resemblance between serotonin (16) and bufotenine(17) prompted a research for a

possible *in vivo* interconversion of the two. More recently, an interconversion of serotonin (16) and N,N-dimethyl/5-methoxy tryptamine (18), or tryptamine (19) and N,N-dimethyl tryptamine (20) has been envisaged. Rabbit lung was demonstrated to possess the required *in vitro* methylating enzyme thus lending encouragement to this hypothesis (254). An attempt to find bufotenine(18) in the urine of fifteen non-psychotic patients was unsuccessful, but the material was found in quantities of 400 µg/l in 25 of 26 hallucinating schizophrenic patients (252). Confirmation of these findings soon followed (255 - 257). In one instance, a "bufotenine-like" substance was found in nine of seventeen urine samples from five schizophrenic patients and none from three mentally deficient patients (256). Conflicting results, however, were obtained using a method claimed to be superior to previous ones used (258); no bufotenine could be found in five normal subjects or twenty-one schizophrenic patients. Still others (259 - 264) have failed to confirm the presence of bufotenine in the urine of either normals or schizophrenics. In 1967, Himwich, et al. (265), using a two dimensional t.l.c. reported conjugated bufotenine in the urine of six schizophrenics and four mental defectives. In schizophrenics, bufotenine was excreted both free and conjugated; in the mentally defective patients, only conjugated bufotenine was found. Moreover, the authors felt that there was a relationship between free bufotenine excreted and exacerbation of psychotic behaviour. Himwich has published numerous confirmatory reports since that

time (266 - 270). Wyatt, et al. (271) has reported that within the limit of sensitivity of the assay (0.5 - 1.8 ng/ml of plasma), there was no difference amongst normals and patients with psychotic depression, and acute and chronic schizophrenia. Mandell and Morgan (272) reported isolation of an enzyme, indole (ethyl) amine N-methyl transferase, in human brain and demonstrated in vitro conversion of tryptamine to N,N-dimethyltryptamine. Saavedra and Axelrod (273) described a similar in vitro transmethylation in brain and in blood (274). Distribution and properties of the transmethylating enzyme in brain have been described (275 - 278). Tolerance of the intraventricular infusion of bufotenine and 5-methoxy N,N-dimethyltryptamine has been preliminarily demonstrated (12). Green, Koslow, and Costa (279) have identified 5-methoxytryptamine in rat hypothalamus, using g.c.-mass spec. (280). An intriguing paper describing the presenece of N,N-dimethyltryptamine in rat brain at 8 μg/g led the authors to speculate about the role of this compound in the dream mechanisms of the brain (281). Oral administration of L-5-hydroxytryptophan, the serotonin precursor, with a peripheral decarboxylase inhibitor produced mild to moderate improvement in six of seven chronic undifferentiated schizophrenics who were resistant to phenothiazine treatment. Two of four chronic paranoid schizophrenics, also resistant to phenothiazine treatment, deteriorated (282).

McIsaac (283 - 284) described a biochemical hypothesis in 1961 based on the resemblance between melatonin, a pineal gland

hormone (23) and harmine (22), the active component of "yaje" (Banisteriopsis Caapi) (285-286). The Serotonin Melatonin Harmaline Hypothesis, as it was called, postulated a biogenesis of serotonin to 5-methoxytryptamine (21), melatonin(23), and 10-methoxy harman (24). 10-Methoxy harman (24) had been demonstrated to posses monoamine oxidase inhibiting and antiserotoninergic properties, as well as being a potent hallucinogen. This compound also disrupts conditioned avoidance responses in animals (287). McIsaac, et al (288) isolated 5-methoxytryptophol, melatonin, 5-hydroxytryptophol, 5-methoxyindole-acetic acid, and 5-hydroxyindole-3-acetic acid from bovine pineal tissue. Multiple forms of hydroxy indole-O-methyl transferase (289) have been isolated and characterized. The metabolism of harmaline in rats has been examined (290-291). β-Carboline derivatives were recently investigated for mode of action (292). 6-Methoxy-1-methyl-1,2,3,4-tetrahydro-β-carboline (25) had previously been reported to specifically elevate levels of serotonin in the brain without alterations in norepinephrine levels (293). Using rats, the efficacy of this compound was attributed to activation of plasma and liver 5-hydroxytryptophan decarboxylase as well as acceleration of serotonin uptake (292). A direct interaction with receptors was ruled out by intra-ventricular injection of 50 µg of the β-carboline.

In 1960, Sprince, et al (294) published an account of isolation from the urine of schizophrenics (over controls) of a substance tentatively identified as 6-hydroxyskatole. Krall, et

al. (295) also made a chromatographic study of the urinary levels of 6-hydroxy skatole and indole-3-acetamide (27) from a group of 72 schizophrenics, 101 manic-depressives, and 55 other psychotic subjects, and a comparison was made with a group of 76 normal controls. In contrast with earlier findings, neither compound was significantly different in level in the urine from schizophrenics compared with the urine from normal subjects. Spatz, et al. (296) isolated 5-hydroxy-3-methyl indole (5-hydroxy skatole) (26) from the urine of epileptics.

The Adrenochrome/Adrenolutin Hypothesis of schizophrenia was originally proposed by Hoffer, Osmond, and Smythies in 1954 (297), revised in 1959 (298), in 1965 (299) and 1968 (300). The suggestion was made that schizophrenics metabolized adrenalin to adrenochrome (28). Further, this suggestion was based on the results of self-administration of adrenochrome and on reports that psychotic reactions had occasionally resulted when "deteriorated" or "pink" adrenaline was used in anesthesia or by chronic asthma sufferers (297 - 300). In 1957, Hoffer reported that adrenolutin (29), a compound related to adrenochrome (28), in oral doses of 25 - 50 mg., produced psychological changes in human volunteers (300 - 304).

A review of reported psychotomimetic properties of adrenochrome (28) has been published (305). In view of its high chemical reactivity (306 - 310), it is doubtful if free adrenochrome (28) could have more than a transient existence in vivo. However, this does not entirely rule out the possible existence

of adrenochrome (28), in a dynamic equilibrium in vivo or by reversible association with some other species, e.g. a naturally occurring thiol (311 - 313).

In 1961, Irvine, et al. (314) observed a distinctive spot in paper chromatographic monitoring of the urine of volunteers administered lysergic acid diethylamide. A similar spot, called "mauve factor" because of its Erlich reaction, was subsequently observed in many psychiatric patients not so treated. The spot was isographic with bufotonin and appeared to behave as a pyrrole. In 1963, Hoffer (315), pointing to the statistical association with psychosis (not specifically schizophrenia) suggested that persons excreting mauve factor could be described as suffering from a disease called "malvaria". Subsequently, association between mauve factor and psychosis has been confirmed by some (316 - 318) and endorsed by others (319 - 321), the factor being present in 30 - 60% range of psychotic patients. Irvine and Majer (322) have isolated a pyrrole by means of a new hybrid two-dimensional thin layer-paper chromatographic system ("autotransfer chromatography"). The "mauve factor" pyrrole and kryptopyrrole (30) were shown to be identical by R_f value and mass spectrometry. Confirmation was forthcoming (323) and pharmacological studies (323 - 325) indicated sedative properties. Preliminary findings indicated that patients with intermittant porphyria excreted increased amounts of urinary kryptopyrrole (30) during acute attacks (326). The assignment of "schizophrenia" may be incorrectly applied in cases such as

the above.

Mattok, et al. (327) reported the presence of a "gray" spot which they found using paper chromatographic (modified Ehrlich Reagent spray) analyses of the urine of 17 of 25 schizophrenics. Only 4 of 31 normal subjects showed a grey spot. A reinvestigation by Keup, et al. (328) could not confirm the specificity reported; i.e. 59 of 68 schizophrenics and 36 of 45 normal subjects excreted a "gray spot". These authors speculated that the reported discrimination based on the "gray spot" could be explained as a dietary artifact as indicated by a preliminary investigation (328). Two normal controls consumed four bananas and excreted a "gray spot" increasing in intensity for two hours, returning to normal in the third hour.

The fact that hospitalized chronic schizophrenic patients exude a peculiar odor has been reported (329 - 330). An investigation of the "odor factor" by Smith, et al. (331) revealed the presence of trans-3-methyl-2-hexenoic acid. Perry (332) has reported that such a finding is an artifact of the plastic bags used to encase the patients whilst they were washed with distilled water. Notwithstanding, Krischer and Pfeiffer (333) have proposed that urinary kryptopyrrole (mauve factor) may be associated with the presence of trans-3-methyl-2-hexenoic acid and have outlined a possible biosynthetic scheme from kryptopyrrolic acid (31). Such a biogenesis has been criticized principally on the basis of instability of the proposed enamine

intermediates by Grant (334).

The Molecular Complex hypothesis was first formulated by Galzinga (335) and was based upon the observation that acetylcholine and noradrenochrome are capable of yielding a molecular complex that is stable toward further transformation to adrenolutin normally brought about by ascorbic acid (336). In simplest terms, this theory states that leakage of one transmitter into the synpase of another may lead to a short circuit by complexation (337).

The Noradrenergic Deficit Hypothesis was proposed by Stein and Wise (338) in 1971. 1-(2,4,5-Trihydroxyphenyl)-2-aminoethane (6-hydroxy dopamine) produces long lasting depletion of noradrenalin from peripheral sympathetically innervated tissues in various species (339 - 341). Uretsky and Inversen (341) have presented evidence that such a depletion results from selective destruction of adrenergic nerve endings. Intraventricular injections of 400 µg of 6-hydroxydopamine in rats produced catatonic-like behaviour ("waxy flexibility") (338). Stein and Wise (338) speculated that malfunction (degeneration) of noradrenergic neurons or reduced dopamine-β-hydroxylase activity could be the root cause of schizophrenia (342).

Intraventricular 6-hydroxydopamine was reported by Redmond, et al. (343 - 346) to produce in free ranging or caged macaques a decrease in "positive social interactions". Wise and Stein (347) assayed regional dopamine-β-hydroxylase activity in post mortem brain specimens from 18 schizophrenic

patients and 12 normal controls. They report a significant reduction in the activity of this enzyme in all brain regions of the schizophrenic group.

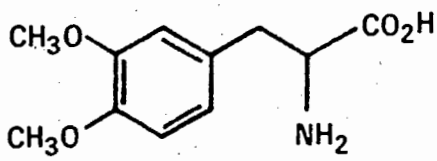
Friedhoff and Alpert (348) have recently evoked a Dopaminergic-Cholinergic Hypothesis to account for the production of psychotic symptoms. In simplest terms, this hypothesis makes the following assumptions: (1) an increase in dopaminergic activity or a decrease in cholinergic activity produces psychotic symptoms and relieves Parkinsonian symptoms. Evidence for these assumptions is based upon a further assumption concerning the mode of action of a battery of anti-psychotic, anti-Parkinsonian, psychoenergizing and psychedelic chemicals. (2) Conversely, a decrease in dopaminergic activity or an increase in cholinergic activity relieves psychotic symptoms, but produces Parkinsonian symptoms.

2-3 Conclusions from the Review

A review of the literature reveals a paucity of knowledge of the biochemistry of cerebral malfunction particularly as it relates to schizophrenia. It was primarily this observation that promoted the described investigation. The focal point of this endeavor centers on offering comment on the Transmethylation Hypothesis of Osmond/Smythies/Harley-Mason (1952).

FIGURE 1

" PSYCHOTOGENS" AND COMPOUNDS IMPLICATED IN THE BIOCHEMISTRY OF SCHIZOPHRENIA



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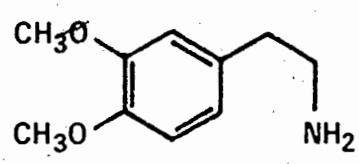

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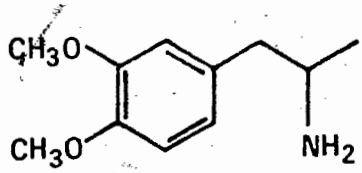

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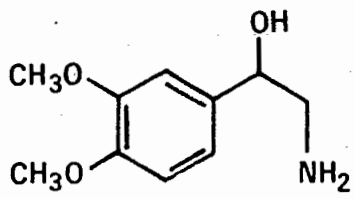

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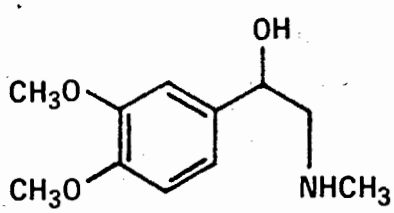

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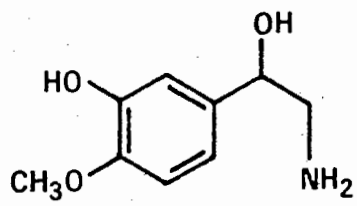

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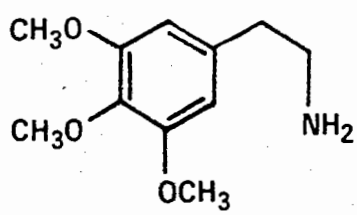

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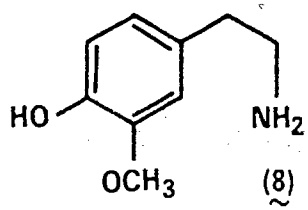

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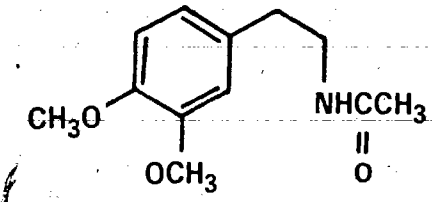

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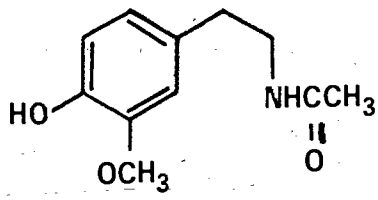

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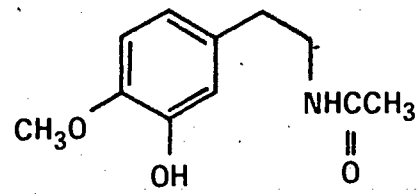

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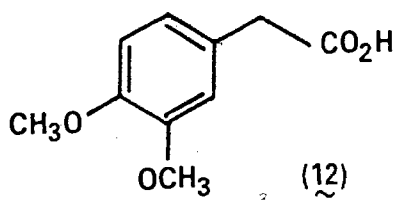

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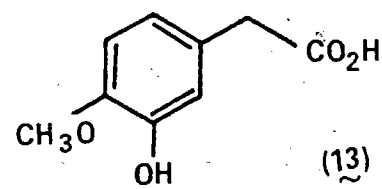

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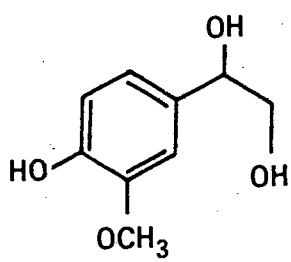

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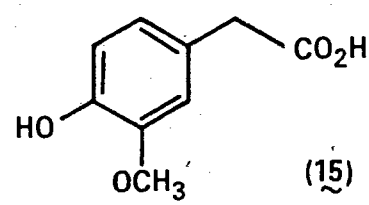

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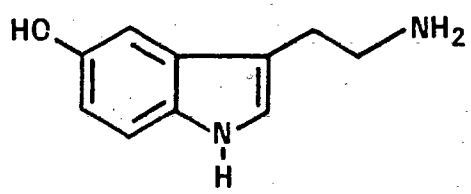

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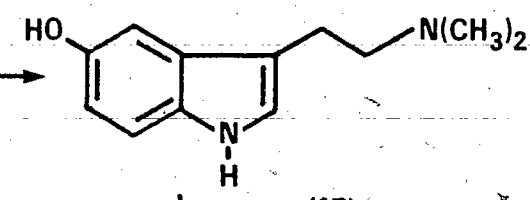

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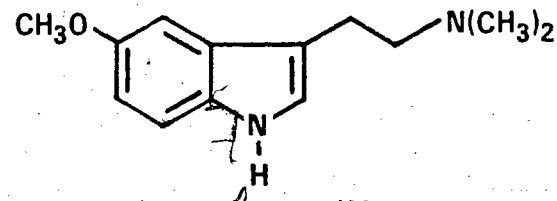

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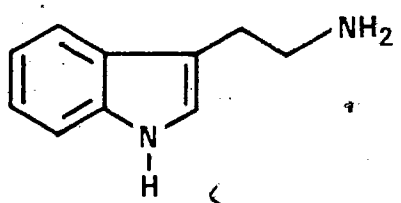

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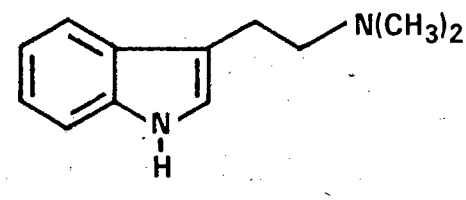

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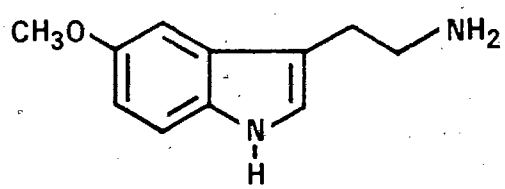

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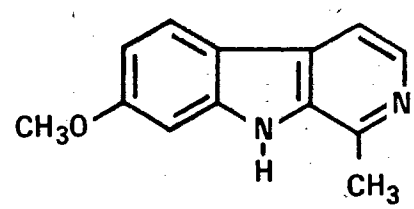

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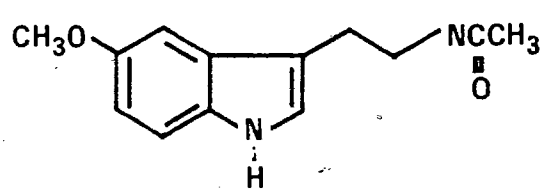

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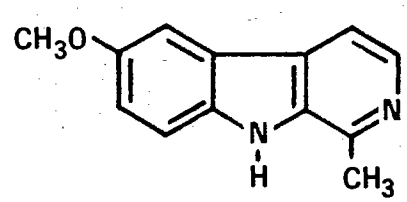

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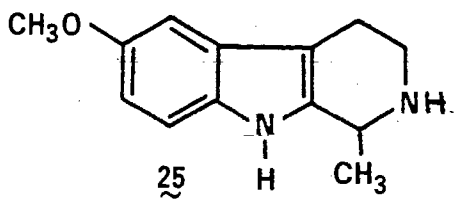

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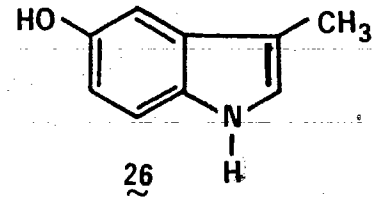

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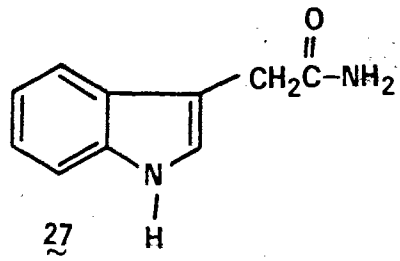

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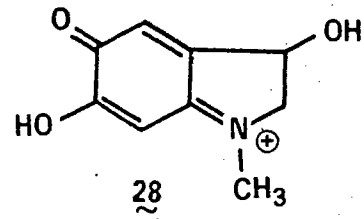

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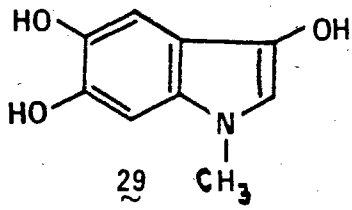

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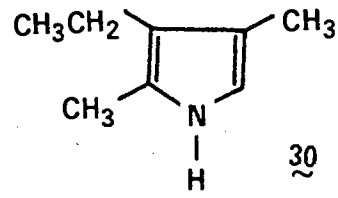

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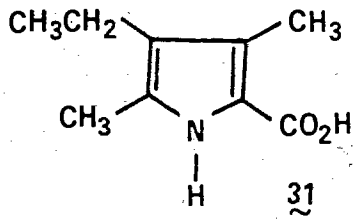

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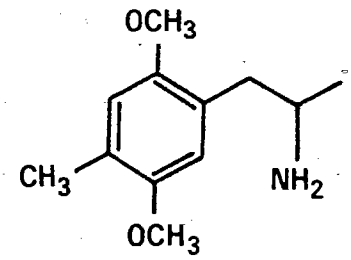

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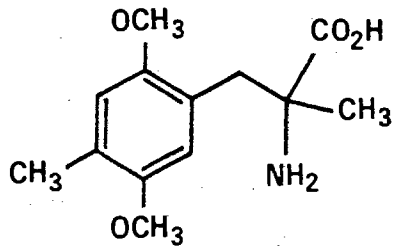

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Chapter 3

Transmethylation Hypothesis of Osmond/Smythies/Harley-Mason (1952)

Statement of the Problem

The Transmethylation Hypothesis of Harley-Mason, Osmond and Smythies (1952) deals with aberrant O-methylation of catechol-amines to possibly psychoactive compounds. It is such a process that was postulated to differentiate normals from schizophrenics.

It occurred to us in 1969 that such a hypothesis would lend itself to immediate experimental examination. Coupled with the realization that this hypothesis was the oldest hypothesis from the "modern" period, we were encouraged to examine its utility in two ways:

1. Synthesis of "methylated" psychotogens (1,2,4,5), concurrently optimizing yields for subsequent ^{14}C-labelling, if metabolic and disposition data was considered critical to the argument.

2. Injection studies of three "methylated psychotogens" (1,4,5) and a reexamination of tolerance of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2), utilizing a simple mammalian system.

Of equal concern, however, would be some method of detection of this hypothetical aberration. One of the main foundations of the Transmethylation Hypothesis of Harley-Mason, Osmond and Smythies rests on the assumption that 4-O-methylation of catecholamines is not a minor metabolic pathway in schizophrenics. Ideally, it would be desirable to isolate and characterize such an enzyme from some organ of a mentally ill person and at the same time demonstrate its relative

absence in the same organ in non-affected individuals (as was attempted by Friedhoff and van Winkle (207)). If, however, such an enzyme lies in small quantities in the area surrounding the projected neural site of action, e.g. in the brain, as some researchers have suggested, it may be difficult to execute a proper comparative study of reactivities of compounds of known neural functions and/or metabolism in appropriate tissue homogenates or even cell-free systems.

A method of approach whereby the above may be circumvented would be to assume for the sake of argument that such an enzyme system is operative in schizophrenics, and that it would only require the presence of some suitably designed, exogenous reagent to make itself manifest, for example, some kind of behavioral change, predictive metabolic transformation, etc.

1-(3,5-Dimethyl-4-hydroxyphenyl)-2-aminopropane (72) could be transmethylated to 1-(3,5-dimethyl-4-methoxyphenyl)-2-aminopropane (73) by the postulated enzyme (if its specificity is large) at the 4-hydroxyl in the brain, diffuse to the neural site of action, and induce behavioral changes in individuals administered. In a schizophrenic, it would show a temporary exacerbation of his psychosis. Prior to submission of the compound to testing with schizophrenic patients and normal subjects the compound would be submitted for preliminary pharmacology. Upon completion of these studies, the compound would then be administered to normal human subjects to compare

behavioral changes that may be distinguished from testing, at a last but necessary recourse, with schizophrenic patients.

1-(3,5-Dihydroxy-4-methylphenyl)-2-aminopropane (74) would be likewise tested in laboratory animals and humans to discover if the body's known 3-OH methylation enzyme system may manifest itself in the production of methylated product and subsequent behavioral changes. A positive result with this reagent in a known enzyme system would serve as indication that the approach postulated above with an unkown system would manifest itself in the manner expected if indeed that unknown system were operative.

A logical sequence of events should take place in our research as follows:

1. Synthesis of two possible "indicator" β -phenylisopropylamines and their two "methylated" counterparts (72-75). Provision for ^{14}C-labelling would be explored and outlined.

2. Preliminary injection studies of four β-phenylisopropylamines (72-75).

3. Metabolism, distribution work and human testing (normals and normals/schizophrenics).

Chapter 4

"Transmethylated" Catecholamines.

Results.

3-1 Chemistry (349)

The synthesis of the catecholamine analogs (±) 3-(3,4-dimethoxyphenyl)-2-alanine (1), 1-(3,4-dimethoxyphenyl)-2-aminoethane (2), (±) 1-(3,4-dimethoxyphenyl)-2-aminopropane (3), (±) 1-(3,4-dimethoxyphenyl)-2-aminoethanol (4), and (±) N-methyl-1-(3,4-dimethoxyphenyl)-2-aminoethanol (5) is described and optimized yields are reported. The availability of carbon-14 labelled compounds has dictated logical starting points in the synthesis of ^{14}C-labelled analogs. (Figure 1)

In recent years, a number of ring substituted phenylalanines have been synthesized (350 - 363). Published syntheses (363) proved, however, to be sensitive to undesirable side reactions. In the course of these investigations, a facile synthesis based on a published outline was substituted. The nature of the side reactions in the published syntheses was also explored.

Veratraldehyde (34) was condensed with hippuric acid* by the method of Buck and Ide (364). The "azlactone" (35a, 35b) was cleaved with potassium carbonate in aqueous acetone to N-benzoyl-1-(3,4-dimethoxyphenyl)-2-aminopropenoic acid. Reduction of 36a, 36b was effected at 0° with 3% sodium amalgam. The resulting N-benzoyl 1-(3,4-dimethoxyphenyl) 2-alanine (37) was unreactive toward the barium hydroxide hydrolysis reported (363); instead, cleavage with 6 M HCl in a sealed tube yielded the desired O-methylated dopa derivative, 1-(3,4-dimethoxyphenyl)-2-alanine (1), in 25% overall yield. (Figure 2)

* Can obtain labelled from glycine-^{14}C.

Cleavage of the azlactone (35a,35b), as described by Deuloffeu and Mendivelzua (363), in sodium hydroxide gave rise to a mixture of N-benzoyl-1-amino-2-(3,4-dimethoxyphenyl)-1-propenoic acid (36a, 36b) and N-benzoyl-1-(3,4-dimethoxyphenyl)-1-hydroxy-2-alanine (38). Such a hydrolytic cleavage to 37 has been recently exploited in the syntheses of substituted phenylpyruvates (40) via the intermediacy of 38 or 39 (365, 366). (Figure 3)

Reduction of the azlactone (35a,35b) with a specially prepared Raney nickel catalyst utilized as described by Badshah, Khan and Kidwai (357) gave rise to 4-(3,4-dimethoxybenzyl)-4-ethoxy-2-phenyl-5-oxazolone (41a) in addition to the cited N'-benzoyl-(3, 4-dimethoxyphenyl)-2-alanine amide (41b). The fact that the authors neglected to mention the requisite washes associated with Raney nickel generation afforded us the opportunity of observing an ambient temperature reaction of ethoxide with the azlactone (35a,35b). (Figure 4)

1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and 1-(3,4-dimethoxyphenyl)2-aminopropane (3) were prepared by methods of Raiford and Fox (367) and Ramirez and Burger (368). In addition, 3 was prepared by a modified procedure (369). Commercial ^{14}C-nitromethane and accessibility of ^{14}C-nitroethane via a Victor Meyer displacement (370) of ^{14}C-ethyliodide renders this route especially attractive for labelling purposes. Overall yields were 68% for 2 and 35% and 70% for 3.

Of three published accounts for the synthesis of 1-(3,4-dimethoxyphenyl)-2-aminoethanol (4), two were unattrac-

FIGURE 2

SYNTHESIS OF (1)

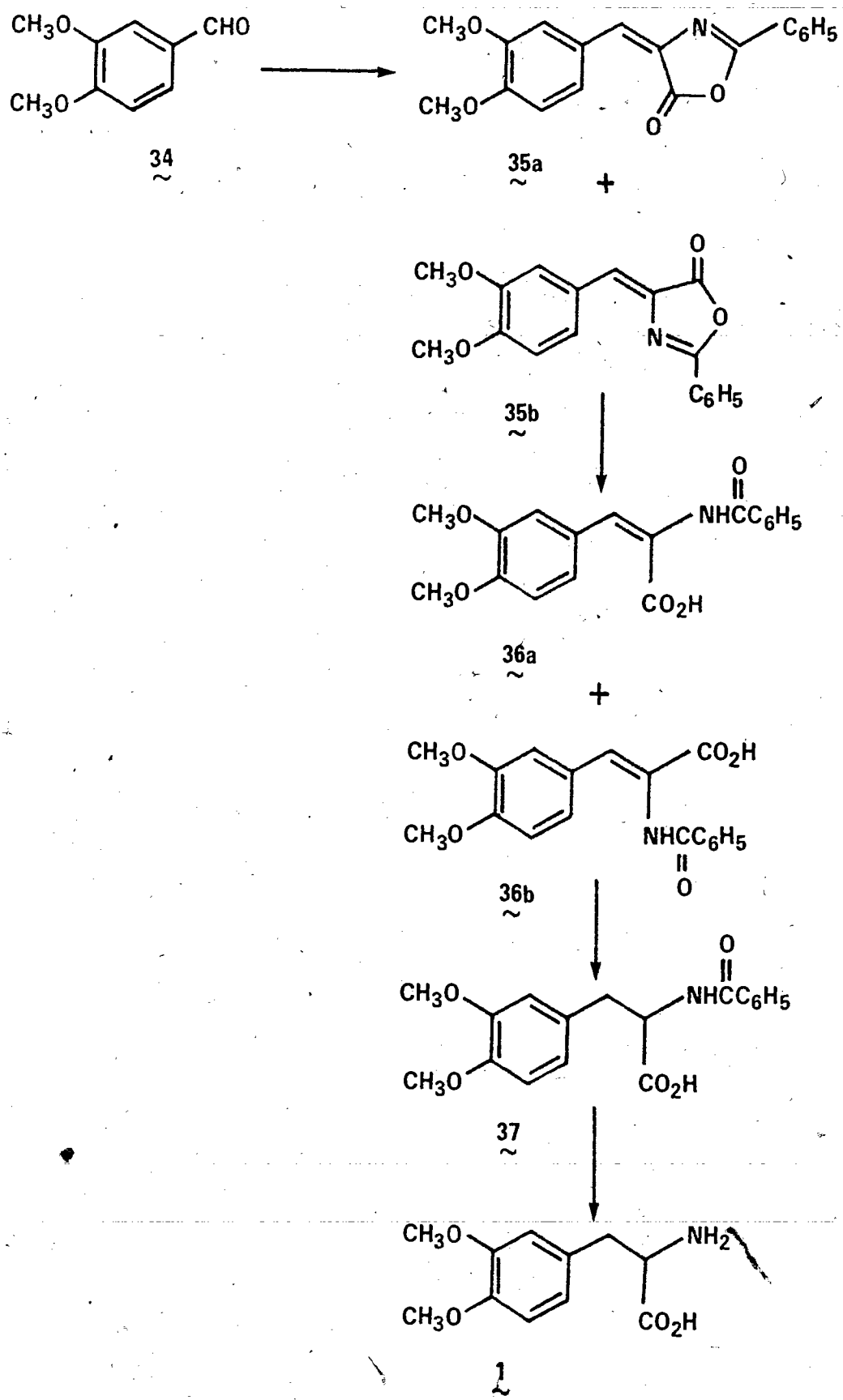


FIGURE 3

CLEAVAGE OF AZALACTONE (35a,35b)

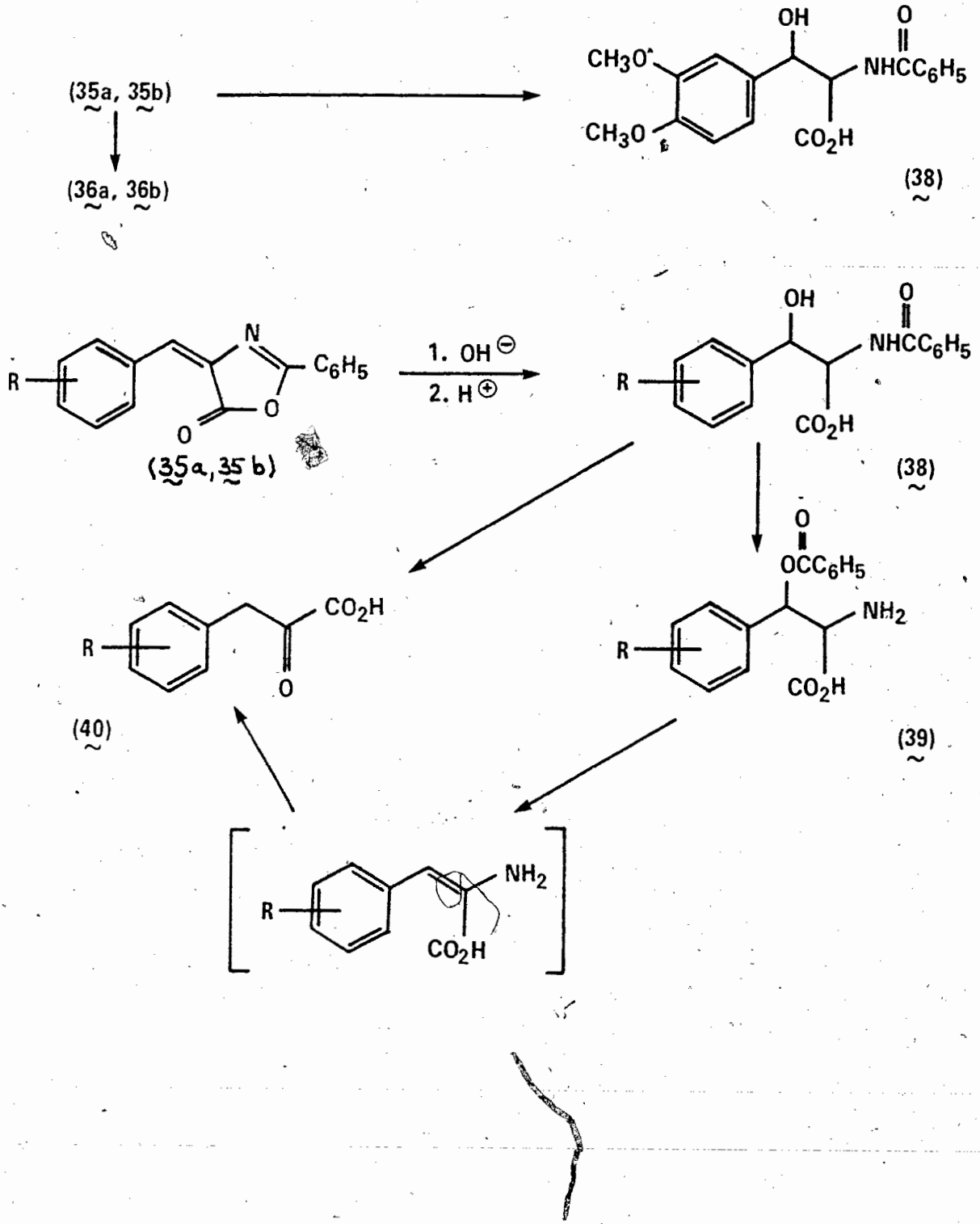
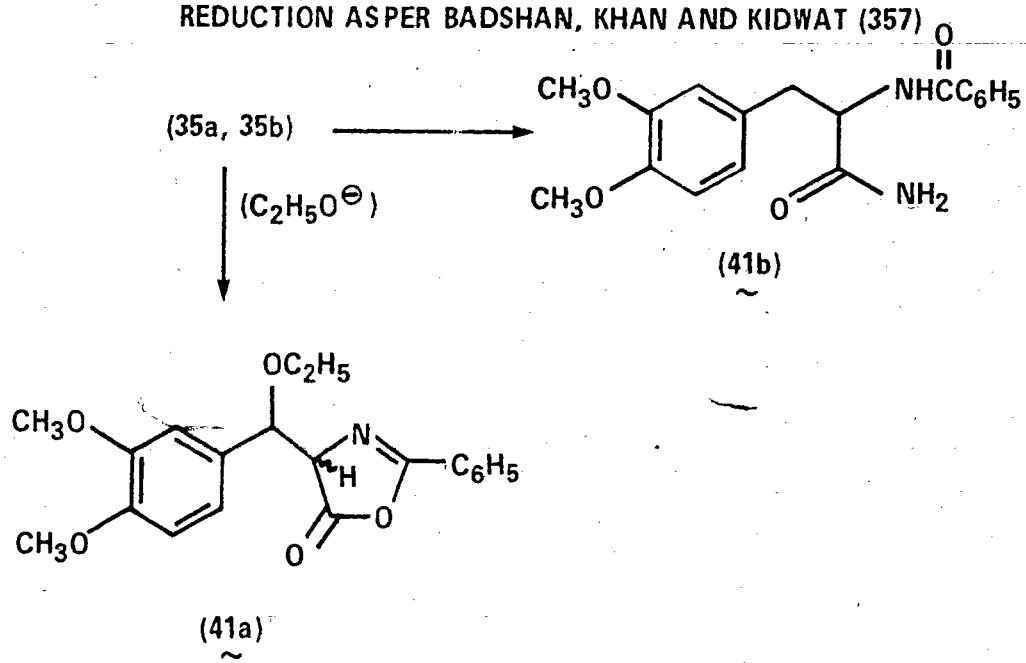


FIGURE 4

REDUCTION ASPER BADSHAN, KHAN AND KIDWAT (357)



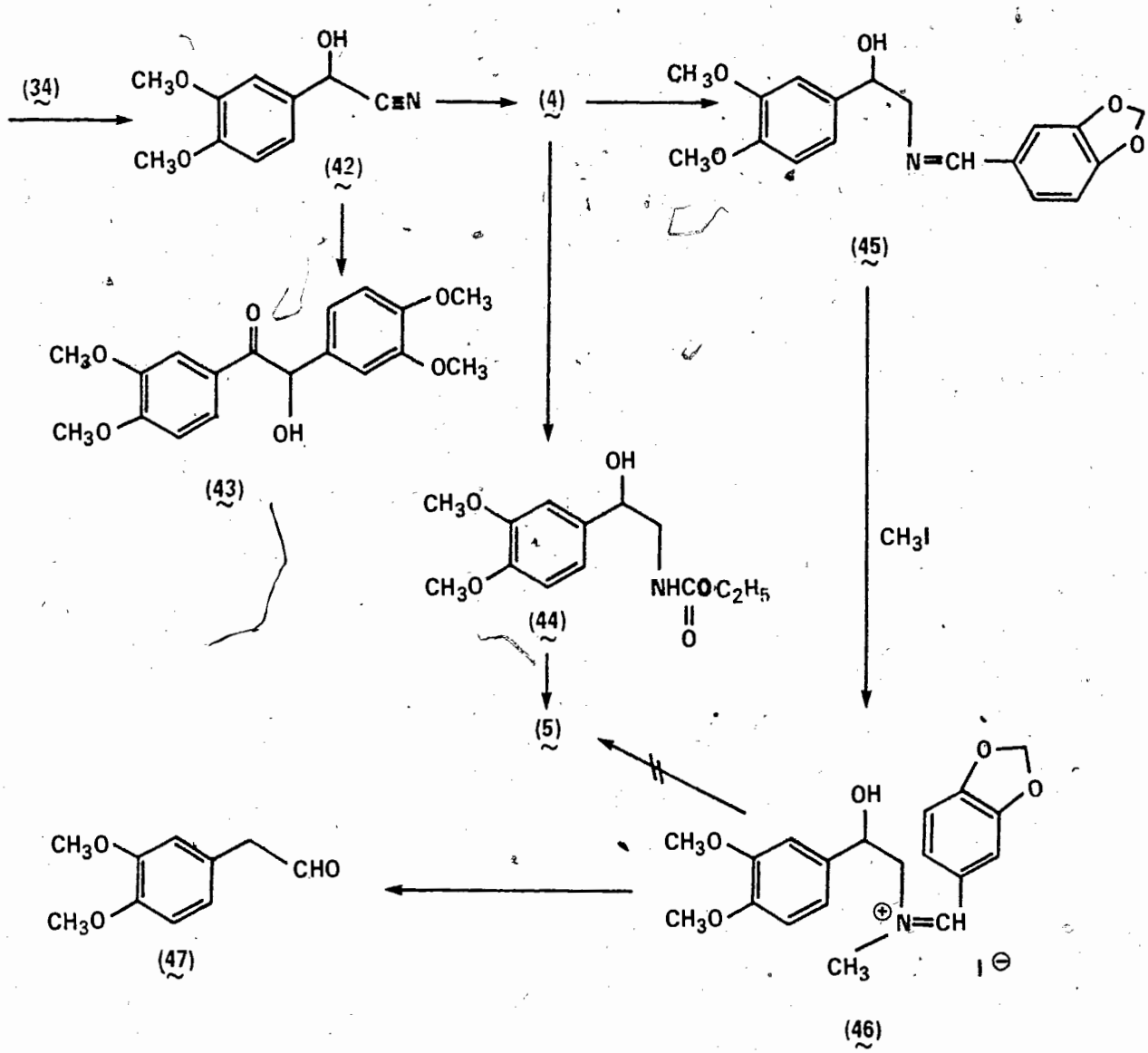
tive because of low yields due to side reactions (371, 372) and one was published without details (381). The synthetic route most attractive to us involved the use of potassium cyanide (can be obtained radioactively labelled). In a modified method of Hahn and Rumpf (373) 3,4-dimethoxybenzaldehyde cyanohydrin (42), was obtained from commercially available veratraldehyde (34). Lithium aluminum hydride reduction (372) of the cyanohydrin gave rise to 1-(3,4-dimethoxyphenyl)-2-aminoethanol (4) in 94% overall yield.

A serious side reaction in the procedure of Hahn and Rumpf (373) results in the formation of 3,3',4,4'-tetramethoxybenzoin (43). (Figure 5)

N-Methyl 1-(3,4-dimethoxyphenyl)-2-aminoethanol (5) was not obtainable by the method of Adityachaudhury and Chatterjee (372) for reasons mentioned below. The method of choice appears to be that of Friedman (374). 1-(3,4-Dimethoxyphenyl)-2-aminoethanol (4) was condensed with ethyl chloroformate and the resulting urethane (44) was reduced with lithium aluminum hybride to yield the desired N-methyl compound (5) in 22% overall yield (starting with veratraldehyde (34)). The method of Adityachaudhury and Chatterjee (372) was explored further. 1-(3,4-dimethoxyphenyl)-2-aminoethanol (4) formed a Schiff's base with piperonal (45) and a methiodide adduct (46) with methyliodide. However, cleavage with hydrochloric acid resulted in 1-(3,4-dimethoxy phenyl)-acetaldehyde (47) instead of the reported N-methyl-1-(3,4-dimethoxyphenyl)-2-aminoethanol (5). The reac-

FIGURE 5

SYNTHESIS OF (5) AS PER ADITYACHAUDHURY AND CHATTERJEE (372) AND FRIEDMAN (374)



tion of 1-aryl-2-amino alcohols with strong acid had been known for some time (375 - 379) and mechanism studies have recently been reported (378).

3-2 Pharmacology (380)

In preliminary injection studies with Swiss Webster mice (five per group, ~35 g.), we demonstrated the inactivity of 1-(3,4-dimethoxyphenyl) 2-alanine (at dosages of 500 mg/kg, i.p.), (1), (±)- 1-(3,4-dimethoxyphenyl)-2-aminoethanol (4), (±)-N-methyl-1-(3,4-dimethoxyphenyl)-2-aminoethanol (5) (at their purported CD_{50}* values (184): 228 mg/kg and 316 mg/kg, respectively) (381), as their hydrochloric salts in saline. Criteria of activity/inactivity was presence or absence of effect on spontaneous activity of isolated animals having food and water available ad libitum.

A reinvestigation of tolerance studies (185, 195) of Swiss Webster mice to 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and mescaline (7) was conducted at the CD_{50} (184). Groups of five drug-naive mice (males only, average body weight, 35 g.) (382) were injected i.p. daily according to the following different schedules: (a) saline (0.9%), (b) saline solution of iproniazid phosphate (80 mg/kg) (383), (c) mescaline sulfate (7) in saline (CD_{50}: 159 mg/kg (184)), (d) 1-(3,4-dimethoxyphenyl)-2-aminoethane hydrochloride (2) in saline (CD_{50}: 132 mg/kg (194)) pretreated with iproniazid phosphate in saline (80 mg/kg) (383) (the pretreatments with iproniazid phosphate occurred 5.5 and 1.5 hours

* catatonic dose for 50% test animals/controls

before injection with 1-(3,4-dimethoxyphenyl)-2-aminoethane (2). The fifth group (control) received no injections.

Tolerance was observed to the gross behavioural effects of mescaline (7) by the rod test (183). A water maze designed by Ho, et al. (385) for evaluation of psychotomimetic or hallucinogenic β-phenylisopropylamines failed to distinguish the subtle effects of any of the drugs in the series. Swim times between non-drug, drug and saline treatments were five seconds for all the test animals trained according to the outlined procedure (385).

Length of tolerance to the effects of mescaline, except to its induced bradycardia (386), have been observed previously as seven days (387-88). On the other hand, 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) treated animals showed no such effects in injection series which extended six months (185, 195). In the present series, however, 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) treated Swiss Webster mice (iproniazid pretreated) also manifested tolerance in seven days. Apparent cross-tolerance to the alternate β-phenethylamine was observed upon intraperitoneal (i.p.) injection five hours after the last injection on day seven.

3-3 Discussion

Our inability to reproduce pharmacology reported by Michaux et al. (182-184) has received support by the studies of Vogel (381) while this work was in progress. Injections of 100 mg/kg

were utilized by these workers in rats and brain levels were determined to be between 5 and 30 μg/g. Since these brain levels are higher than those found for hallucinogenic compounds which do interfere with the conditioned avoidance response we concluded that these compounds were not psychoactive. Michaux's original studies (182 - 184) did not include analytical data.

The fact that amino acid analogs of hallucinogenic compunds have been reported to be inactive (358, 365, 389) even at doses comparable to psychoactive doses of L-3,4-dihydroxy phenylalanine (L-DOPA), viz, 500 mg/kg) has been explained by assuming that these compounds are not substrates for *in vivo* decarboxylase systems. In support for this hypothesis, Ho, et al. (358) failed to detect the presence of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (32) in mouse (*in vivo*) and in mouse brain homogenates (*in vitro*) after injection studies and incubation studies respectively using 2-methyl 3-(2,5-dimethoxy-4-methylphenyl)alanine (33). These authors further explored the possible self-inhibition of DOPA decarboxylase in mouse brains at concentrations as high as 1×10^{-2}M; 2-methyl-3-(2,5-dimethoxy-4-methylphenyl)alanine (33) didnot inhibit this enzyme relative to DOPA, while α-methylDOPA, a known inhibitor of the enzyme, had an I_{50} value of 3.3×10^{-4}M. It may be, in retrospect, not overly surprising that 3-(3,4-dimethoxyphenyl)alanine (1) should be inactive. (Figure 1)

Tolerance studies with postulated psychotogens can yield

information concerning the suitability of drug-induced models to reflect upon the clinical syndrome, "schizophrenia" (12). As already stated, Takeo and Himwich (177) reported that a considerably larger dose of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) than that of mescaline (7) was required to produce electroencephalographic arousal in the rabbit. They suggested that in the brain, 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) is more rapidly inactivated by its corresponding amine oxidase (178). As a result of in vitro studies, they claim that iproniazid markedly depressed the oxidative deamination of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) but not that of mescaline (7) (178). The "multiple" amine oxidase" theory of the brain's defense against exogenous amines has been reinforced by studies in a number of mammalian systems (390 - 393). It appeared to us that selective blocking of deamination of 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) by pretreatment with iproniazid phosphate afforded an experimental situation wherein behavioural effects of the two β-phenethylamines, one, a known hallucinogen, and the other, a suspected intracerebral psychotogen, could be more easily compared (in a simple mammalian system, for example).

The published data on the metabolism of 1-^{14}C-1-(3,4-dimethoxyphenyl)-2-aminoethane (165,171-2) and on chronic mescaline metabolism (193) lends support to the fact that we were not observing a metabolite tolerance (396), and a behavioural tolerance (397) has to date not been demonstrated in mice. A factor we are unable to rigorously eliminate from our argument is the genetic

strain of the mice (398).

Further, Isbell and his coworkers (395) have pointed out the usefullness of cross-tolerance studies to support a similar mode of action for various hallucinogens. They claimed that the development of cross-tolerance between two psychotomimetics argues in favor of the induction of behavioural disturbances "by some common mechanisms or by different mechanisms which act through a common final pathway".

We have demonstrated cross tolerance between 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and mescaline (7) at their CD_{50} in this study. Using Isbell's criteria, we have presented data which is indicative of a common receptor site for two β-phenethylamines in a system designed to null out metabolic differences (399). Work as we have performed is inevitably tentative since as yet no rigorous demonstration of receptor sites for the hallucinogens has been reported. Work of this nature would be extremely welcome and could be envisaged as occurring along the lines of Snyder's demonstration of the opiate receptor (401) as a first approach. In addition, the mechanism of tissue tolerance of any drug has not been adequately explored. One could postulate deformation of the tertiary structure of the receptor site by "continual usage" ("wear and tear") or an ongoing inhibition by the irreversible binding of the drug itself.

Conclusions

Transmethylation of catecholamines as the root cause of all schizophrenics appears to be dubious at this time. In addition to the data reported here, 1-(3,4-dimethoxyphenyl)-2-aminoethane (2)

has been reported to possess half the potency of mescaline in humans (7), which at high doses (132 mg/kg) in test animals produces "catatonic-like" states. This has been observed by us and by others many times previously (15 - 18, 182 - 184). G.l.c. and t.l.c. analyses of body fluids, taking the literature as a whole, remain equally balanced between those who can detect and those who cannot detect the presence of this possible metabolite of dopamine. Artifacts from diet, medication and intestinal flora, instrumental limits of detection, and lack of adequate controls has hampered definitive statements on the validity of this and other biochemical hypotheses of "schizophrenia". With the introduction of capillary g.c. columns and analysis automated for multisample injection and data processing as outlined by Pauling (402 - 403) perhaps a wealth of fundamental data may eventually be acquired.

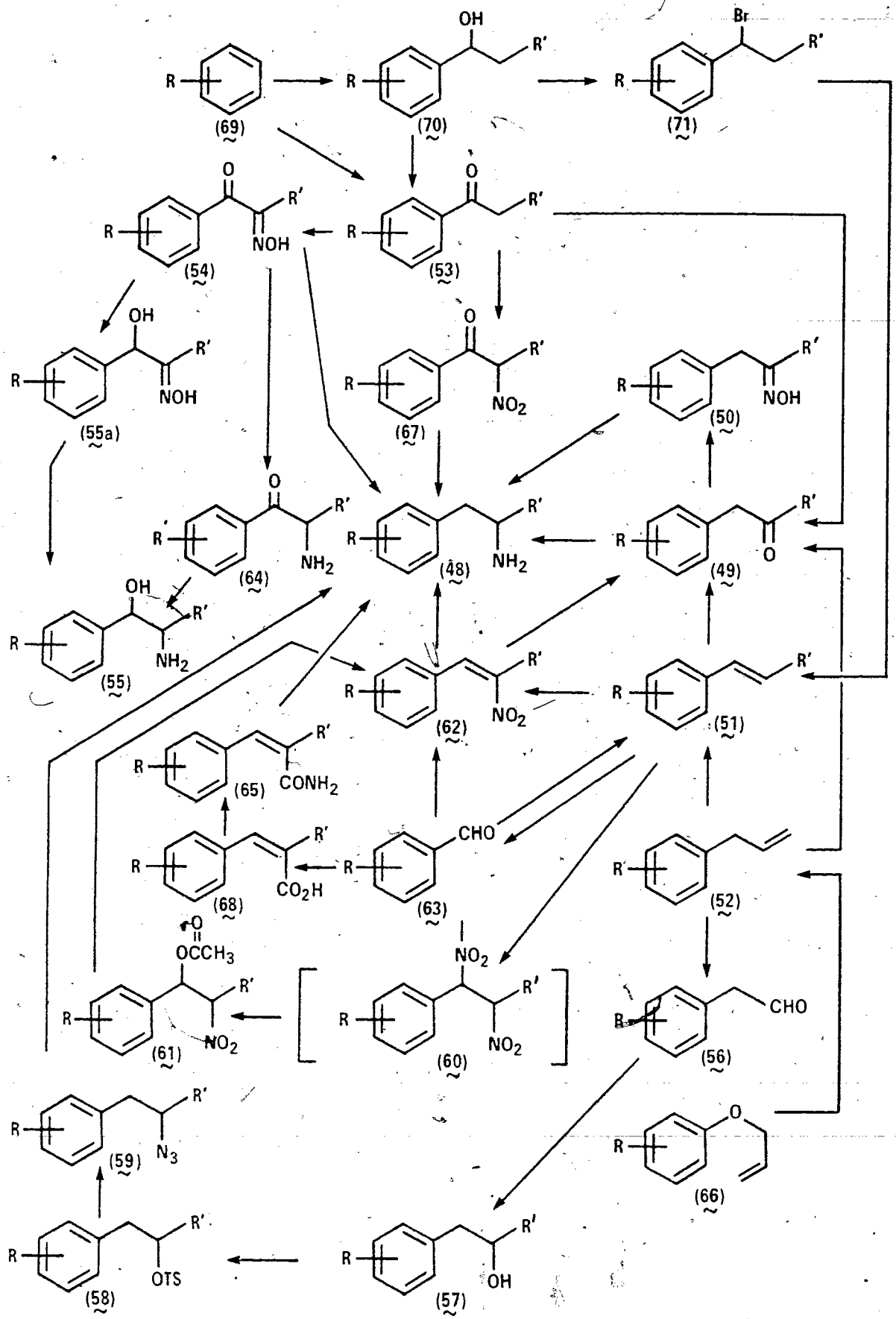
CHAPTER 5

SYNTHESIS OF PSYCHODYSLEPTIC β-PHENYLISOPROPYL AMINES.

LITERATURE SURVEY.

FIGURE 6

SYNTHESIS OF RING SUBSTITUTED β-PHENYLISOPROPYL AMINES



Ring substituted β-arylisopropylamines (48) constitute a class of psychodysleptics of psychopharmacological versatility (404). They are as well chemical cardiac stimulants and bronchiodilators (405) of some potency. In general, β-arylisopropylamines, 48 (R' = CH_3) and related β-arylethylamines, 48 (R' = H) have been generated by various synthetic procedures (405 - 479). Routes of high yield are outlined in a general manner in figure 6 and will be discussed in turn below.

Hey (480) developed a procedure for the synthesis of β-phenylisopropylamine itself, 48 (R = H, R' = CH_3) involving 1-phenyl 2-propanone, 49 (R = H, R' = CH_3). Its oxime, 50 (R = H, R' = CH_3) was reduced with 3% sodium amalgam in acetic acid/H_2O to yield the amine, 48 (R = H, R' = CH_3). Two developments have rendered this route somewhat profitable: 1) Facile syntheses (481 - 482) for 1-(3,4-methylenedioxyphenyl) 2-propanone, 49 (R = 3,4-OCH_2O, R' = CH_3) from isosafrole, 51, 1-(3,4-methylenedioxyphenyl) 1-propene (R = 3,4-OCH_2O, R' = CH_3), which in turn may be obtained from safrole, 52, 3-(3,4-methylenedioxyphenyl) 1-propene, (R = 3,4-OCH_2O, R' = CH_3) by a variety of synthetic procedures (483 - 490); 2) The introduction of lithium aluminum hydride (491) or catalytic reduction (491 - 494) as alternate reductants for the transformation of the oxime to the amine. 1-Phenyl-2-propanones, 49, (R = H, R' = CH_3) have also been subjected, with some success, to reductive amination (424, 496 - 497) or a Leukart reaction

(481) utilizing formamide. Recently, a procedure has been developed for preparing optical isomers of β-arylisopropylamines utilizing the 1-phenyl-2-propanone, 49, (R = H, R' = CH_3) and reducing the imine, formed with either (+) or (-)-α-methylbenzylamine. Hydrogenolysis of the resultant N-(α-phenethyl) β-phenylisopropylamines (496,497) gives the desired antipode.

Propiophenones, 53, (R = H, R' = CH_3) have been converted to isonitrosopropiophenones, 54 (R = H, R' = CH_3) by reaction with alkyl nitrites (498 - 500). Isonitrosopropiophenones have been reduced to 2-amino-1-phenyl-1-propanol hydrochlorides, 55, (R = H, R' = CH_3) (501) using a Pd/C - HCl/CH_3OH system. Kindler reports (502) the reduction of an isonitrosoacetophenone, 54 (R = R' = H). Hydrogenolysis of the benzyl-OH would afford the requisite amine, 48 (R = H, R' = CH_3). Limitations of this route include undesirable conditions to accomplish hydrogenolysis (501) as well as ready access to starting propiophenone. A route explored by Lindeke and Cho (490) consists of Grignard reaction on phenylacetaldehyde (56) utilizing methyl magnesium iodide (503). The resulting 1-phenyl-2-propanol, 57 (R = H, R' = CH_3) was converted to its tosylate, 58 (R = H, R' = CH_3) which in turn was converted to 1-phenyl-2-azido propane, 59 (R = H, R' = CH_3) and consequently reduced with $LiAlH_4$ to yield the amine, 48, (R = H, R' = CH_3). Synthesis of ring substituted analogues by this route have not been explored. Accessibility to appropriately substituted phenylacetaldehydes would command further research.

In 1933, Bruckner (504) pioneered a route from asarone, 1-(2,4,5-trimethoxyphenyl)-1-propene, 51 (R = 2,4,5-CH_3O, R' = CH_3). This compound (51) was treated with nitrous acid and it was reported to form a dimeric pseudonitrosite, tentatively assigned the structure 60 (R = 2,4,5-CH_3O, R' = CH_3). Treatment of 60 with acetic anhydride and sulfuric acid yielded 1-(2,4,5-trimethoxyphenyl)-1-acetoxy-2-nitropropane 61 (R = 2,4,5-CH_3O, R' = CH_3). Reaction with alcoholic potassium hydroxide generated 1-(2,4,5-trimethoxyphenyl) - 2-nitro-1-propene 62 (R = 2,4,5-CH_3O, R' = CH_3). Electrolytic reduction of 62 (R = 2,4,5-CH_3O, R' = CH_3) yielded the β-phenylisopropylamine, 1-(2,4,5-trimethoxyphenyl)-2-amino propane, 48 (R = 2,4,5-CH_3O, R' = CH_3). Yields were not reported and procedures were not fully described. Shulgin (505 - 506) obtained 1-(2,4,5-trimethoxy phenyl)-2-nitro 1-propene, 62 (R = 2,4,5-CH_3O, R' = CH_3) directly by selectively nitrating 1-(2,4,5-trimethoxyphenyl)-1-propene 51 (R = 2,4,5-CH_3O, R' = CH_3) with tetranitromethane. Reduction with $LiAlH_4$ afforded the amine 48 (R = 2,4,5-CH_3O, R' = CH_3).

Redeuilh, Rumpf and Viel (507) have recently explored hydroboration of substituted styrenes and their subsequent amination with hydroxylamine-O-sulfonic acid to yield 1-(3,4-dimethoxyphenyl)-2-aminoethane (2) and mescaline (7). Yields of 37% and 35% respectively are reported (507).

A route of general utility consists of condensation of an appropriately substituted benzaldehyde, 63, (R = alkyl, alkoxy,

halo, etc.) in a Knoevenagel fashion with a nitroalkane under a variety of acidic and basic conditions: zinc chloride (508), alcoholic potassium hydroxide (373, 509 - 513), alcoholic alkyl amine (448 - 449, 368, 514 - 516) or ammonium acetate in acetic acid (517 - 523). Lithium aluminum hydride (368, 525) or Raney nickel (494, 543 - 544) reduction (elevated temperature, pressure) of the intermediate β-nitrostyryl derivative (62) afforded the β-phenethylamine. In the past, electrolytic reduction (446, 447, 504, 441) or hydrogenation over platinum metals had been employed in acidic media (528 - 531) to some advantage. Reduction by means of a Zn/HOAC-Na/Hg system is of historical interest only (512).

Hey (447) and Buck, et al. (436) explored Hofmann degradations of α-methyl-2-phenylproprionamides (65). The standard Hoffmann procedure for degradation of the amide to the amine was found to be poor. Hey (447) employed a modification of Jeffreys (532) in which the isocyanate was trapped to yield the urethane upon hydrolysis. On the other hand, Buck, et al. (436) found the modification of Woodruff and Conger (533), viz. use of dioxane to dissolve the starting amide, to work satisfactorily.

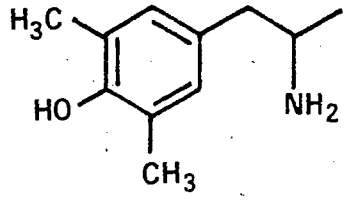
CHAPTER 6

SYNTHESIS OF PSYCHODYSLEPTIC β-PHENYLISOPROPYLAMINES

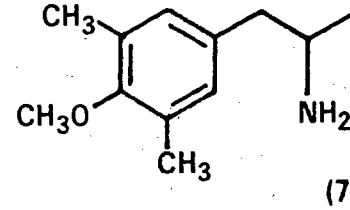
RESULTS

FIGURE 7

FIVE β-PHENYL ISOPROPYL AMINES



(72)



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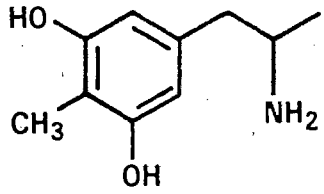
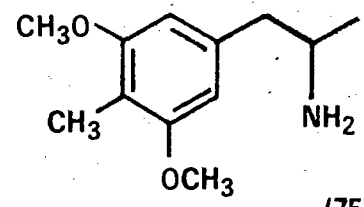
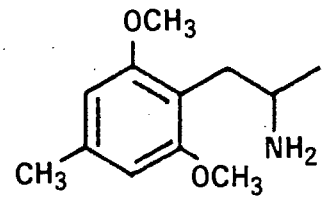


(74)



(75)



(76)

5-1 Results

As part of the present research program, syntheses of five potentially active ring-substituted β-phenylisopropylamines were completed: 1-(3,5-dimethyl-4-hydroxy phenyl)-2-aminopropane (72), 1-(3,5-dimethyl-4-methoxyphenyl)-2-aminopropane (73), 1-(3,5-dihydroxy-4-methylphenyl)-2-aminopropane (74), 1-(3,5-dimethoxy-4-methylphenyl)-2-aminopropane (75) and 1-(2,6-dimethoxy 4-methylphenyl)-2-amino propane (76). Provision for introduction of a ^{14}C-Label in the side chain was explored for subsequent metabolic and distribution work of this particular series.

As part of the pharmacological testing of (72) - (76), we envisaged use of 1-(3,5-dimethyl-4-hydroxyphenyl)-2-aminopropane (72) as a possible substrate for catechol-O-methyl transferase (COMT) and a chemical agent of possible utility in distinguishing "normals" from "schizophrenics" should the Osmond/Smythies/Harley-Mason Hypothesis be operative. As an indication of the wisdom of such an approach, we envisaged testing 1-(3,5-dihydroxy 4-methylphenyl)-2-aminopropane (74) in normals. The "methylated" products, 1-(3,5-dimethyl-4-methoxy)-2-aminopropane (73) and 1-(3,5-dimethoxy-4-methyl phenyl)-2-aminopropane (75) would also be tested at that time. Synthesis of (76) arose in the course of synthetic studies of (74) and (75).

Synthesis of 1-(3,5-dimethyl-4-hydroxy phenyl)-2-aminopropane (72) and 1-(3,5-dimethyl-4-methoxyphenyl)-2-aminopropane (73)

1,3- Dimethyl-2-propioxybenzene 69, (R = 1,3-diMe 2-propioxy, R' = CH_3) was subjected to a Fries rearrangement to

yield 1-(3,5-dimethyl-4-hydroxyphenyl) propanone, 53, (R = 3,5-diMe, 4-OH, R' = CH_3) using the procedure of Benington, et al. (479). Methylation (479) with dimethylsulfate gave rise to 1-(3,5-dimethyl-4-methoxyphenyl)propanone, 53, (R = 3,5-diMe 4-MeO, R' = CH_3). Both phenyl propanones formed keto oximes with methyl nitrite/HCl (500), 54, (R = 3,5-DiMe, 4-OH, R' = CH_3) and 54, (R = 3,5-diMe, 4-MeO, R' = CH_3). With 10% Pd/C or PtO_2 in acetic acid-H_2SO_4, both keto oximes gave rise to amines, 72, and 73, respectively, in fair yield. Reduction of 54, (R = 3,5-diMe, 4-OH, R' = CH_3) and 54, (R = 3,5-diMe, 4-MeO, R' = CH_3) with 5% Pd/C or Pt_2O in HCl/EtOH gave rise to amino ketones 64, (R = 3,5-diMe, 4-OH, R' = CH_3) and 64 (R = 3,5-diMe 4-MeO, R' = CH_3). Reduction of 64, (R = 3,5-diMe, 4-OH, R' = CH_3) and 64 (R = 3,5-diMe, 4-MeO, R' = CH_3) with sodium borohydride gave rise to oximino alcohols 55a, (R = 3,5-diMe, 4-OH, R' = CH_3) and 55a, (3,5-diMe, 4-MeO, R' = CH_3). A lithium aluminum hydride reduction of 54, (R = 3,5-diMe, 4,OH, R' = CH_3) was unsuccessful since the metal phenolate was insoluble in ether, tetrahydrofuran or dioxane. Complete reduction was unsuccessful even after 4 hours reflux, whereas 54 (R = 3,5-diMe,4-Me, R' = CH_3) was readily reduced to amino alcohol 55, (R = 3,5-diMe,4-MeO, R' = CH_3).

A more facile synthesis of amines 72, and 73 was effected via 3,5-dimethyl-4-hydroxy benzaldehyde 63, (R = 3,5-diMe,4-OH, R' = CH_3), obtained for a Duff-Bills reaction on 2,6-dimethyl

phenol. Methylation gave 3,5-dimethyl-4-methoxy benzaldehyde 63, (R = 3,5-diMe,4-MeO, R' = CH_3). A Knoevenagel condensation of nitroethane with benzaldehydes 63 (R = 3,5-diMe 4-OH, R' = CH_3) and 63 (R = 3,5-diMe 4-MeO, R' = CH_3) by a modified procedure (369) gave good yields of the β-nitrostyryl 62, (R = 3,5-dime 4-OH, R' = CH_3) and 62 (R = 3,5-DiMe 4-MeO, R' = CH_3). The β-nitrostyryl 62, (R = 3,5-DiMe 4-OH, R' = CH_3), found to be incompletely reduced by lithium aluminum hydride in tetrahydrofuran, underwent reduction with sodium bis(2-methoxyethoxy) aluminum dihydride in benzene. β-Nitrostyryl 62 (R = 3,5-DiMe 4-MeO, R' = CH_3) was reduced with lithium aluminum hydride in the manner of Rameriz (368) and Shulgin (505 - 506).

Synthesis of 1-(3,5-dihydroxy-4-methyl phenyl)-2-aminopropane (74), 1-(3,5-dimethoxy-4-methylphenyl)-2-aminopropane (75), and 1-(2,6-dimethoxy-4-methylphenyl)-2-aminopropane (76)

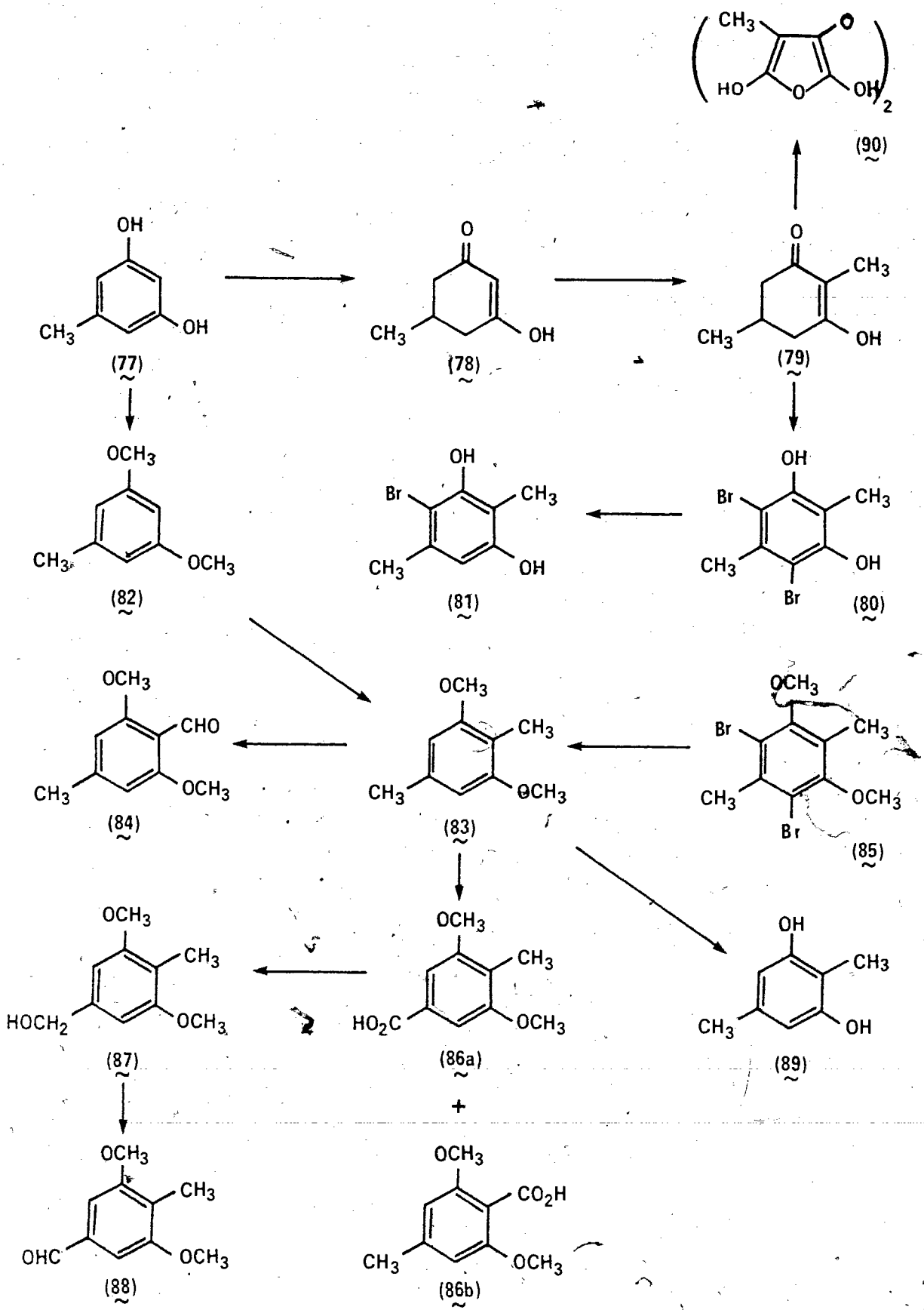
A synthetic route for amines 74 and 75 centered around the accessibility for 3,5-dimethoxy-4-methylbenzaldehyde 63, (R = 3,5-DiMeO 4-Me). Two syntheses (534, 535) of 3,5-dihydroxy-4-methylbenzoic acid, based on alkali fusion of potassium 3,5-disulphonato 4-methylbenzoic acid, failed to give for us and for Rasmussen, et al. (536) a good yield of 3,5-dihydroxy-4-methylbenzoic acid. Attempts to form the bis-diazonium salt of 3,5-diamino-4-methylbenzoic acid, formed by Raney nickel reduction of 3,5-dinitro-4-methylbenzoic acid, led to a complex mixture of products. The route most attractive to us was the benzylic oxidation of 1,3-dimethoxy-2,5-dimethyl benzene

69, (R = 1,3-DiMeO, 2,5-DiMe) as described by Fujikawa and Kurugi (537) and explored by Rasmussen, et al. (536).

A search of the literature at the time this project was conceived, revealed four syntheses of [redacted]dihydroxy-2,5-dimethyl benzene (89)(538,541-543). Of these, Sonn's method seemed most direct (542). Synthesis of 1,3-dimethoxy-2,5-dimethylbenzene (83) was effected by C-methylation of 1,3-dimethoxy-5-methyl benzene (82). Methyl iodide and n-butyl lithium were found to be superior to dimethyl sulfate and phenyl lithium described by Rasmussen (536). (Figure 8)

Concurrently, synthesis of 1,3-dihydroxy-2,5-dimethyl benzene (89) was attempted based on the synthesis by Sonn (542). Orcinol, 1,3-dihydroxy-5-methylbenzene (77), was reduced with Raney nickel at elevated temperature and pressure (539) to yield 5-methylcyclohexane-1,3-dione (78). Methylation with potassium hydroxide and methyl iodide by Sonn's method (542) and that of Stetter and Meisel (540) led to incomplete methylation and oxidation of both the 5-methylcyclohexane-1,3-dione (78) and 2,5-dimethylcyclohexane-1,3-dione (79). The main contaminant of these reactions was postulated to be di(2,5-dihydroxy-3-methyl furfuryl) peroxide (90). Methylation with methyl iodide and alkali in a sealed tube appeared to circumvent problems of distillation loss of methyl iodide and oxidation reactions at optimum reaction temperatures. Bromination of 2,5-dimethylcyclohexane-1,3-dione (79) gave rise to 4,6-dibromo -1,3-dihydroxy-2,5-dimethylbenzene (80) as reported by

FIGURE 8
SYNTHESIS OF (84) & (88)



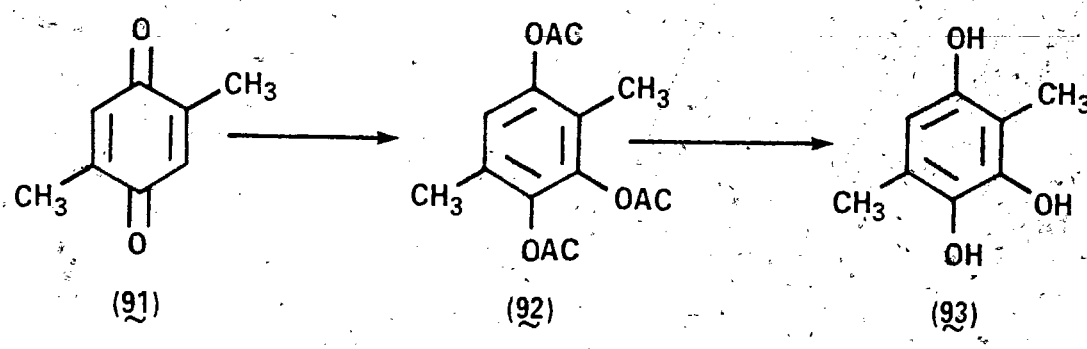
Sonn (542). However, Sonn's debromination with $Pd/CaCO_3$ and piperidine led to the monobromo compound, 4-bromo-1,3-dihydroxy-2,5-dimethylbenzene (81) in our case. Methylation of 4,6-dibromo-1,3-dihydroxy-2,5-dimethylbenzene with dimethylsulfate proceeded smoothly and the dibromo compound (85) was debrominated with sodium aluminum bis-(ethoxymethoxy)-dihydride (548) to yield the 1,3-dimethoxy-2,5-dimethylbenzene (83) by a more circuitous route.

An exploration of Sonn's alternate route to 2,5-dimethylcyclohexane-1,3-dione (38) via p-xyloquinone (91) was carried out (542). 1,4-Dimethyl-2,3,5-triacetoxybenzene (92), formed from acetylation of p-xyloquinone (91) in H_2SO_4, gave 1,4-dimethyl-2,3,5-trihydroxybenzene (93) on treatment with alcohol HCl instead of the reported "p-xylo-oxy-hydrochinon-di-acetat" (542). (Figure 9)

Our difficulty with the published lengthy syntheses of substituted resorcinols has been echoed by others (544 - 547) and modifications and/or novel approaches have been recently published (543 - 547).

1,3-Dimethoxy-2,5-dimethylbenzene (83) was subjected to a variety of oxidation conditions. Cerium (IV) ammonium nitrate gave 2,6-dimethoxy-4-methylbenzaldehyde (84). Potassium permanganate in the presence of pyridine gave a 40% yield of 3,5-dimethoxy-4-methylbenzoic acid (86a) and 40% of 2,6-dimethoxy-4-methylbenzoic acid (86b) (536, 537). Separation by T.L.C. was found to be facile. (Figure 8)

FIGURE 9



(91) (92) (93)

Condensation of 2,6-dimethoxy-4-methylbenzaldehyde (84) with nitroethane under our modified conditions (369) gave 1-(2,6-dimethoxy-4-methyl phenyl)-2-nitro 1-propene, 62 (R = 2,6-DiMeO, 4-Me, R' = CH_3) in 81% yield. Reduction with sodium aluminum bis(ethoxymethoxy) dihydride (369) in benzene gave 1-(2,6-dimethoxy-4-methyl phenyl)-2-aminopropane (76).

Routes involving the conversion of 2,5-dimethoxy-4-methyl benzoic acid (86a) to 3,5-dimethoxy-4-methylbenzaldehyde (88) including Rosenmund (46%) (549, 550), lithium tri-tertbutoxy aluminum hydride (30%) (581), modified McFayden-Stevens (0%) (551) reductions, were found to be inferior to reduction with lithium aluminum hydride and oxidation with Attenburrow's MnO_2 (552 - 555).

Condensation of 88 with nitroethane to yield 1-(3,5-dimethoxy-4-methylphenyl)-2-nitro-1-propene, 62, (R = 3,5-dimethoxy 4-methyl, R = CH_3) and reduction of this β-nitrostyryl with lithium aluminum hydride gave 1-(3,5-dimethoxy-4-methylphenyl)-2-aminopropane (75). Treatment of 1-(3,5-dimethoxy-4-methyl phenyl)-2-aminopropane (25) with 48% hydroiodic acid at 100° gave 1-(3,5-dihydroxy-4-methylphenyl)-2-aminopropane as the hydroiodide (74).

Preliminary studies toward a feasible synthesis of ^{14}C-nitroethane and ^{14}C-side chain labelled phenylisopropylamines were conducted. Nitroethane was prepared from ethyl iodide by a modified Victor Meyer reaction (370 556) in 35% yield. No ethyl nitrite was detected and unreacted ethyl iodide was recovered on distillation.

Synthetic studies with application to ring-substituted β-phenyl isopropylamines.

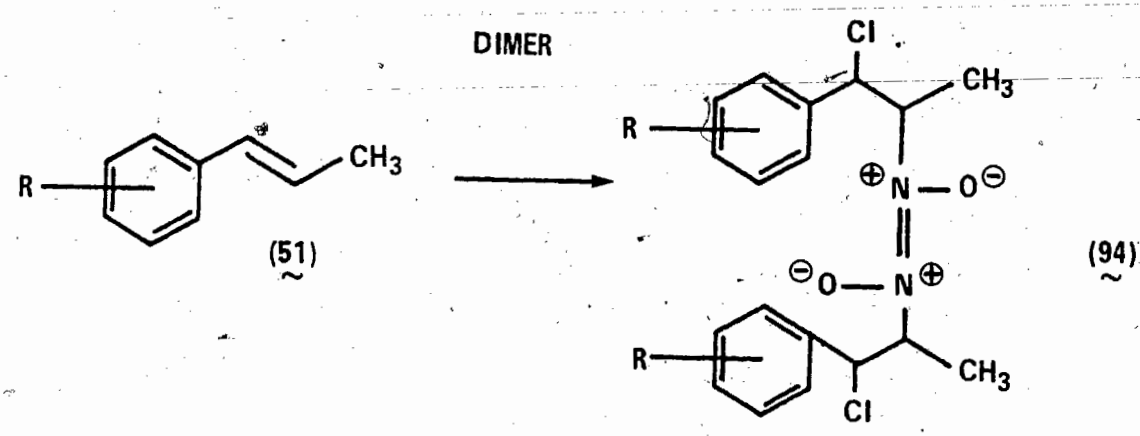
Shulgin (505, 506) has commented on the variability of conditions reported for the ozonolysis of isomyristicin, 52 (R = 3-methoxy-4,5-methylenedioxy, R' = CH_3) to myristicin aldehyde, 63 (R = 3-methoxy-4,5-methylenedioxy) (557 - 560). We have developed optimal conditions for the conversion of isosafrole, 52 (R = 3,4-methylenedioxy, R' = CH_3) to piperonal, 63 (R = 3,4-methylenedioxy), including distillation of the ozonide (561). Such a reaction should find synthetic applicability for aldehydic cases where naturally occurring phenylpropenyl benzene derivatives are readily available.

Synthesis of ring-substituted 1-phenyl-2-propanones (49) from 3-phenyl-1-propene was explored using air and a $PdCl_2$-$CuCl_2$ redox system (562). A direct conversion of safrole, 52 (R = 3,4-methylenedioxy, R' = CH_3) to 1-(3,4-methylenedioxy phenyl)-2-propanone (R = 3,4-methylenephenyl)-2-propanone, 49 (R = 3,4-methylenedioxy, R' = CH_3) was effected in 50% yield. Conditions for recovery of the palladium are still to be worked out in order to make this a facile and economical synthesis.

Isosafrole, 51, (R = 3,4-methylenedioxy, R' = CH_3) was nitrated with tetranitromethane by the procedure of Shulgin (590) and in this case the optimum reaction conditions involved a temperature of -4° C. Isosafrole, 51, (R = 3,4-methylenedioxy, R' = CH_3) was reacted with nitrosyl chloride after Tilden and Forester (564). The compound that formed appeared to be a dimer

FIGURE 10

DIMER



(51) (94)

94 (R = 3,4-methylenedioxy) (572) and was resistant to hydrogenation over 5% Pd/C. T.L.C. analysis of the lithium aluminum hydride reduction product of the dimer, 94, (R = 3,4-methylenedioxy) indicated two compounds which await characterization. (Figure 10)

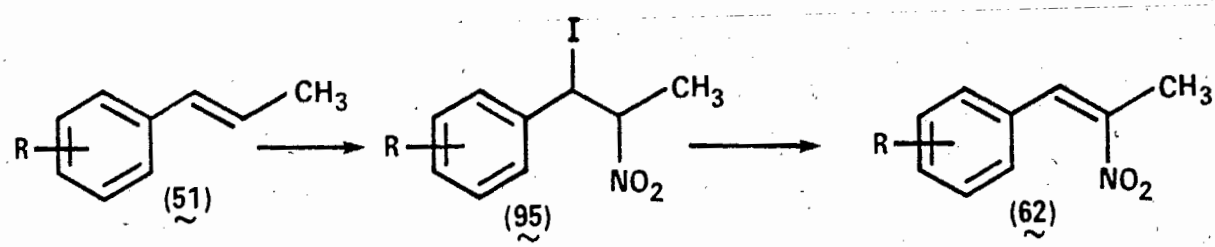
Isosafrole, 51, (R = 3,4-methylenedioxy, R' = CH_3) was reacted with nitryl iodide and the intermediate 1-iodo-1-(3,4-methylenedioxyphenyl)-2-nitro-1-propene, 95, (R = 3,4-methylenedioxyphenyl) was dehydrohalogenated with pyridine, 1-(3,4-methylenedioxyphenyl)-2-nitropropene, 62, (R = 3,4-methylenedioxy, R' = CH_3) was formed in 35% over all yield (573). Pyridine appeared to be superior solvent to collidine or triethylamine in the present case. (Figure 11)

1-(3,5-Dimethyl-4-methoxyphenyl)-1-propanone, 53, (R = 3,5-dimethyl-4-methoxy, R' = CH_3) was nitrated with n-butyl nitrate in the presence of potassium t-butoxide to yield the potassium enolate of 1-(3,5-dimethyl-4-methoxyphenyl)-2-nitro-1-propanone, 67 (R = 3,5-DiMe 4-MeO, R' = CH_3). Attempted acetylation with acetic anhydride at elevated temperature of the potassium enolate, 96 (R = 3,5-DiMe, 4-MeO), or the enolate itself, 97 (R = 3,5-DiMe, 4-MeO, R' = CH_3) resulted in cleavage to 3,5-dimethyl-4-methoxybenzoic acid, 98, (R = 3,5-dimethyl-4-methoxy).

Phenyl-2-propanone oxime, 50, (R = H, R' = CH_3) was synthesized from phenyl-2-propanone, 49 (R = H, R' = CH_3) in yields of 90% as a model for the keto-oxime route to substituted β-phenyl-

FIGURE 11

NITRYL IODIDE REACTION



isopropylamines. $LiAlH_4$ reduction afforded phenyl-2-amino propane.

In an attempt to synthesize the hydrazide, 100 (R = H) of methyl benzoate utilizing a procedure that Dornow and Petsch (567) applied to 3,4,5-trimethoxybenzoic acid methylester, 99 (R = 3,4,5-TriMeO), the product which was formed in 60% yield was assigned the structure of 101 (R = H), i.e. 1-amino-4-phenylphthalazine, on the basis of spectral data (568). (Figure 12)

5-2 Discussion

Table 2 provides a listing of the psychodysleptic β-phenyl isopropylamines synthesized to date. Table 3 provides a listing of polyhydroxyphenethylamines active as cardiac stimulants. Compounds synthesized in the course of our work on model systems for schizophrenia are included as a contribution.

Facile condensation conditions for trisubstituted benzaldehydes and nitroethane are provided in Table 4. The resulting β-nitrostyryls were reduced with lithium aluminum hydride (573) or "Redal" (sodium aluminum bismethoxyethoxy dihydride). Introduction of this reducing agent should circumvent synthetic difficulties sometimes encountered with lithium aluminum hydride reductions.

Carbon-14 labelling in the side chain of this series is now made possible by a facile preparation of ^{14}C-nitroethane. Scrambling of label is not slated to be a worrisome process. As seen from synthetic studies of higher homologues, no branch chain isomers were detected (583). Such carbon-14 labelled β-phenylsiopropyl amines should find application in metabolic and distribution work in the

field of psychobiochemistry. For example, a screening for binding to subcellular fractions from rat brain (569) could be provided without the possibility of biological exchange invalidating such data, or a demonstration of receptors in nervous tissue could be conducted as has been reported for the opiates (401).

Interesting reactions which have been observed in the course of this work, for example, direct conversion of methyl benzoate to 1-amino-4-phenylphthalazine (101) and cleavage of the enolate of 1-(3,5-dimethyl-4-methoxyphenyl)2-nitro 1-propanone, 96 (R = 3,5-DiMe 4-MeO) with acetic anhydride, have been included. Side reactions in Sonn's synthesis of 2,5-dimethyl 1,3-dihydroxy benzene (89) have been elucidated. A lithium aluminum hydride reduction of the nitrosyl chloride adduct (94) of isosafrole, 51 (R = OCH_2O) is reported and could form the basis of a further extended investigation.

Conclusions

In general, synthetic reproducibility is a function of the following variables:

(1) the "operator" (both the recording operator and receiving operator)

(2) availability of sophisticated analytical methods

(3) competitive free enterprise, pressures to please and to publish.

As an example of number (1), I would like to point to Padshah, Khan and Vidwai (357). To the recording operator the preparation of the Raney Nickel catalyst therein is fully

described. To the receiving operator, it is unclear on paper where "modifications" of the standardized Organic Synthesis procedure begin and end.

Examples of variable (2) must of necessity include an as yet undetermined proportion of the literature prior to 1960. My own experiences with such literature begins with Tsao's synthesis of mescaline (7) (438). Without unduly boring the reader, one could easily cite Hahn and Rumpf's (440) synthesis of 3,4-dimethoxybenzaldehyde cyanohydrin (42), Deulofeu and Mendivelzua's (363) synthesis of 1-(3,4-dimethoxyphenyl)-2-alanine (1), Dornow and Petsch's synthesis of 3,4,5-trimethoxybenzoic acid hydrazide (567), Sonn's synthesis of β-orcinol (83) (542), Aditachaudhury and Chatterjee's synthesis of N-methyl-1-(3,4-dimethoxyphenyl)-2-aminothanol (5), Michaux's injection studies (182-184) with 1-(3,4-dimethoxyphenyl)-2-aminoethanol (4) and N-methyl 1-(3,4-dimethoxyphenyl)-2-aminoethanol (5), and Kawai's synthesis of 1,2-dihydroxybenzoic acid from catechol (581).

It is commonplace to exagerate one's yield, for example, in Smidrkad and Trojanek's synthesis of 2,3-dihydroxybenzaldehyde recently (582). However, for possibly the purest example of variable (3), one should refer to Charlesworth and Robinson (534) and Asahina and Asano (535).

Great care has been taken to insure reproducibility in the syntheses presented here for two reasons: (1) controversies

of reproducibility have continually marred progress in the area of schizophrenia research with concomittant loss in time and energy; (2) to present a case throughout the synthetic literature for a return to standards established by Organic Synthesis. Coupled with modern analytical techniques, such standards should eliminate a great deal of the daily speculations of the synthetic chemist.

Moreover, the ^{14}C-labelling envisaged as a logical outcome of this thesis has placed serious restraints on the applicability of published synthetic procedures. A synthetic procedure must by these restraints permit incorporation of label from commercially available starting material at a point as close as possible to final product. Conversion to final product then must be obtained in the highest possible yield overall. For this reason, for example, amines (72) and (73) are best obtained via a Knoevenagel condensation and a hydride reduction rather than a Fries rearrangement, oximination and reduction/ hydrogenolysis as originally explored.

FIGURE 12

CLEAVAGE OF (96) & (97)

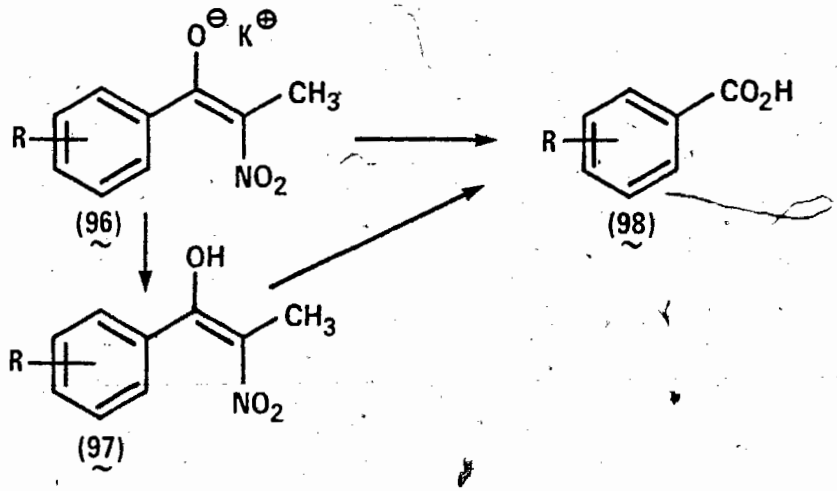


FIGURE 13

PHTHALAZINE FORMATION

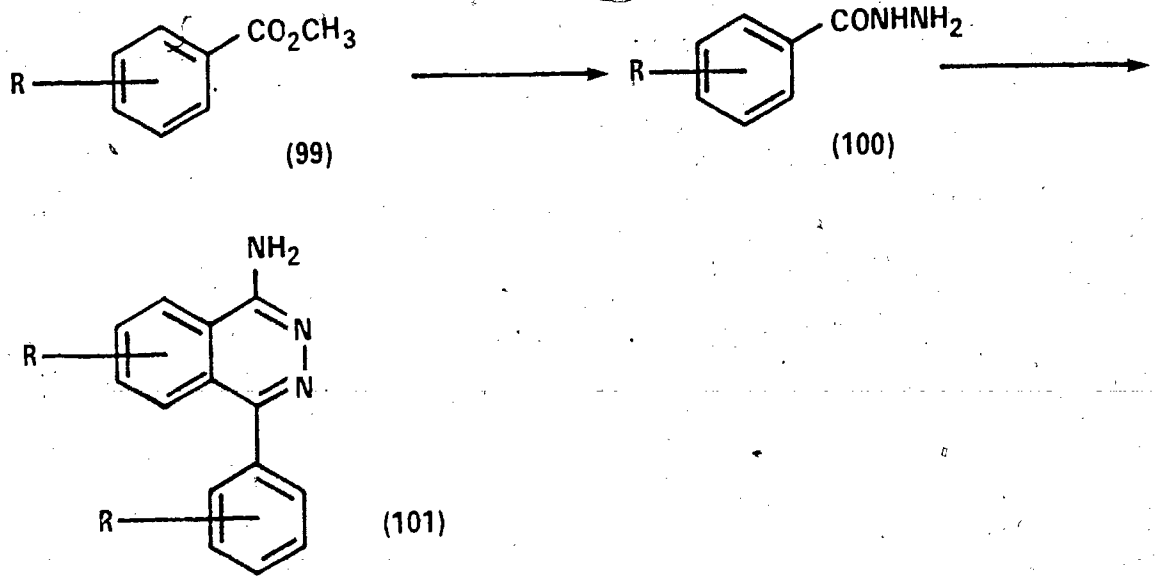
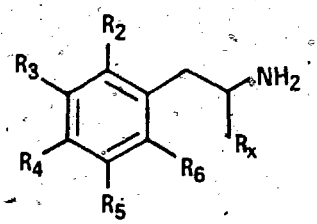


TABLE 2

PSYCHODYSLEPTIC β-PHENYL ISOPROPYL AMINES AND THEIR POTENCY (M.U.)* IN MAN (AFTER SHULGIN (570))



	R_2	R_3	R_4	R_5	R_6	R_x	Activity (mu)*	Footnotes
1.	H	H	OCH_3	H	H	CH_3	5	a,b
2.	OCH_3	OCH_3	H	H	H	CH_3	–	c
3.	OCH_3	H	OCH_3	H	H	CH_3	5	b
4.	OCH_3	H	H	OCH_3	H	CH_3	8	b
5.	OCH_3	H	H	H	OCH_3	CH_3	–	c
6.	H	OCH_3	OCH_3	H	H	CH_3	< 1	d
7.	H	OCH_3	H	OCH_3	H	CH_3	–	c
8.	H	OCH_3	OCH_3	OCH_3	H	CH_3	2.2	e
9.	OCH_3	H	OCH_3	OCH_3	H	CH_3	17	f
10.	OCH_3	OCH_3	OCH_3	H	H	CH_3	< 2	f
11.	OCH_3	OCH_3	H	OCH_3	H	CH_3	4	f
12.	OCH_3	OCH_3	H	H	OCH_3	CH_3	13	b
13.	OCH_3	H	OCH_3	H	OCH_3	CH_3	10	b
14.	$O-CH_2-O$		H	H	H	CH_3	–	c
15.	H	$O-CH_2-O$		H	H	CH_3	3	d
16.	H	OCH_3	$O-CH_2-O$		H	CH_3	2.7	g
17.	OCH_3	H	$O-CH_2-O$		H	CH_3	12	f,h
18.	OCH_3	$O-CH_2-O$		H	H	CH_3	10	f,h
19.	$O-CH_2-O$		OCH_3	H	H	CH_3	3	f
20.	$O-CH_2-O$		H	OCH_3	H	CH_3	–	c
21.	$O-CH_2-O$		H	H	OCH_3	CH_3	–	c
22.	OCH_3	$O-CH_2-O$		OCH_3	H	CH_3	12	i
23.	OCH_3	OCH_3	$O-CH_2-O$		H	CH_3	5	i
24.	H	OCH_3	$O-(CH_2)_2-O$		H	CH_3	< 1	g
25.	OCH_3	OCH_3	OCH_3	OCH_3	H	CH_3	6	f
26.	OCH_3	OCH_3	OCH_3	H	OCH_3	CH_3	–	c
27.	OCH_3	OCH_3	H	OCH_3	OCH_3	CH_3	–	c
28.	OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	CH_3	–	c
29.	OC_2H_5	H	OCH_3	OCH_3	H	CH_3	< 7	b,j
30.	OCH_3	H	OC_2H_5	OCH_3	H	CH_3	15	b,j
31.	OCH_3	H	OCH_3	OC_2H_5	H	CH_3	7	b,j
32.	OC_2H_5	H	OC_2H_5	OCH_3	H	CH_3	–	j,k
33.	OC_2H_5	H	OCH_3	OC_2H_5	H	CH_3	–	j,k
34.	OCH_3	H	OC_2H_5	OC_2H_5	H	CH_3	–	j,k
35.	OC_2H_5	H	OC_2H_5	OC_2H_5	H	CH_3	–	j,k
36.	OCH_3	H	CH_3	OCH_3	H	CH_3	80	b,l
37.	OCH_3	H	CH_3	H	OCH_3	CH_3	–	u,r,k
38.	H	OCH_3	CH_3	OCH_3	H	CH_3	–	r,k
39.	CH_3	H	OCH_3	H	CH_3	CH_3	–	c,k
40.	H	CH_3	OCH_3	CH_3	H	CH_3	–	r,s,k
41.	OCH_3	H	C_2H_5	OCH_3	H	CH_3	–	t
42.	OCH_3	H	$C(CH_3)_3$	OCH_3	H	CH_3	–	u

TABLE 2 CONTINUED

	R_2	R_3	R_4	R_5	R_6	R_x	Activity (mu)*	Footnotes
43.	OC_2H_5	H	CH_3	OC_2H_5	H	CH_3	–	u
44.	OC_2H_5	H	C_6H_{13}	OCH_3	H	CH_3	–	u
45.	OC_2H_5	H	CH_3	H	OCH_3	CH_3	–	u
46.	OCH_3	H	C_3H_7	OCH_3	H	CH_3	–	u
47.	OC_4H_9	H	C_6H_{13}	OC_4H_9	H	CH_3	–	u
48.	OC_4H_9	H	C_4H_9	OC_4H_9	H	CH_3	–	u
49.	OCH_3	H	Br	OCH_3	H	CH_3	150	v,w
50.	OCH_3	H	Cl	OCH_3	H	CH_3	–	k,v
51.	OCH_3	H	I	OCH_3	H	CH_3	–	k,v
52.	OCH_3	H	NO_2	OCH_3	H	CH_3	–	k,v
53.	OCH_3	H	NH_2	OCH_3	H	CH_3	–	k,v
54.	OCH_3	H	NHAC	OCH_3	H	CH_3	–	k,v
55.	Br	H	H	OCH_3	H	CH_3	–	x
56.	H	Br	OCH_3	H	H	CH_3	–	x
57.	H	OCH_3	Br	H	H	CH_3	–	x
58.	Br	H	OCH_3	OCH_3	H	CH_3	–	x,y
59.	H	OCH_3	Br	OCH_3	H	CH_3	–	x
60.	Br	H	$O-CH_2-O$		H	CH_3	<1.2	y
61.	OCH_3	H	OCH_3	Br	H	CH_3	4.4	y
62.	OCH_3	H	CH_3	H	H	CH_3	–	s
63.	H	H	CH_3	OCH_3	H	CH_3	–	s
64.	OCH_3	CH_3	OCH_3	H	H	CH_3	–	s
65.	CH_3	H	CH_3	H	CH_3	CH_3	–	s

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o. REFERENCE COMPOUND, MESCALINE, WHICH DEFINES M.V.
p. JANSEN, REC. TRAV. CHIM., *50,* 291(1931)
q. SHULGIN, EXPERIENTIA *17,* 127(1963)
r. BUTTERICK, unpublished
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u. SHULGIN, BRIT 1, 147, 739(1969); CHEM. ABS., *71,* 12781j(1969)
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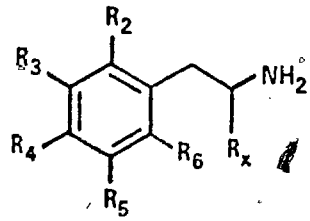
w. SHULGIN, PHARMACOL. *5,* 103(1971)
x. BARFKNECHT, J. MED. CHEM., *14,* 370(1971)
y. SEPULVEDA, J. MED. CHEM., *15,* 413(1972)
*. MOLAR MESCALINE UNITS: EFFECTIVE DOSE OF MESCALINE (mmoles/kg)/ EFFECTIVE DOSE OF COMPOUND (mmoles/kg); EFFECTIVE DOSE OF MESCALINE 0.0178 mmoles/kg.

TABLE 3

POLYHYDROXYPHENETHYLAMINES (CHEMORELEASE OF NOREPINEPHRINE-^{3}H FROM MOUSE HEARTS BY CATECHOLAMINES AND RELATED COMPOUNDS (AFTER DALY, CREVELING AND WITKOP (405))



	R_2	R_3	R_4	R_5	R_6	R_x	Dose (my/ug)	Norepinephrine-^{3}H in heart, % of control
1.	OH	OH	H	H	H	H	5	43
2.	H	OH	OH	H	H	H	5	50
3.	H	OH	OH	H	H	CH_3	5	39
4.	H	OH	OH	H	OH	H	5	28
5.	H	OH	OH	H	OCH_3	H	5	80
6.	H	OH	OH	CH_3	H	H	5	22
7.	H	OCH_3	OH	OH	H	H	2,5	57
8.	H	OCH_3	OH	H	H	H	10	104
9.	H	OCH_3	OH	H	H	CH_3	10	105
10.	H	OCH_3	OH	OCH_3	H	H	10	105
11.	H	OH	OCH_3	H	H	H	10	100
12.	OH	OCH_3	H	H	H	H	10	90
13.	H	OCH_3	OCH_3	OH	H	H	10	94
14.	OH	H	OH	OCH_3	H	H	10	88
15.	OH	H	OCH_3	OH	H	H	10	78
16.	H	OH	OCH_3	OH	H	H	10	12
17.	H	OH	H	OH	H	H	5	50
18.	H	OH	OCH_3	OH	H	CH_3	2,5	36
19.	H	OH	OC_2H_5	OH	H	H	10	64
20.	H	OH	CH_3	OH	H	H	5	54
21.	H	OH	CH_3	OH	H	CH_3	–	–*
22.	H	CH_3	OH	CH_3	H	CH_3	–	–*

*Butterick, unpublished

Chapter 7

Experimental

Melting points were measured on a Fischer-Johns apparatus and are uncorrected. U.V. spectra were measured on a Unicam SP 800 with ethanol as solvent. I.R. spectra were measured on a Perkin-Elmer 457 spectrometer. N.M.R. spectra were recorded using a Varian A56/60 and the requisite data are reported as δ versus an internal TMS standard. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-7 instrument using an ionization voltage of 80 e.v. GLPC analyses were performed on a Bendix Chroma-Lab series 2200 equipped with a T.C. detector.

"O-Transmethylated" Catecholamines

4-(3,4-Dimethoxybenzal)-2-Phenyl-5-Oxazolones (35a,35b)

The procedure by Buck and Ide (573) was found to be satisfactory, (65% yield) m.p. 151-152, lit. m.p. 151-152 (581). N.M.R. ($CDCl_3$): δ 3.90 (m-OCH_3, s, 6), 4.00 (p-OCH_3, s, 6), 6.75-7.25 (olefinic H, 2s, 2), 7.40-8.20 (Ar-H, m. 16), ν_{max} (KBr) 1745, 1760 cm^{-1} (carbonyls 1625 cm^{-1} (C=N); λ_{max} (EtOH): 298 mμ (ε = 10,500), 350 mμ (ε = 5,000). Anal. Calcd. for $C_{18}H_{15}NO_4$ (mol. wt. 309): C, 69.89; H, 4.89; N, 4.52. Found: (m/e, 309); C, 69.46; H, 4.85; N, 4.49.

N-Benzoyl-1-amino-2-(3,4-dimethoxyphenyl)-1-propenoic acid(36a,36b)

The azlactones (35a,35b) (81 g, .262 mol) were refluxed (12 hr) in a liter 10% K_2CO_3 solution/200 ml acetone. The reaction mixture was poured over 1 liter 10% HCl/500 g ice. The product was collected, recrystallized from acetic acid/water, 78.0 g (92.0% yield) m.p. 196-198°. n.m.r. (d^6-DMSO): δ 3.60 (m-OCH_3, s, 6), 3.75 (p-OCH_3, s, 6), 6.80-

8.10 (Ar-H, olefinic, $-NHCOC_6H_5$, m, 20), 9.85 ($CO_2\underline{H}$, s, 1) (D_2O exchange, 4.00-4.70, broad s); ν_{max} (KBr): 3200 cm^{-1} ($N\underline{H}COC_6H_5$), 2500 ($CO_2\underline{H}$), 1600-1690 (C=C, C=O); λ_{max} (EtOH): 295 mμ (ε = 12,500). Anal. Calcd. for $C_{18}H_{17}NO_5$ (mol. wt. 327): C, 66.04; H, 52.24; N, 4.28. Found: (m/e, 327); C, 66.01; H, 5.21; N, 4.30.

N-Benzoyl 3-(3,4-Dimethoxyphenyl)-2-Aminopropionic acid (37)

The propenoic acid (36a,36b), (1 g, 3.06 mmole) was suspended in deionized water (10 ml), cooled and stirred in an ice bath (0° C). Powdered 3% sodium amalgam (3 g) was added in three portions at 15 minute intervals; 15 minutes after the last addition, the solution was stirred at room temperature (25° C) for 30 min, Hg was filtered through a gravity funnel with two thicknesses of filter paper and washed with 10 ml deionized water. The filtrate was cooled in an ice bath, acidified (20% HCl), stored at 4°C overnight and the precipitate subsequently dried. The compound after recrystallization from acetic acid/water, 62 g (1.89 mmole, 57.5% yield) had m.p. 182-184°. n.m.r. (d^6-DMSO): 3.20 (CH_2, m, 2), 3.70 (CH_3, s, 6), 4.6 (CH, m, 1), 6.80-7.00 (Ar-H, m, 3), 7.4-8.0 (Ar-H, m, 5), 8.50 ($NHCOC_6H_5$, s, 1), 9.00 ($CO_2\underline{H}$, s, 1), D_2O exchange, 4.00-4.70, broad, s, 1). ν_{max} (KBr): 3300 ($N\underline{H}OOC_6H_5$), 2500 ($CO_2\underline{H}$), 1690-1670 (C=O's). Anal. Calcd. for $C_{18}H_{19}NO_5$ (mol. wt. 329): C, 65.64; H, 5.81; N, 4.25. Found: (m/e, 329); C, 65.64; H, 5.87; N, 4.44.

(±)-3-(3,4-Dimethoxyphenyl)-2-Alanine (1)

The N-benzoyl amino acid (37) (130.3 mg, .396 mmol) dissolved in 6 M HCl (5 ml) was hydrolysed for 1 hr in a sealed tube (97°). The solution was cooled in an ice bath, extracted immediately with 5 ml ether to remove benzoic acid and the aqueous acidic layer evaporated on a vacuum pump (1 mm) at room temperature. The crude material (111.7 mg) was taken up in water and eluted with the same from a silica gel column and the effluent was evaporated on a vacuum pump. The residue was dried in vacuo over P_2O_5, 62.9 mg (.280 mmole, 70.8% yield), m.p. 249-250°. T.L.C. (silica gel GF-254): $CHCl_3$:CH_3OH:NH_4OH (conc)/80:20:1; R_f 0.20. GLPC of the trifluoroacetic acid/n-butyl ester (379) (1.5% GE-XF1150 on Chromosorb W) (160°) showed a single component. n.m.r. (D_2O): 3.30 (CH_2, m, 2), 3.92 (OCH_3, s, 6), 4.60 (CH, m, 1), 4.75 (NH_2, CO_2H exchanged, s, 3), 6.98 (Ar-H, m, 3). ν_{max} (KBr): 3000 cm^{-1} (NH_2), 2100 cm^{-1} (CO_2H). Anal. Calcd. for $C_{11}H_{15}O_4N$ (mol. wt. 225): C, 58.65; H, 6.71; N, 6.22. Found: (m/e, 225); C, 58.64; H, 6.70; N, 622.

Hydrolysis of Azlactones (35a,35b) (574).

The azlactones (35a,35b) (5 g, 16 mmol) were refluxed in 2% NaOH solution (500 ml) for 10 hr. On cooling in ice, the mixture was acidified with dilute HCl and the crude product collected. T.L.C. (silica gel GF-254) acetone-water (1:1 v/v) revealed two major components. The N-benzoyl 3-(3,4-dimethoxyphenyl)-2-amino-acrylic acids (36a,36b) (20%) which chromato-

graphed as one component were characterized by mass spec. and m.p. as described previously. The other compound, N-benzoyl 3-(3,4-dimethoxyphenyl)-3-hydroxy-2-alanine (38), (65% yield) had m.p. 211-212°. n.m.r. (d^6-DMSO): 3.70 (OCH_3, s, 6), 4.60-5.20 (CH's, OH, m, 3), 7.40-8.00 (Ar-H, m, 8), 8.50 ($NHCOC_6H_5$, s, 1), 9.00 (CO_2H, s, 1). D_2O exchange, 4.00-4.50 broad s, 2). Anal. Calc. for $C_{18}H_{19}NO_6$ (mol. wt. 345). C, 62.60; H, 5.54; N, 4.06. Found: (m/e, 345); C, 62.58; H, 5.52; N, 4.02.

4-(3,4-Dimethoxybenzyl)-4-Ethoxy-2-Phenyl-5-Oxazolone (41a)

The azlactones (35a,35b) (3.86 g, 12.5 mmol) in 100 ml 95% EtOH, were hydrogenated with a mixture of 4.25 g NH_3 (anhydrous) and 1.5 g catalyst (prepared as described by Badshah et al (357) at 42 psi H_2 for 14 hr using a Parr shaker. The catalyst was filtered. washed with hot ethanol and the filtrate evaporated. The product (92% yield), recrystallized from EtOH(95), has m.p. 215-17°. n.m.r. (d^6-DMSO): 2.10 (CH_3, t, 3), 4.55 (CH_2, quartet, 2), 3.70 (OCH_3, s, 6), 4.60-5.00 (CH's, m, 2), 6.75-8.20 (Ar-H, m, 8). Anal. Calcd. for $C_{20}H_{21}NO_5$ (mol. wt. 355): C, 67.59; H. 5.96; N, 3.94. Found (m/e, 355): C, 67.55; H, 5.94; N, 3.90. Presence of N'-benzoyl-(3,4-dimethoxyphenyl)-2-alanineamide (42b) was detected in crude product as fragment (M =308) in mass spectrum and tentatively so assigned.

1-(3,4-Dimethoxyphenyl)-2-Aminoethane (2)

Condensation of veratraldehyde (34) with nitromethane and ammonium acetate in acetic acid (367) gave the known nitrostyrene, m.p. 140-141. lit. m.p. 140-141 (367). n.m.r ($CDCl_3$): 2.9

(OCH_3, s, 6), 6.85-7.45 (Ar-H, m, 3), 7.71 (CH=CH, dd, 2, J=15 Hz). ν_{max} (KBr): 1570 cm^{-1} (CH=CH). λ_{max} (EtOH): 290 mμ (ϵ = 10,000). m/e 209. $LiAlH_4$ reduction of the nitro styrene in ether (368) gave 2, (68% yield), m.p. (HCl salt) 143-145° lit. m.p. 143-145 (171). n.m.r. (d^6-DMSO): 2.70-3.00 (CH_2CH_2, m, 4), 3.80 (OCH_3, s, 6), 6.8-7.0 (Ar-H, m, 3), 8.40 ($NH_3^{\oplus}$, s, 3). ν_{max} 3400 cm^{-1} (NH_2). T.L.C. (Silica gel GF-254) $CHCl_3$: CH_3OH: NH_4OH (conc) 80:20:1 showed a single compound, Rf 0.30, as did GLPC on 3% OV-17/Gas Chrom Q (220°).

(±)-1-(3,4-Dimethoxyphenyl)-2-Aminopropane (3)

Condensation of veratraldehyde (34) with nitroethane in presance of ammonium acetate in acetic acid as well as with nitroethane (neat) (369, 385), gave the nitrostyryl derivative, 50% and 95% yield respectively, m.p. 145-146° n.m.r. ($CDCl_3$): 2.50 ($\underline{CH_3}$-C=C, s, 3), 3.95 (OCH_3, s, 6), 6.9-7.0 (Ar-H, m, 3), 8.0 ($\underline{CH}$=C, broad s, 1). ν_{max}: 1590 cm^{-1} (CH=C). λ_{max} (EtOH): 296 mμ (ϵ = 11,000). Calc. mol. wt. 223, Found. m/e, 223.

$LiAlH_4$ reduction of the β-nitropropene in anhyd. THF (368) gave 3 (74% yield) m.p. (HCl salt) 147-8°. lit. m.p. 147.5-148° (385) n.m.r. ($CDCl_3$): 1.05 (CH_3, d, 3), 2.5-3.0 (CH_2CH, m, 3), 3.80 (OCH_3, s, 6), 6.80-7.00 (Ar-H, m, 3). ν_{max} (KBr): 3400 cm^{-1} (NH_2). Calc. mol. wt. 195. Found: m/e, 195. T.L.C. (Silica gel GF-254) $CHCl_3$:CH_3OH:NH_4OH (conc) 80:20:1, Rf 0.35, and GLPC on 3% OV-17/Gas Chrom Q (220°) both showed a single component.

1-(3,4-Dimethoxyphenyl)-1-Hydroxyacetonitrile (42) (373)

Freshly distilled veratraldehyde (34) (0.1 mol.) was ground in a mortar and slurried with 0.172 mole KCN dissolved in 23

ml water. HCl (17 ml) was added dropwise with rapid stirring until the temperature of the mixture reached 45°-50° and maintained at this level by cooling with ice. The mixture was allowed to come to room temp., cooled in ice, the solid removed by filtration and washed with cold water (5 x 50 cc) and dried in vacuo (m.p. 59-69°). The crude material was stirred in 100 ml cold anhydrous benzene (2 x), filtered and dried in vacuo, 18.7 g (.097 mol, 97.2% yield) m.p. 87-90°. n.m.r. ($CDCl_3$): 3.40 (OH, s, 1), 4.05 (OCH_3, s, 6), 5.65 (CH, s, 1), 6.90-7.60 (Ar-H , m, 3). ν_{max} (KBr): 3430 cm^{-1} (OH), 2000 cm^{-1} (C≡N). λ_{max} (EtOH): 295 mμ (ε = 10,000). Anal. Calcd. for $C_{10}H_{11}NO_3$ (mol. wt. 193): C, 62.16; H, 5.74; N, 7.25. Found: m/e, 193); C, 62.17; H, 5.70; N, 7.12.

1-(3,4-Dimethoxyphenyl)-2-aminoethanol (4)

The cyanohydrin (42) (12.3 g, 64 mmol), dissolved in anhydrous THF, was added dropwise to an ice-cooled slurry of $LiAlH_4$ (12 g, 318.5 mmol) in dry THF (250 ml). The mixture was stirred at room temperature (15 min), refluxed thereafter for five hr. followed by hydrolysis with H_2O under cooling until the salts that formed coagulated. The mixture was filtered and the filtrate dried and evaporated in vacuo, leaving a high boiling liquid. Vacuum distillation afforded a fraction collected at 160°-164° (0.7 mm), 11.5 g (.058 mol, 97%) which had as the solid HCl salt m.p. 163-165°, lit. m.p. 163° (372). n.m.r. (d^6-DMSO): 2.70-3.00 (CH_2-NH_2, m, 2), 3.50 (OH,NH_3, broad s, 4), 3.75 (OCH_3, 2s, 6), 4.60-4.80 ($CH(OH)CH_2$, m, 1) 6.8-7.0 (Ar-H, m,

3), ν_{max} 3400-3500 cm^{-1} (NH_2,OH), T.L.C. (Silica Gel GF 254): $CHCl_3$:CH_3OH:NH_4OH (conc) 80:20:1, Rf, 0.33. GLPC on 5% SE 30/Chromosorb W DMCS A/W, 60/80, 160°, showed a single peak for the Trisil/BSA derivative. Anal. Calc. for $C_{10}H_{15}NO_3$ (mol. wt. 197): C, 60.90; H, 7.67; N, 7.10. Found: (m/e, 197); C, 60.85; H, 7.50; N, 7.05.

N-[1-(3,4-Dimethoxyphenyl)-2-Ethanol] Carbamate (44)

The ethanolamine 4 (.349 g, 2 mmol), slurried in water (10 ml) and 2 g chopped ice, was treated with ethylchloroformate by the method of Friedman (374) to yield(44),(0.349 g, 65%), m.p. 63-65°. n.m.r. (d^6-DMSO): 1.30 (CH_3, d, 3), 2.80-3.30 (CH_2NH, m, 2), 3.50 (OH, NH_2, s, 2), 3.75 (OCH_3, 2s, 6), 4.50 (CH_2, q, 2), 4.60-4.80 ($CH(OH)CH_2$, m, 1), 6.80-7.00 (Ar-H, m, 3), ν_{max} 1750 cm^{-1} (C=O), 3430-3500 cm^{-1} (NH, OH). Anal. Calc. for $C_{13}H_{19}NO_5$ (mol. wt. 269): C, 57.98; H, 7.11; N, 5.20. Found: (m/e, 269); C, 57.96; H, 7.10; N, 5.16.

(±)-N-methyl 1-(3,4-dimethoxyphenyl)-2-aminoethanol (5)

The carbamate (44) (0.345 g, 131 mmol) dissolved in anhydrous THF, was added with stirring to a slurry of 266 mg (7.0 mmol) $LiAlH_4$ in anhydrous THF (10 ml) at room temperature. The mixture was refluxed for 80 hr, then hydrolyzed with water and precipitated salts removed. The filtrate was dried ($MgSO_4$) and evaporated yielding the crude amino alcohol which was purified by elution with ether from a silica gel column. The combined ether fractions were dried over $MgSO_4$, evaporated to a

small volume followed by saturation with anhydrous HCl. The ethanolamine hydrochloride (5) was collected and dried, 97 mg (.46 mmole, 35%), m.p. 132-133°. n.m.r. (d^6-DMSO): 2.44 (CH_3-NH, s, 3), 2.7-3.0 (CH_2-NH_2, m, 2), 3.70-3.80 (OCH_3, 2s, 6), 4.6-5.0 (CH-OH, s, 1), 6.8-7.0 (Ar-H, m, 3). ν_{max}: 3400-3500 cm^{-1} (NH,OH). Anal. Calcd. for $C_{11}H_{15}NO_3$ (mol. wt. 211). C, 62.53; H, 8.11; N, 6.63. Found: (m/e, = 211); C, 62.50; H, 8.09; N, 6.61. T.L.C. (silica gel GF 254): C_6H_6:$CHCl_3$:CH_3OH:NH_4OH (conc), 8:6:5:1 and GLPC of the Trisil/BSA derivative on 5% Se-30 as above (160°) showed one compound.

Conversion of (4) to 1-(3,4-Dimethoxyphenyl)acetaldehyde (47)

1-(3,4-Dimethoxyphenyl) 2-aminoethanol (4) formed, as has been reported (372), the Schiff's base (46) with piperonal. n.m.r. ($CDCl_3$): 3.50 (OH, s, 1) 3.7-3.8 (OCH_3, s, 6), 4.6-5.0 ($CHCH_2$, m, 3), 6.0 (OCH_2O, s, 2), 6.8-7.0 (Ar-H, m, 6), 7.20 (CH, s, 1). Anal. Calcd. for (mol. wt. 329): C, 65.64; H, 5.81; N, 4.25. Found: (m/e, 329); C, 65.62; H, 5.75; N, 4.15. The Schiff's base (46) was reacted with CH_3I (372) to form the adduct. n.m.r. 2.30 (=N-CH_3, s, 3), 2.70-3.00 (CH_2-N, m, 2), 3.50 (OH, s, 1), 3.75 (OCH_3, 2s, 6), 4.60-4.80 (CH(OH)CH_2, m, 1), 5.50 (CH, s, 1), 6.00 (O-CH_2-O, s, 2), 6.80-7.50 (Ar-H, m, 6). Anal. Calc. for $C_{19}H_{22}NO_5I$ (mol. wt. 471): C, 48.42; N, 4.70; N, 2.97; Found: (m/e, 471); C, 48.35; H, 4.69; N, 2.95.

The adduct (46) (2.4 g, 0.535 mol) was refluxed in a mixture of water (25 ml) and HCl (2.5 ml, 12 M) for 2 hr. The solution was extracted with ether and the aqueous solution

treated with 30% NaOH. The neutral solution was extracted with $CHCl_3$, the $CHCl_3$ layer dried ($MgSO_4$) and evaporated leaving an oil which was distilled in vacuo. b.p. 125° (1.5 mm). n.m.r. ($CDCl_3$): 3.50 (CH_2, d, 1), 4.75 (OCH_3, s, 6), 6.8-7.0 (Ar-H, m, 3), 9.0 (CHO, t, 1). ν_{max} (NaCl plate): 1725 cm^{-1}. Calc. mol. wt. 180. Found: m/e, 180.

Psychodysleptic β-Phenylisopropylamines

1,3-Dimethyl-2-Propioxybenzene 69

(R = 1,3-DiMe 2-Propioxy)

2,6-Dimethylphenol (98.7 g., .808 mole) and propionic anhydride (206 g., 1.57 mole) were refluxed for 4 hours. The reaction mixture was distilled in vacuo, b.p. 68-70° (0.4 mm). Yield: 137.9 g. (0.775 mole, 96%). n.m.r. (CCl_4): δ 1.25 (CH_3, t, 3), 2.10 (CH_3 - Ar, s, 6), 2.50 (CH_2, q, 2), 6.92 (Ar-H, s, 3); ν_{max} (salt plate) 1743 cm^{-1} (C = O). Anal. calcd. for $C_{11}H_{14}O_2$ (mol. wt. 178): C, 74.13; H, 7.92. Found: (m/e, 178); C, 74.08; H, 7.91.

1-(3,5-Dimethyl-4-Hydroxyphenyl)propanone 53

(R = 3,5-DiMe 4-OH)

1,3-Dimethyl 2-propioxybenzene (137.9 g., .775 mole), 69 (R = 3,5-DiMe 2-Propioxy), and $AlCl_3$ (anhyd.) were mixed at room temperature under drying and heated to melting for 3 hours. The reaction mixture was poured on 500 g. ice - HCl (conc) and mother liquors extracted with CH_2Cl_2. The combined CH_2Cl_2 extract was dried and evaporated to give colorless crystals which were recrystallized from methanol - water. Yield: 73.5 g. (.242 mole,

31.2%) with m.p. 157-158°. n.m.r. ($CDCl_3$): 1.20 (CH_3, t, 3), 2.30 (CH_3 - Ar, s, 6), 3.00 (CH_2, q, 2), 6.59 (OH, s, 1). 7.70 (Ar - H, s, 2). ν_{max} (KBr): 1690 cm^{-1} (C = O). Anal. calcd. for $C_{11}H_{14}O_2$ (mol. wt. 178): C, 74.13; H, 7.92. Round: (m/e, 178); C, 74.11; H, 7.92.

1-(3,5-Dimethyl-4-Methoxyphenyl) propanone, 53 (R = 3,5-DiMe 4-MeO)

1-(3,5-Dimethyl-4-methoxyphenyl)propanone (25 g., .140 mole), (14, R = 3,5-DiMe 4-OH), was dissolved in 75 ml. methanol. Me_2SO_4 (40.6 g., .322 mole) was added and the solution chilled in an ice bath. NaOH (24.1 g., .602 mole)/27 ml. H_2O was slowly dropped in with stirring and the temperature kept below 30°. After addition, the mixture was refluxed for 15 minutes and poured over 500 g. of ice. The mixture was refrigerated (4°C) overnight and crystals were filtered with suction. Yield: 24.3 g. (.127 mole, 90.6%). n.m.r. ($CDCl_3$): 1.30 (CH_3, t, 3), 2.40 (CH_3 - Ar, s, 6), 3.05 (CH_2, q, 2), 3.85 (CH_3O, s, 3), 7.72 (Ar - H, s, 2); ν_{max} (KBr) 1700 cm^{-1}; Anal. calcd. for $C_{12}H_{16}O_2$ (mol. wt. 192): C, 74.97; H, 8.39. Found: (m/e, 192); C, 74.55, H, 8.25.

2-Oxime-1-(3,5-Dimethyl 4-Hydroxyphenyl)-1,2-Propanedione, 54 (R = 3,5-DiMe 4-OH) and 2-Oxime-1-(3,5-dimethyl 4-methoxyphenyl)-1,2-propanedione, 54 (R = 3,5-DiMe 4-MeO) were prepared after Hartung and Crossley (500) in 84.5% and 86% yields respectively. For 54 (R = 3,5-DiMe 4-OH), n.m.r. (DMSO-d_6); 2.05 (CH_3, s, 3), 2.22 (CH_3, s, 6), 3.62 (Ar - OH, broad s, 1), 7.55 (Ar - H, s,

2), 11.80 (NOH, broad s, 1). Anal. calcd. for $C_{11}H_{13}O_3N$ (mol. wt. 207); C, 63.76; H, 6.32; N. 676. Found: (m/e, 207); C, 63.73; H, 6.30; N, 6.75.

For 54 (R = 3,5-DiMe 4-MeO), n.m.r. (DMSO-d_6): 2.05 (CH_3, s, 3), 2.22 (CH_3, s, 6), 3.90 (CH_3O, s, 3), 7.30 (Ar - H, s, 2), 11.78 (NOH, broad s, 1). Anal. calcd. for $C_{12}H_{15}O_3N$ (mol. wt. 221): C, 65.16; H, 6.89; N, 6.33. Found: (m/e, 221); C, 65.11; H, 6.83; N, 6.25.

Generation of 1-(3,5-Dimethyl-4-Hydroxyphenyl)-2-Aminopropane, 72 from 54 (R = 3,5-DiMe 4-HO)

A mixture of oximinoketone (207 mg., 1 mmole) 54 (R = 3,5-DiMe 4-OH) was hydrogenated in 40 ml. glacial acetic acid/.10 ml. H_2SO_4 (conc) solution over 200 mg. 10% Pd/C or 100 mg. PtO_2. The catalyst was removed by filtration and the solution neutralized to pH 8 and extracted with ether. The combined extracts were washed with H_2O and dried ($MgSO_4$). Coloured material was removed on a column and the amine was eluted with ether. Treatment with anhydrous HCl precipitated the hydrochloride salt, yield: 35.8 mg. (0.20 mmole, 20%). m.p. 212-3 (free amine 103-5). n.m.r ($CDCl_3$): 1.09 (CH_3,d, 3), 2.15 (CH_3, s, 6), 2.07 (OH, NH_2, s, 3), 6.72 (Ar - H, s, 2). ν_{max} (KBr) 3300 cm^{-1} (NH_2, OH). Anal. calcd. for (as free amine) $C_{11}H_{17}ON$ (mol. wt. 179): C, 75.69; H, 9.56; N, 7.81. Found: (m/e, 179); C, 74.12; H, 11.14; N, 7.84.

1-(3,5-Dimethyl-4-Methoxyphenyl)-2-Aminopropane, 73, was prepared in a similar manner to 72. Yield: 48 mg. (0.25 mmole, 25%).

n.m.r. (DMSO-d_6) : 1.15 (CH_3, d, 3), 2.22 (Ar - CH_2, m, 2). ν_{max} (KBr) 3300 cm^{-1} (NH_2); Anal. calcd. for as free amine $C_{12}H_{19}ON$ (mol. wt. 193): C, 74.56; H, 9.91; N, 7.25. Found: (m/e, 193; C, 74.95; H, 9.40; N, 7.22.

1-(3,5-Dimethyl-4- Hydroxyphenyl)-1-Hydroxy-2-Propanone Oxime, 55 (R = 3,5-DiMe 4-OH)

Oximinoketone (1 g., 5 mmole) 54 (R = 3,5-DiMe 4-OH) was dissolved in methanol (50 cc.) and cooled to 0°. A solution of sodium borohydride (6 mmole, 0.227 g.) in 2 cc 1 M NaOH also cooled to 0° was added to the first solution over 5 minutes. The reaction mixture was stirred at ambient temperature (23°) for 2 hours. Methanol was removed in vacuo at room temperature after which 25 cc. water was added and the pH adjusted to 8 with 17% HCl and sat'd. $NaHCO_3$. Extraction of the mixture with ether followed by drying ($MgSO_4$) and evaporation yielded 645 mg product, recrystallized from Et_2O-hexane (3.00 mmole, 60%. n.m.r (DMSO-D_6): 1.52 (CH_3, s, 3), 2.10 (CH_3-Ar, s, 6), 3.30 (Ar-OH, s, 1), 5.22 (CH, OH, AB quartet, 2), 6.83 (ArH, s, 2(, 5.35 (NOH, s, 1). ν_{max} (KBr): 3400 cm^{-1} (Ar-OH, NOH, CHOH). Anal. calcd. for $C_{11}H_{15}O_3N$ (mol. wt. 209): C, 63.14; H, 7.22; N, 6.69. Found: (m/e, 209); C, 63.10; H, 7.21; N, 6.65.

1-(3,5-Dimethyl-4-Methoxyphenyl)-1-Hydroxy-2-Propanone Oxime, 55 (R = 3,5-DiMe 4-MeO) was prepared in the above manner. Yield: 724 mg. (3.25 mmole, 65%). n.m.r. (DMSO-d_6): 1.52 (CH_3, s, 3), 2.10 (CH_3-Ar, s, 6), 3.80 (CH_3O, s, 3), 5.20 (CH, OH, AB quartet, 2), 6.70 (Ar-H, s, 2), 5.35 (NOH, s, 1). ν_{max} (KBr): 3400 cm^{-1}

(NOH). Anal. calcd. for $C_{12}H_{17}O_3N$ (mol. wt. 223): C, 64.55; H, 7.68; N, 6.27. Found: (m/e, 223); C, 64.50; H, 7.65; N, 6.24.

1-(3,5-Dimethyl-4-Hydroxyphenyl)-2-Amino-1-Propanone, 64 (R = 3,5-DiMe 4-OH)

Oximinoketone, 54 (R = 3,5-DiMe 4-OH) (2.07 g., 10 mmole) was dissolved in a solution of 300 ml. 95% EtOH containing 1.8 g. (.05 mole) dry HCl gas followed by addition of 200 mg. PtO_2 or 750 mg. 5% Pd/C and the mixture hydrogenated at 50 lb./in.^{2} for 24 hours. The catalyst was filtered off and solvent evaporated, yielding 1.7 g. (8.8 mmole, 88%). n.m.r. (DMSO-d_6): 1.52 (CH_3-CH, d, 3), 2.30 (CH_3-Ar, s, 6), 4.35 (OH, NH_2, broad s, 3), 5.02 (CH-CH_3, q, 1), 7.70 (Ar-H, s, 2). ν_{max} (KBr): 1650 cm^{-1} (C = O), 3400 cm^{-1} (NH_2, OH). Anal. calcd. for $C_{11}H_{15}O_2N$ (mol. wt. 193): C, 68.37; H, 7.82; N, 7.24. Found: (m/e, 193); C, 68.32; H, 7.80; N. 7.21.

1-(3,5-Dimethyl 4-Methoxyphenyl)-2-Amino-1-Propanone, 64 (R = 3,5-DiMe 4-MeO) was prepared in the manner described above. Yield: (85%). n.m.r. (DMSO-d_6): 1.52 (CH_3-CH, d, 3), 2.30 (CH_3-Ar, s, 6), 3.80 (CH_3O, s, 3), 4.35 (OH, NH_2, broad s, 3), 5.02 (CH-CH_3, q, 1), 7.70 (Ar-H, s, 2). ν_{max} (KBr): 1650 cm^{-1} (C = O), 3500 cm^{-1} (NH_2). Anal. calcd. for $C_{12}H_{17}O_2N$ (mol. wt. 207): C, 69.53; H, 8.27; N, 6.75. Found: m/e, 207; C, 68.86; H, 8.15; N, 6.24.

1-(3,5-Dimethyl 4-Methoxyphenyl)1-Hydroxy-2-Aminopropane, 55 (R = 3,5-DiMe 4-MeO)

Lithium aluminum hydride reduction of oximinoketone, 54

(R = 3,5-DiMe 4-MeO) in anhydrous ether (reflux: 24 hr.) and standard work up gave 72% yield. n.m.r. ($CDCl_3$): 1.25 (CH_3, d, 3), 2.20 (CH_3-Ar, s, 6), 3.00 (C<u>H</u>-CH_3, m, 1), 3.90 (OCH_3, s, 3), 4.08 (CH(OH), m, 1), 5.02 (NH_2,OH, Ar-OH, broad s, 4), 7.50 (Ar-H, s, 2). ν_{max} (KBr): 3600 cm^{-1} (OH,NH_2). Anal. calcd. for $C_{12}H_{17}O_2N$ (mol. wt. 209): C, 69.86; H, 9.15; N, 6.61. Found: (m/e, 209); C, 69.83; H, 9.10; N, 6.61.

<u>3,5-Dimethyl-4-Hydroxybenzaldehyde</u>, 63 (R = 3,5-DiMe, 4-OH)

An overhead stirred mixture of 370 ml. glycerol and 108 g. (.687 mole) boric acid (dried in an oven at 110°) in a 1 liter 3-necked flask fitted with a thermometer and a condenser for downward distillation was heated to exactly 170° for 2 hours, and then allowed to drop in temperature. At 150°, a melt of 61.0 g (.5 mole) 2,6-dimethylphenol and 77.0 g. (.55 mole) hexamethylenetetraamine (alternatively, individually pelletized phenol and tetraamine) were added. The temperature dropped to 130° during addition. The mixture was heated to 145° at which time the heat of the reaction increased the temperature to 154°. After 6 minutes at 154°, the reaction was cooled to 110° and a solution of 92 ml. concentrated H_2SO_4 in 310 ml. H_2O was added. After stirring for one hour at 100°, the reaction was cooled to 25°, boric acid filtered off and washed with 200 cc. H_2O. The filtrate was extracted with 3 x 250 ml. $CHCl_3$.

The $CHCl_3$ solution was then extracted with a solution of 90 g. $NaHSO_3$ in 360 cc. H_2O by vigorous stirring for one hour.

A second extract of 30 g. $NaHSO_3$ in 120 cc. H_2O was made. Both extracts were combined, extracted once with 25 cc. $CHCl_3$, cooled and acidified with a solution of 38 ml. H_2SO_4 in 38 ml. H_2O. The solution was brought to a boil, air bubbled through to expell SO_2, and the aldehyde that separated upon cooling was collected by filtration. Column chromatography ((silica); $CHCl_3$: Hexane (1: 3)) and recrystallization from benzene - heptane yielded 19.8 g. (.132 mole, 26%)m.p.116-18°. n.m.r. ($CDCl_3$): 2.30 (CH_3-Ar, s, 6), 5.70 (Ar-OH, s, 1), 7.45 (Ar-H, s, 2), 12.45 (CHO, s, 1). ν_{max} (KBr): 1700 cm^{-1} (C = O), 3520 cm^{-1} (OH). (m/e, 150).

3,5-Dimethyl-4-Methoxybenzaldehyde, 62 (R = 3,5-DiMe 4-MeO)

3,5-Dimethyl-4-hydroxybenzaldehyde (15.0 g., 0.10 mole) was dissolved in a solution of 12.5 g. (0.31 mole) sodium hydroxide and 100 ml. H_2O, and heated to reflux under N_2. Dimethylsulfate, 15.8 g. (.125 mole), was added dropwise with stirring and the mixture refluxed for 30 minutes. An additional 17.8 g. (.142 mole) of $(CH_3)_2SO_4$ was added and reflux continued for 10 minutes. A solution of 4.0 g. NaOH (0.10 mole) in 25 cc. H_2O was further added, followed by addition of 10.5 g. (.083 mole) $(CH_3)_2SO_4$, the mixture refluxed for 20 minutes longer. The solution was cooled to room temperature, extracted with ether, the combined extract dried ($MgSO_4$), and evaporated. Distillation of the residue in vacuo 85-90° (0.6 mm.) gave 10.5 g. (0.0635 mole, 64.0%). n.m.r. ($CDCl_3$): 2.34 (Ar-CH_3, s, 6), 3.33 (OCH_3, s, 3), 7.57 (Ar-H, s, 2), 10.02 (CHO, s, 1). ν_{max} (KBr):

1695 cm^{-1} (C = O). (m/e, 164).

1-(3,5-Dimethyl-4-Hydroxyphenyl)-2-Nitro-1-Propene, 62 (R = 3,5-DiMe 4-OH), and 1-(3,5-Dimethyl 4-Methoxyphenyl)-2-Nitro 1-Propene, 62 (R = 3,5-DiMe 4-MeO)

3,5-Dimethyl-4-hydroxybenzaldehyde, 63 (R = 3,5-DiMe 4-OH) or 3,5-Dimethyl-4-methoxybenzaldehyde, 63 (R = 3,5-DiMe 4-MeO) was dissolved (1 mmole) in 10 cc. nitroethane, 1.25 mmole NH_4OAc was added, and the reaction refluxed for 10 minutes in the case of 63 (R = 3,5-DiMe 4-OH) and 5 minutes in the case of 63, (R = 3,5-DiMe 4-MeO). The reaction mixture was cooled immediately in liquid N_2 or acetone-dry ice, followed by dilution with CH_2Cl_2 and filtration. After in vacuo removal of solvent, the β-nitrostyryl, 1-(3,5-dimethyl 4-hydroxyphenyl)-2-nitropropene, 62 (R = 3,5-DiMe 4OH) or 1-(3,5-dimethyl 4-methoxyphenyl)-2-nitropropene, 62 (R = 3,5-DiMe 4-MeO) was recrystallized from MeOH-H_2O yields of 81% or 88% (549), m.p. 135-6, and. 128-9 respectively. (Table 4)

62 (R = 3,5-DiMe 4-OH) n.m.r. ($CDCl_3$): 2.25 (Ar-CH_3, s, 6), 2.45 (=C(CH_3), broad s, 3), 3.90 (Ar-OH, broad s, 1), 7.10 (Ar-H, s, 2), 8.00 (olefinic H, broad s, 1). ν_{max} (KBr): 1570 cm^{-1} (C = C), 3600 cm^{-1} (OH). Anal. calcd. for $C_{11}H_{13}O_3N$ (mol. wt. 207): C, 63.76; H, 6.32; N, 6.76. Found: (m/e, 207); C, 63.50; H, 6.31; N, 6.69.

62 (R = 3,5-DiMe 4-MeO) n.m.r ($CHCl_3$): 2.30 (Ar-CH_3, s, 6), 2.42 (=C(CH_3), broad s,3), 3.65 (CH_3O, s, 3), 7.10 (Ar-H, s, 2), 8.00 (olefinic H, broad s, 1). ν_{max} (KBr): 1565 cm^{-1} (C = C). Anal.

calcd. for $C_{12}H_{15}O_3N$ (mol. wt. 221): C, 65.14; H, 6.83; N, 6.33. Found: (m/e = 221); C, 65.08; H, 6.81; N, 6.30.

1-(3,5-Dimethyl-4-Hydroxyphenyl)-2-Amino Propane (72)

In a N_2 dry box, 1.035 g. (5 mmole) β-nitrostyryl, 62 (R = 3,5-DiMe 4-OH) was dissolved in 50 cc. anhyd. benzene. This solution was added dropwise to a stirred and chilled (0° C) mixture of 25 g. 70% "Redal" solution in benzene (80 mmole) (previously diluted with 100 ml. benzene). The mixture was brought to room temperature (24° C), then refluxed for 17 hours. The product (cooled in ice) was hydrolyzed with water, the mixture filtered with suction and evaporated (vacuum pump). The residue was taken up in $CHCl_3$, the solution dried over anhydrous $MgSO_4$, filtered and evaporated. Yield: 668 mg. (3.75 mmole, 75%) (analytical data as above). T.L.C. (Silica gel GF-254) $CHCl_3$: CH_3OH: NH_4OH (conc) 80:20:1, R_f = .50, and glpc on 3% OV-17/Gas Chrom Q (22°) as Trisil Z derivative both showed a single component.

1-(3,5-Dimethyl-4-Methoxyphenyl)-2-Amino propane (73)

In a similar manner, 1-(3,5-dimethyl-4-methoxyphenyl) 2-nitro 1-propene, 62 (R = 3,5-DiMe 4-MeO), was reduced with "Redal" (87%) or with lithium aluminum hydride (80%) after the method of Shulgin (506) (dry box not used). The product had m.p. (as HCl salt) 255-257°, other analytical data as above. T.L.C. (Silica gel GF-254) $CHCl_3$: CH_3OH: NH_4OH (conc) 80: 20:1, R_f = .35, and glpc on 3% OV-17/Gas Chrom W (200°). Both preparations showed a single component.

3,5-Dimethoxy-1,4-Dimethylbenzene, 83

1,3-Dimethoxy-5-methylbenzene (63), 9.55 g (62.8 mmole), prepared in 95% yield after Mirrington and Feutrill (576), was added to 25.0 g. of 18% n-butyl lithium in hexane cooled to 0°. Methyl iodide, 8.92 g. (62.8 mole) was then added drop-wise and the reaction mixture raised to room temperature. The react on was refluxed for 30 minutes, cooled, washed with $NaHCO_3$ solution, dried and evaporated. The crude product was distilled 60°-65° (.7 mm) to yield 6.64 g. (40 mmole, 64%).

3.5-Dimethoxy-4-Methylbenzoic Acid (86a) (536, 537)

A solution of 8.00 g. (4.8 mmole) 1,3-dimethoxy-2,5-dimethylbenzene in 60 ml. pyridine was heated to 85°. A hot solution of 17.5 g (111 mmole $KMnO_4$ in 100 ml. H_2O was added over 45 minutes. The reaction mixture was kept at 85° for 15 minutes longer, then cooled and filtered. The filtrate was washed with ether (2 x 100 ml.) and acidified under cooling. Starting material was recovered from the ether extract (2.0 g.).

The acids that precipitated were extracted with ether, the extract washed with H_2O (50 ml) and dried ($MgSO_4$). Evaporation of the solvent left a mixture of crude acids which could be best separated on t.l.c. (CH_3OH). Routinely, however, two recrystallizations from CH_3OH afforded 3.0 g (1.53 mole, 32%) 3,5-dimethoxy-4-methyl benzoic acid (86a). Comparison of melting point and n.m.r data with that reported (536) permitted assignment of structure (86a) for this product. The other product, recovered from preparative t.l.c., was assigned structure (86b) in the same way (584).

5-Methyl-cyclohexane-1,3-dione (78)

Orcinol (12.4 g, .100 mole) (recrystallized under N_2 from benzene-heptane) was added to a solution of 4.8 g (.12 mole)

sodium hydroxide in 400 ml. deionized and degassed H_2O and the mixture transferred into a pressure bomb carefully excluding air and light. Raney nickel W-2 (500mg), prepared by the method of Mozingo (575), was added and the mixture hydrogenated at 1500 lb/in^2 at 50° C for 15 hours. The reaction mixture was cooled to room temperature and suction filtered directly into a HCl/ice mixture in a N_2 glove box. The HCl filtrate was subjected to continuous extraction with $CHCl_3$ also under N_2 and after 3 hours the $CHCl_3$ was dried and evaporated. The residue was subjected to column chromatography under N_2 ($CHCl_3$) and recrystallized from $CHCl_3$-pentane. Yield: 6.0 g (0.048 mole, 48%) m.p. 124-5°. n.m.r. (DMSO-d_6): 1.00 (CH_3-CH, d of d, 3), 2.10 (CH_2, CH_3-CH, m, 5), 3.45 (=C(OH), broad s, 1), 5.17 (CH=, s, 1). ν_{max} (KBr): 3400 cm^{-1} (=C(OH)). Anal. Calcd. for $C_7H_{10}O_2$ (mol. wt. 126): C, 66.64; H, 7.99. Found: (m/e = 126); C, 66.60; H, 7.95.

2,5-Dimethyl-cyclohexane-1,3-Dione (79)

In a N_2 atmosphere, 5.88 g. (.0467 mole) 5-methyl-cyclohexane-1,3-dione (78) was dissolved in a solution of 2.61 g. (.0467 mole) KOH in 30 ml. CH_3OH/H_2O (2:1). This solution was placed in a pressure bomb along with 6.60 g. (.0467 mole) CH_3I, frozen in liquid N_2 and the bomb evacuated to 1 mm. The bomb was heated at 70° for 18.5 hours, cooled in an ice bath, and the contents transferred under N_2 to a round bottom flask. The methanol was evaporated *in vacuo*. The residue was made alkaline (50 ml. 4% NaOH) and extracted with ether. The aqueous layer was acidified and extracted with $CHCl_3$, dried ($MgSO_4$) and evaporated. Silica column chromatography of the residue under

N_2 (EtOAc-Hexane 70:30) and recrystallization from EtOAc-hexane gave 4.00 g. (.0285 mole, 61%). m.p. 175-76° n.m.r. (DMSO-d_6): 1.00 (CH_3-CH, d of d, 3), 1.55 (CH_3=, s, 3), 2.20 (CH_2, CH, m, 5), 4.00 (=C(OH), broad s, 1). ν_{max} (KBr): 1570cm^{-1}(C=O), 1500cm^{-1}(C=C), 3400cm^{-1}(=C(OH)). Anal. calcd. for $C_6H_{12}O_2$ (mol. wt.=140): C, 68.54; H, 8.63. Found (m/e=140): C, 67.78; H, 8.59. Methylation of 5-Methylcyclohexane-1,3-dione according to Sonn's method (542) and that of Stetter and Meisel (540) consistently gave rise to an impurity. The structure of di(2,5-dihydroxy-3-methylfurfuryl)peroxide (90) was tentatively assigned on the basis of (M^+=129) in the mass spectrum and a postulated mechanistic scheme.

4,6-Dibromo-1,3Dihydroxy-2,5-Dimethylbenzene (80) (549)

Under N_2, 7.00g (.050 mole) 2,5-dimethyl-cyclohexane-1,3-dione (79) was dissolved in 18 ml. ether. Bromine, 24.3 g (.152 mole) dissolved in 63.6 ml $CHCl_3$, was added dropwise with stirring. The reaction was left 3 hours at room temperature, after which time solvent and excess Br_2 was removed and the product recrystallized from benzene-hexane, yielding 9.15 g (.031 mole, 62%). m.p. 145-147. n.m.r (DMSO-d_6): 2.10 (CH_3-Ar(OH), s, 3), 2.40 (CH_3Ar(Br)), s, 3), 3.40 (OH, broad s, 2). ν_{max} (KBr): 3500 cm^{-1} (OH). Anal. calcd. for $C_8H_8O_2Br_2$ (mol. wt. 296), C, 32.46; H, 2.72; Br, 54.00. Found: (m/e=2.96); C, 32.46; H, 2.40; Br, 52.13.

4,6-Dibromo-1,3-Dimethoxy-2,5-Dimethylbenzene (85)

Under N_2, 1.40 g (.048 mole) 4,6-dibromo-1,3-dihydroxy benzene (80) was dissolved in a solution of 25 ml. EtOH (95) containing $(CH_3)_2SO_4$, 2.00 g. (.159 mole). KOH, o.885 g. (.158 mole dissolved in 10 ml. H_2O was added dropwise at room temperature and repeated in 30 minutes. The mixture was refluxed for 3 hours, cooled in an ice-bath, and the pro-

duct filtered. After washing with H_2O, the crude material was dried and recrystallized from methanol-H_2O, yield: 1.06 g. (.033 mole, 68.8%). m.p. 62-3°. n.m.r. ($CDCl_3$): 2.25 ($CH_3Ar(OCH_3)$, s, 3), 2.55 ($CH_3Ar(Br)$, s, 3), 3.75 (OCH_3, s, 6). Anal. calcd. for $C_{10}H_{12}O_2Br_2$ (mol. wt. 324), C, 37.07; H, 3.73; Br, 49.32. Found (m/e = 324), C, 37.00; H, 3.71; Br, 49.10.

3,5-Dimethoxy-1,4-Dimethylbenzene (83)

2,6-dibromo-3,5-dimethoxy benzene, 1.06 g. (3.27 mmole), dissolved in 8 ml. anhyd. benzene was added dropwise at 0° to a solution of 28.7 g. 70% "Redal" solution (.100 mole) in benzene. The reaction mixture was raised to room temperature and refluxed for 24 hour. The mixture was cooled, hydrolyzed at 0° with dilute hydrochloric acid, diluted with ether, washed with H_2O, dried ($MgSO_4$), and evaporated.

The residue was refluxed with Ac_2O (23 ml.) and pyridine (4 ml.) for 1 hour, cooled to room temperature, and 100 ml. ether added. The reaction mixture was washed with 10% HCl and with H_2O. The water layer was washed with ether and combined ether solutions were washed with $NaHCO_3$ (saturated) solution. The solution was dried ($MgSO_4$) and ether and product were distilled in vacuo, yield: 255 mg. (1.54 mmole, 47%). b.p. 60-5° (.7 mm).

1,4-Dimethyl-2,3,5-triacetoxybenzene (92)

Compound 92 was prepared according to Sonn's procedure (549). Yield: 42%. m.p. 109-110. n.m.r. ($CDCl_3$): 1.95 (CH_3-Ar(OAc), s, 3), 2.15 (CH_3-Ar$(OAc)_2$, s, 3), 2.30 (CH_3CO_2,

s, 9), 6.85 (ArH, s, 1). Anal. calcd. for $C_{14}H_{15}O_6$ (mol. wt. 280), C, 59.99; H, 5.75. Found: (m/e = 280); C, 60.20; H, 5.62.

1,4-Dimethyl-2,3,5-Trihydroxybenzene (93)

(Sonn's "p-Xylo-Oxy-Hydrochin-Diacetat" (542))

Triacetate, 400 mg., (1.43 mmole) dissolved in 2 ml. EtOH(95) was treated with 1 ml. 1.43M HCl/H_2O. The mixture was refluxed for 4.3 hours. Solvent was evaporated and the residue was recrystallized from Et_2O-30/60 pet. ether to yield 193 mg. 1,4-dimethyl-2,3,5-trihydroxy benzene (93) (87%, 1.25 mmole) m.p. 154-5°. n.m.r. ($CDCl_3$): 1.98 ($CH_3Ar(OH)$, s, 3), 2.08 ($CH_3Ar(OH)_2$, s, 3), 3.20 (Ar-OH, s, 3), 6.00 (Ar-H, s, 2). Anal. calcd. for $C_8H_{10}O_3$ (mol. wt. 154): C, 62.32; H, 6.54. Found: (m/e = 154); C, 61.52; H, 6.52.

2,6-Dimethoxy 4-Methyl Benzaldehyde (84)

3,5-Dimethoxy-1,4-dimethylbenzene, 83, (797 mg., 4.8 mmole) was dissolved in 100 ml. 50% HOAc-H_2O at room temperature and the solution cooled to 5°. Ceric (IV) ammonium nitrate (14.8 g., 27 mmole) dissolved in 75 ml. H_2O was chilled to 10° and added to the first solution dropwise with vigorous stirring. A blue colour was formed approximately halfway through the addition. The total time for addition was 6 minutes. The reaction was then allowed to come to room temperature, extracted with ether, which was in turn washed with $NaHCO_3$ (saturated) solution, then water, dried ($MgSO_4$), and evaporated. The aldehyde was eluted from a column (silica) with ether. Yield: 366 mg. (2.03 mmole, 42%). m.p. 90-91° n.m.r ($CDCl_3$): 2.40 (Ar-CH_3, s, 3), 3.90

(OCH_3, s, 6), 6.40 (Ar-H, s, 2), 10.40 (CHO, s, 1). ν_{max} (KBr): 1680 cm^{-1}. Anal. calcd. for $C_{10}H_{12}O_3$ (mol. wt. 180): C, 66.65; H, 6.71. Found: (m e = 180): C, 66.50; H, 6.70. Comparison of n.m.r obtained andthat previously reported (584) led to assignment of structure (84) to the product.

1-(2,6-Dimethoxy 4-methyl Phenyl) 2-Nitro 1-Propene, 62

(R = 2,6-DiMeo, 4-Me)

2,6-Dimethoxy 4-methyl benzaldehyde (84) (366 mg, 2.07 mmole) was dissolved in 2.5 ml. nitroethane. Ammonium acetate (230 mg., 2.99 mmole) was added. The mixture was refluxed 5 minutes, quenched by cooling in liquid N_2, CH_2Cl_2 (5 ml.) added and the ammonium acetate filtered while cold. The filtrate was evaporated and the residue recrystallized from methanol-H_2O to yield the product, 439 mg (1.85 mmole, 81%). m.p. 123-4° n.m.r ($CHCl_3$): 2.10 (CH_3C, s, 3), 2.40 (CH_3Ar, s, 3), 3.85 (CH_3O, s, 6), 6.40 (ArH, s, 2), 7.95 (olefinic H, s, 1). ν_{max}: 1590 cm^{-1} (C=C). Anal. calcd. for $C_{12}H_{15}O_4N$ (mol. wt. 237), C, 60.75; H, 6.37; N, 5.90. Found: (m /e = 237); C, 60.70; H, 6.35; H, 5.85.

1-(2,6-Dimethoxy 4-methyl Phenyl) 2-Amino Propane (76)

1-(2,6-Dimethoxy 4-methyl phenyl) 2-nitro 1-propene, 62, (R = 2,6-DiMeO, 4-Me) 439 mg was dissolved in 10 ml anhyd. benzene and added dropwise at room temperature to 3.13 g 70% solution "Redal" in benzene (8 mmole) (diluted with 12 ml. benzene) over 3 minutes. The mixture was refluxed for 2 hours, cooled, and hydrolyxed with H_2O. The salts were filtered and the benzene dried ($MgSO_4$). Evaporation and distillation (95-100°, .9 mm) gave 237 mg product (1.13 mmole, 61%). n.m.r. ($CDCl_3$): 1.05 (CH_3, d, 3), 1.85 (NH_2, broad s, 2), 2.35 (Ar-CH_3, s, 3),

3.70 (OCH_3, s, 6), 6.27 (Ar-H, s, 2). ν_{max} (KBr): 3450 cm^{-1} (NH_2). Anal. calcd. for $C_{12}H_{19}NO_2$ (mol. wt. 209): C, 68.87; H, 9.15; N, 6.69. Found: (m/e = 209): C, 68.70; H, 9.08; N, 6.65.

3,5-Dimethoxy-4-Methylbenzaldehyde (88)

3,5-Dimethoxy-4-methyl-benzoyl chloride, obtained in 57% yield in the manner of Cason and Herzburg (577), was subjected to a modified Rosenmund reaction (549) (46%) as well as lithium tri-t-butoxy aluminum hydride after Brown (579)(30%). (Anal. data p.114)

3,5-Dimethoxy-4-Methylbenzyl Alcohol (87)

3,5-Dimethoxy 4-methyl-benzoic acid (86a) (100 mg., .510 mmole) was dissolved in anhyd. THF (10 ml.) and added to a slurry of 114 mg. lithium aluminum hydride (3 mmole)/20 ml. anhydrous THF at ambient temperature. The reaction mixture was stirred at room temperature for 16 hours (24°), hydrolyzed with H_2O, the mixture extracted with ether and dried ($MgSO_4$). Solvent was distilled in vacuo and the acid was silica column chromatographed (ethyl acetate). Yield was 70 mg. m.p. 86-8°. (.384 mmole, 75%). n.m.r ($CHCl_3$): 2.00 (CH_3Ar, s, 3), 3.70 (OCH_3, s, 6), 4.50 (CH_2, s, 2), 6.40 (Ar-H, s, 2). ν_{max} (KBr): 3500 cm^{-1} (OH). Anal. calcd. for $C_{10}H_{14}O_3$ (mol. wt. 182): C, 65.91; H, 7.74. Found: (m/e = 182); C, 65.85; H, 7.70.

3,5-Dimethoxy 4-Methylbenzaldehyde (88)

Attenburrow's MnO_2 4.00 g (552-555) was added to a solution of 450 mg. (2.47 mmole) 3,5-dimethoxy-4-methyl-benzylalcohol in 20 ml. anhyd. benzene. The mixture was refluxed for five

hour (apparatus equipped with a Dean-Stark trap), filtered (Celite), and evaporated. Distillation (120°, .7 mm) and recrystallization for cyclohexane gave 320 mg product (1.78 mmile, 72%). m.p. 75-6°. n.m.r. ($CDCl_3$): 2.25 (CH_3-Ar, s, 3), 3.80 (CH_3O, s, 6), 6.95 (Ar-H, s, 2), 9.60 (CHO, s, 1). ν_{max} (KBr): 1700 cm^{-1} (C=O). Anal. calcd. for $C_{10}H_{12}O_3$ (mol. wt. 180): C, 66.65; H, 6.71. Found: (m/e = 180): C, 66.50; H, 6.65.

1-(3,5-Dimethoxy-4-Methyl phenyl)-2-Nitro-1-Propene (62)

(R = 3,5-DiMeO 4-Me)

3,5-Dimethoxy-4-methyl benzaldehyde (320 mg, 1.78 mmole) (88) was dissolved in a solution of 171 mg. (2.22 mmole) ammonium acetate and 2 ml. nitroethane and refluxed for 5 minutes. The reaction was quenched by cooling in liquid N_2, CH_2Cl_2 added, NH_4OAc filtered, and solvent removed in vacuo. The crude product was recrystallized from methanol-water. Yield: 300 mg (1.05 mmole, 71%). m.p. 119-20°. n.m.r ($CDCl_3$): 2.10 (CH_3C, s, 3), 2.50 (CH_3Ar, s, 3), 6.65 (ArH, s, 2), 7.95 (olefinic H, s, 1). ν_{max}: 1590 cm^{-1} (C=C). Anal. calcd. for $C_{12}H_{15}NO_4$ (mol. wt. 237): C, 60.75; H, 6.37; N, 5.90. Found: (m/e = 237): C, 60.60; H, 6.32; N, 5.89.

1-(3,5-Dimethoxy-4-Methyl phenyl)-2-Amino propane (75)

1-(3,5-Dimethoxy-4-methyl phenyl)-2-nitro-1-propene, 62, (R = 3,5-DiMeO 4-Me) (100 mg., .422 mmole) in 2 ml. THF was added to a slurry of lithium aluminum hydride (80.1 mg, 2.11 mmole) in 10 ml. THF at 0°. The mixture was allowed to come to room temperature, then refluxed for 3 hours. After cooling

in ice, the mixture was hydrolyzed with H_2O and filtered with suction. The hydroxides were slurried in ether and filtered. The combined ethereal filtrates were dried ($MgSO_4$) and evaporated. The amine was vacuum distilled (95-100°, .1 mm) to yield 56.5 mg product (.270 mmole, 64%). n.m.r. ($CDCl_3$): 1.10 (CH_3CH, d, 3), 1.90 ($CHCH_2$, m, 3), 2.15 ($ArCH_3$, s, 3), 3.80 (CH_3O, s, 6), 6.50 (ArH, s, 2). ν_{max}: 3500 cm^{-1} (NH_2). Anal. calc. for (as free amine) $C_{12}H_{19}NO_2$ (mol. wt. 209): C, 68.87; H, 9.15; N, 6.69. Found: (m/e = 209): C, 68.84; H, 9.12; N, 6.50. T.l.c. (silica gel GF-254) $CHCl_3$: CH_3OH: NH_4OH (conc) 80:20:1, R_f = .45, and g.l.p.c. on 3% OV-17/gas chrom Q (220°) both showed a single component.

1-(3,5-Dihydroxy-4-Methyl phenyl)-2-Amino propane (74)

1-(3,5-Dimethoxy-4-methyl phenyl) 2-amino propane (56.4 mg, .270 mmole) (75) was refluxed with 47% HI (.810 mmole) for 3 hour under N_2. The reaction mixture was evaporated, the residue purified by silica column chromatography (MeOH) under N_2 and recrystallized from methanol-ether to yield 20.4 mg (.113 mmole, 42%). m.p. 225-27° n.m.r (DMSO-d_6): 1.10 (CH_3CH, d, 3), 2.15 ($ArCH_3$, s, 3), 3.87 (OH, s, 2), 6.49 (Ar-H, s, 2). ν_{max}: 3500cm^{-1} (NH_2, OH). Anal. calcd. for (as free amine) $C_{10}H_{15}NO_2$ (mol. wt.181): C, 66.27; H, 8.34; N, 7.72. Found: (m/e=181): C, 66.20; H, 8.31; N, 7.68. T.l.c. (Silica Gel GF-254) $CHCl_3$: CH_3OH; NH_4OH (conc) 80:20:1, R_f = .65, and g.l.p.c. on 3% OV-17/Gas chrom Q (220°) as Trisil Z derivative both showed a single component.

3,5-Dimethoxy-4-Methyl Benzoyl Hydrazide (100)

3,5-Dimethoxy-4-methyl benzoyl chloride (125 mg., .584 mmole) was dissolved in 2 ml. anhyd. ether. Hydrazine 99-100%, 500 mg. (10 mmole) mixed with 2 ml. anhyd. Et_2O was added dropwise with stirring at ambient temperature. Stirring was continued 2 hour, the mixture was evaporated (vacuum pump) and recrystallized (EtOH H_2O). Yield: 122.6 mg (.584 mmole, 100%). n.m.r (DMSO-d_6): 2.05 (CH_3Ar, s, 3), 3.80 (CH_3O, s. 6), 7.13 (ArH, s, 2), 6.00 ($NH-NH_2$, broad s, 3). ν_{max} (KBr): 1700 cm^{-1} (C=O). Anal. calcd. for (mol. wt. 210: C, 57.14; H, 6.71; N, 13.31. Found: (m/e = 210); C, 57.00; H, 6.70; N, 13.31.

Nitroethane

Ethyl iodide (3.12 g, .02 mole) freshly distilled was stirred in an ice bath at 0° C. Small portions of vacuum dry $AgNO_2$ (3.08 g., .02 mole) prepared as described (579) were dropped in. The internal temperature rose to 16° C. The reaction mixture was left overnight (12 hr.) in a cold water bath at 15° C and distilled at atmospheric pressure (739 mm). First fraction (70-75° C) (ethyl iodide 1.84 g.) and second fraction (108-115° C). (nitroethane, 570 mg) were collected. Yield: 38% (95% conversion).

Ozonolysis of Isosafrole, 51 (R = 3,5-Methylenedioxy)

Isosafrole (8.44 g., 52 mmole) was dissolved in 150 ml. anhyd. $CHCl_3$, cooled to -20° (CCl_4/dry ice). Ozone was bubbled through at 1.5 l./min. (calibrated for 1.2 mol./hour O_3), for 4.5 hours (positive starch-iodide test). The chloroform was

evaporated in vacuo and the ozonide residue quickly steam distilled. The piperonal was collected by filtration and vacuum distilled to yield 6.64 g., 85%.

Reaction of Isosafrole with Nitrosyl Chloride (94)

Isosafrole (162.2 mg., 1 mmole) was dissolved in 2 ml. CCl_4 cooled to -10° C. A 15% solution of NOCl, 2 ml., in CCl_4 was added with stirring. The temperature rose from -10° to 0° and a white precipitate formed immediately. Filtration yielded 156.3 mg. (.34 mmole) (m/e = 454). The compound was insoluble in $CHCl_3$, CCl_4, DMSO, H_2O, Et_2O, and soluble in hot benzene, cold toluene and cold THF. No movement was observed with THF on silica gel t.l.c. (GF-254).

Lithium Aluminum Hydride Reduction of (94)

Adduct (94) (500 mg., 1.10 mmole) was reduced by the Soxhlet method of Ramirez and Burger (368) over 18 hours. Hydrolysis with H_2O (pH 10), extraction with ether, drying ($MgSO_4$), and evaporation gave 329.1 mg. brown oil. T.L.C. (Silica GF-254), 1:2 acetone-1,2-dichloro ethane, R_f = 8.10 and 6.20.

1-(3,4-Methylenedioxyphenyl)-2-Propanone, 49 (R = 3,4-methylenedioxy)

$PdCl_2$ (.248 mg., 1.4 mmole) and $CuCl_2$ (1.98 g., 14.7 mmole) were dissolved in 50 ml. H_2O and heated to 54°. A stream of air 30 ml/min. was passed through and 1 g. (6.17 mmole) isosafrole was added. The reaction was allowed to proceed for 2.5 hours after which time the mixture was cooled and extracted with ether. The ketone distilled at 108-110° (2 mm), yield: 549 mg. (3.09 mmole, 50%). n.m.r. ($CDCl_3$): 2.10(CH_3, s, 3), 3.52 (CH_2, s,

2), 5.88 (OCH_2O, s, 2), 6.60 (Ar-H, s, 2), 6.63 (Ar-H, s, 1) (m/e = 178).

1-(3,4-Methylendioxyphenyl)-2-Nitro Propene, 51 (R = 3,4-Methylene-dioxy)

Isosafrole (1.62 g., .01 mole) was dissolved in a mixture of 750 mg pyridine and 9.0 g dry acetone (over $MgSO_4$) and cooled to -4° C with vigorous stirring, $C(NO_2)_4$ (Aldrich) (1.9 g, .01 mole) was added over a period of 1 minute and stirring was continued for an additional 2 minutes, at which time the reaction was quenched by addition of .56 g KOH in 10 ml H_2O. The mixture was allowed to come to room temperature and was extracted with CH_2Cl_2. The CH_2Cl_2 was washed with 5% HCl and with H_2O, dried ($MgSO_4$) and evaporated. Recrystallization from CH_3OH-H_2O gave 1.84 g (8.9 mmole, 89%).

$AgNO_2$ (579) (2.96 g, 19.2 mmole) and I_2 (9.75 g, 38.4 mmole) were stirred in ether (75 ml) under a nitrogen atmosphere for 30 min. and isosafrole (3.11 g, 19.2 mmole) added. The mixture was stirred for 5 hours at room temperature (23° C). 1.52 g, 19.2 mmole pyridine was added and the mixture stirred for an additional hour. Upon evaporation, the oil was taken up in 10 ml of CH_2Cl_2. After filtering, the CH_2Cl_2 was washed with thiosulfate solution, 5% HCl, H_2O and the solution finally dried ($MgSO_4$). Column chromatography (SiO_2), evaporation, and recrystallization from methanol-water gave 1.39 g product (6.72 mmole, 35%). m.p. 92-94°. n.m.r ($CDCl_3$): 2.45 ($CH_3C=$, s, 3), 6.05 (OCH_2O, s, 2), 6.95 (Ar-H, s, 3), 8.00 (olefinic, s, 1) (m/e = 207).

Potassium Enolate of 1-(3,5-Dimethyl-4-Methoxyphenyl)-2-nitro 1-propanone (96)

Potassium, 1.75 g (.045 g-atom) was dissolved by heating t-BuOH (110 ml, 88.5 g, 1.20 mole) in a N_2 atmosphere to make a 3.75% potassium-t-butoxide/t-butanol solution. The solution was cooled to 17° in a water bath and 1.48 g (.008 mole) 1-(3,5-dimethyl-4-methoxyphenyl)-1-propanone (53) (R = 3,5-DiMe 4-MeO, R' = CH_3) was dissolved in it. n-Butylnitrate (3.1 ml, 2.8 g, .027 mole) was added with stirring in a 5 minute period. A yellow precipitate formed after 10 min. stirring. The reaction was then allowed to stand at ambient temperature (24° C) for 1 hour, cooled in ice and filtered. Yield: 2.21 g (.008 mole, 100%). m.p. 238-240° d.

1-(3,5-Dimethyl-4-methoxyphenyl)2-nitro propanone (97)

The potassium enolate (96), 275 mg (.001 mmole) was added with stirring to 5 ml. 10% HCl. The reaction mixture was stirred at ambient temperature (23°) for 3 hours, cooled in ice and filtered yielding 189 mg product (8.01 mmole) (80%).

Potassium enolate (96) (25 mg, .09 mmole) was added with stirring to 5 ml. glacial acetic acid and the mixture was stirred at ambient temperature (22° C) for 3 hour. 35 ml H_2O was added and the solution extracted with $CHCl_3$. The $CHCl_3$ was extracted with H_2O and dried ($MgSO_4$). Vacuum distillation of $CHCl_3$ and HOAc gave 20 mg. product (.084 mmole, 84%). n.m.r. (DMSO-d_6): 2.00 (CH_3C, s, 3), 2.20 (CH_2-Ar, s, 6), 3.65 (CH_3O, s, 3), 6.89 (Ar-H, s, 2). ν_{max} (KBr):1700 cm-1 (C=O). Anal. calcd. for (mol. wt. 237): C, 60.75; H, 6.37; N, 5.90. Found:(m/e = 237);

C, 60.30; H, 6.32; N, 5.08.

Cleavage of Potassium Enolate of 1-(3,5-Dimethyl-4-Methoxyphenyl) 2-Nitro-1-Propanone (96)

Potassium enolate (96) (275.3 mg, 1.00 mole) and Ac_2O (5 ml.) were heated to dissolution and poured over ice. Extraction with $CHCl_3$, drying ($MgSO_4$) and evaporating gave 171.1 mg. crude product. Column chromatography (silica) with $CHCl_3$ as eluant gave 170 mg. (.944 mmole, 94%) 3,5-dimethyl 4-methoxy benzoic acid, m.p. 158-160° (recrystallized from acetone).

Cleavage of 1-(3,5-Dimethyl-4-Methoxyphenyl)-2-Nitro 1-Propanone (97)

1-(3,5-Dimethyl-4-methoxyphenyl)-2-nitro 1-propanone (51) (R = 3,5-DiMe 4-MeO) (15 mg., .063 mmole), was dissolved in 7 mg. (.069 mmole) acetic anhydride mixed with 1 mg. pyridine. The mixture was stirred at ambient temperature (25° C.) for 5 hours, and worked up as above. 3,5-Dimethyl 4-methoxy benzoic acid (7 mg., .039 mmole, 62%), m.p. 158-160°, was recovered. n.m.r. ($CDCl_3$): 2.30 (CH_3-Ar, s, 6), 3.75 (CH_3O, s, 3), 7.80 (Ar-H, s, 2), 10.64 (CO_2H, s, 1) (m/e = 180).

Phenyl-2-Propanone Oxime (50, R = H)

Hydroxylamine hydrochloride (1.39 g, .02 mole) was dissolved in .5 cc H_2O heated to 125°C in an oil bath. Phenyl-2-propanone (1.34 g., .01 mole) was added with stirring. The mixture was maintained at 125° for 5 minutes. Cooling, extraction with warm $CHCl_3$, drying ($MgSO_4$) and evaporation furnished 1.05 g. oxime (.007 mole, 70%). (m/e = 149) m.p. 68-70°.

1-Phenyl-2-Propane (48, R = H)

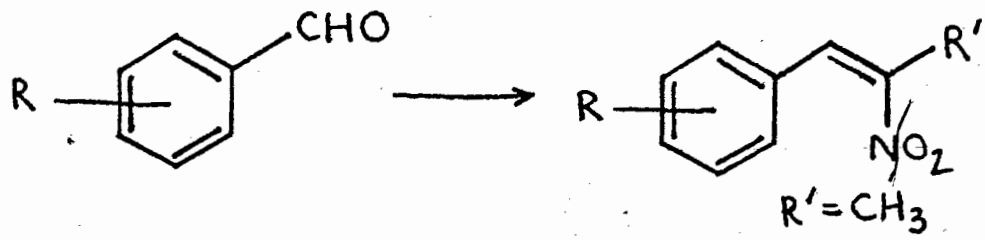
$LiAlH_4$ reduction of 50 (R = H) gave 1-phenyl-2-amino propane 48 (R = H), according to the method of Larsson (580). Yield: 65%, m.p. (HCl salt) 145-147°.

1-Amino-4-Phenyl phthalazine (101)

Methyl benzoate (99) (362 mg., 2.66 mmole) was added to 173 mg. (3.40 mmole) hydrazine hydrate and the mixture refluxed for 2.5 hours. The reaction was cooled, 5 ml. 50% H_2SO_4 added at 0°, the mixture filtered and the crude material washed with H_2O. The crude phthalazine was taken up in ether and eluted from a column (silica) with ether:hexane (3:2). Upon evaporation and recrystallization from CH_3OH-H_2O, 100 mg. (.518 mmole, 19%), of 1-amino 4-phenyl phthalazine remained, m.p. 200-201. lit. m.p. 201-202 (574). n.m.r. ($CDCl_3$): 6.94 (NH_2, s, 2), with D_2O 4.50 (NH_2, broad s, 2), 7.35-8.20 (Ar-H, m, 9). UV (EtOH) λ_{max} = 210 (ε = 43,500), 314 (ε = 10,020). Anal. calcd. for $C_{14}H_{11}N_3$ (mol. wt. 221): C, 76.00; H, 5.01; N, 18.98. Found: (m/e = 221); C, 75.06; H, 5.19; N, 15.83.

TABLE 4

Knoevenagel Condensations Substituted Benzaldehydes and Nitroethane (369).



R	Yield	Reflux (min)
3,5-dimethyl 4-hydroxy	81	10
3,5-dimethyl 4-methoxy	88	5
2,6-dimethoxy 4-methyl	85	6
3,5-dimethoxy 4-methyl	82	5
2,5-dimethoxy 4-bromo	80	7

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