LIST OF CONTRIBUTORS

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Preface

      While excellent reviews in depth covering selected fields of medicinal chemistry are available, no publication outlines the current developments and trends in the whole area. The present volume is the first of a planned annual publication in which more than thirty authors present a critical summary of new and significant contributions appearing in the literature of the past year concerning various fields of medicinal chemistry. Its main purpose is to enable readers to "catch up" in fields of their peripheral interests and, perhaps, to find some different views in fields of their major interests.

      The breadth of the subject and limitations of space presented to the authors a very difficult task of selection of material and condensation of discussion. Recent reviews and leading references are cited to guide readers to further information if desired. Topics were chosen to achieve reasonable coverage, but a few chapters initially listed had to be postponed to future volumes. Organization of the material is primarily by pharmacological action, although some chapter titles represent concepts, chemical classes, methods, etc. The manner of presentation varies, as is to be expected from the various disciplines of the authors, the nature of the subjects and the lack of a previous volume to serve as a model.

      I know of no adequate way to express my thanks for the cheerful, enthusiastic and dedicated efforts of all who were involved in this undertaking. Especially to be mentioned are the section editors and the chapter authors, but secretaries, proof-readers, assistants and all who supplied moral support and encouragement should not be forgotten.

      Comments, criticisms, suggestions and, hopefully, praise will be welcomed by authors and editors.

Fort Washington, Pa.   Cornelius K. Cain
June, 1966

Section I - CNS Agents
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Chapter 1. Antipsychotic and Anti-anxiety Agents
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   Most basic biological work concerned with CNS agents that was reported in 1965 falls into the biochemical area. The belief that the antipsychotic drugs function through some interference with adrenergic processes in the brain is widely accepted. Reserpine, for example, is known to deplete the brain of its stores of catecholamines whereas chlorpromazine has a central adrenolytic action. Although the antipsychotic agents can be shown to inter- fere with the brain amines, the causal relationship between the changes and the behavioral effects is less clear. The mode of action of the anti-anxiety drugs remains unknown.

   A symposium on catecholamines held in Milan in 1965 and recently published[1] does much to clarify present views of their role in the central nervous system. Other reviews on the biochemical effects of drugs acting on the central nervous system and on the pharmacology of the central nervous system were prepared by Decsi[2] and by Bradley.[3] More detailed reviews on serotonin[4] and γ-aminobutyric acid[5] appeared. These papers provide excellent background for any fundamental consideration of the CNS drugs.

   If the brain amines are conceded to play a crucial part in the function- ing of the central nervous system, some disorder in the supply, action or disposal of these agents might be responsible for abnormal behavior. Gellhorn[6], for example, has hypothesized that a disturbance in the noradrena- line/adrenaline ratio forms a neurophysiological basis for fear and anxiety. The suggestion that toxic substances in the brain might be responsible for schizophrenia is an old one and the search for a faulty metabolic process in schizophrenics has remained a popular pursuit. Bourdillon[7] has recently reemphasized the finding of a "pink spot," probably 3,4-dimethoxyphenethyl- amine, in the urine of schizophrenics. Work by Ernst[8] supports the possibility of an abnormal metabolism of dopamine to 3,4-dimethoxyphenethylamine in schizophrenia. He studied the structure-activity relationships of a group of methoxylated phenethylamines in the production of catatonia in cats. He found the presence of a p-methoxy group and the absence of m-hydroxy group to be required with the duration of action determined by the number of methoxy groups in the molecule. Prior treatment with iproniazid eliminated the requirement for the absence of a m-hydroxy group. The blocking of the amino- oxidase resulted in m-methylation by O-methyltransferase. A behavioral study[9] of this compound in the dog and cat also indicates some relationship to schizophrenia.

   Woolley and Gommi[10] have detected in the blood of schizophrenics a substance that is synergistic with serotonin in its action on the rat uterus and are studying the possibility of a causal relationship to the mental disorder.

   An excellent review[11] on biochemistry and mental function has been published by Kety who has also republished his 1959 review[12] criticizing some

of the methodology involved in finding the "needle-in-the-haystack" that might explain the causes of schizophrenia. Six rejoinders from other scientists are included.

Most of the compounds cited below were tested by two general methods: 1) the study of animal behavior following drug treatment in experimental models designed to mimic a clinical situation (conflict, avoidance, etc.) and 2) the measurement of classical pharmacological reactions caused or modified by the agent under test (anticonvulsant, antiemetic, etc.). These methods have been collected in a recent Hahnemann symposium volume.[13] The testing of the anti-psychotic compounds has been reviewed by Janssen, et al.,[14] who rely strongly upon the production of catalepsy and the antagonism of the emetic effect of apomorphine for predicting the clinical response. In fresh work on test methods, Marriott and Spencer[15] have observed that the anti-anxiety agents increase exploratory behavior in inexperienced rats whereas the antipsychotic compounds reduce such activity. The use of a treadmill in approach and avoidance studies of anti-anxiety compounds has been described by Gluckman.[16] A criticism of some of the behavioral tests used for evaluating anxiety in animals has been made by Ray.[17] The electronencephalographic effects of the psychotropic agents have been reviewed.[18]
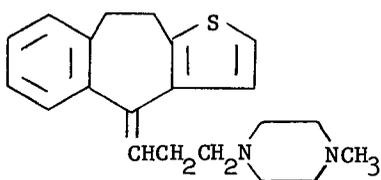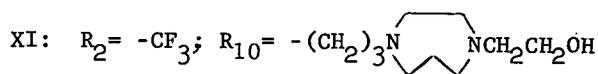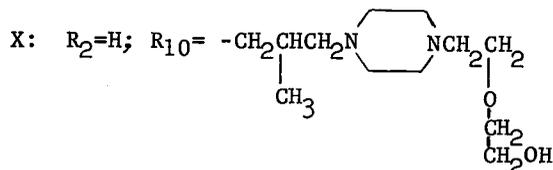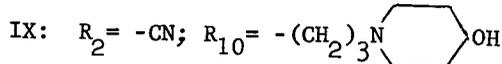
Methods of clinical study of psychotropic drugs have also been discussed and criticized.[19,20]

Phenothiazines and Analogs - Chemical work directed toward modification of the phenothiazine drugs is presently characterized by the preparation of novel tricyclic systems to which the common basic side chains can be attached. Variation of the central ring is most frequent but the peripheral rings are attracting some attention.

A group of compounds having a seven-membered central ring has been described by Stille, et al.[21,22] The synthesis of the intermediate lactams was accomplished by ring closure of the appropriate isocyanates.[23] The most active of these compounds is the oxazepine (I) which is approximately equipotent with haloperidol in cataleptic and antiapomorphine effects. In a more extensive study of the thiazepine analog (II, clothiapine) an intense anti-serotonin effect was measured in the paw-edema test, thus differentiating it from chlorpromazine. It is noteworthy that opening of the piperazine ring as in compound III practically eliminates activity.

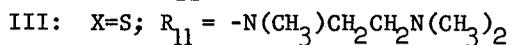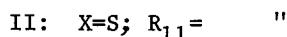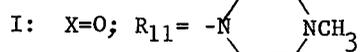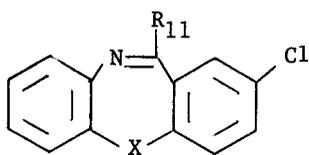The Czech group led by Protiva prepared a host of compounds containing seven-membered rings. Two of these having good central depressant effects are IV (octoclothepine) and V.[24] Compound IV which has antiserotonin and antihistamine activities as well, is about three times as strong in its central depressant effects as its unchlorinated analog. The compounds were prepared conventionally from the corresponding dibenzothiepinone which, in turn, resulted from ring closure of the requisite o-phenylthiophenylacetic acid.[25]

Reports have been made on several thioxanthene derivatives: VI (thiothixene),[26,27] VII (SKF 10812),[28,29] and VIII (N-7009).[30] Each was indicated to be effective in the treatment of psychotic states. Thiothixene was said to cause only a low incidence of extrapyramidal symptoms.

I: X=O; R_{11}= -N(piperazinyl)NCH_3

II: X=S; R_{11}=   "

III: X=S; R_{11} = -$N(CH_3)CH_2CH_2N(CH_3)_2$

IV: R_{10}= -N(piperazinyl)NCH_3

V: R_{10}= -$OCH_2CH_2N(CH_3)_2$

$CHCH_2CH_2R$

VI: R_2= -$SO_2N(CH_3)_2$; R= -N(piperazinyl)NCH_3

VII: R_2= -CF_3; R= -$N(CH_3)_2$

VIII: R_2= -CF_3; R= -N(piperazinyl)NCH_2CH_2OH

IX: R_2= -CN; R_{10}= -$(CH_2)_3N$(piperidinyl)OH

X: R_2=H; R_{10}= -CH_2CHCH_2N(piperazinyl)$NCH_2CH_2OCH_2CH_2OH$ with CH_3 branch

XI: R_2= -CF_3; R_{10}= -$(CH_2)_3N$(homopiperazinyl)NCH_2CH_2OH

$CHCH_2CH_2N$(piperazinyl)NCH_3

XII

SCH_3 with O ($\downarrow$)

CH_2CH_2 piperidine with CH_3

XIII

Propericiazine (IX)[31] has been tried in psychopathic patients having severe behavioral disorders with fair success and dixyrazine (X)[32] has been found effective in anxiety associated with autonomic disturbances. Compound XI,[33] available in Europe, is a homolog of fluphenazine. Although it produces catalepsy it does not have antiemetic properties.

Neuroleptic activity has been reported for XII[34] which has a novel ring system.

A metabolite of thioridazine has been identified as XIII and shown to have a much lower neuroleptic potency than its parent.[35] Since there was some suggestion of activating properties (suppression of the tetrabenazine syndrome in rabbits, potentiation of serotonin fever and central anticholinergic activity) it was tested clinically as antidepressant agent with negative results.[36] However the activity in schizophrenia seems to be good.

In the continuing study of the metabolism of chlorpromazine, 2-chloro-phenothiazine and 2-chlorophenothiazine 5-oxide have now been identified in human urine.[37]

Butyrophenones - None of the fluorobutyrophenone compounds is at present in use in the United States although they are extensively used in Europe. The recent review by Haase and Janssen is a useful summary of these compounds.[38] An extension from their use in psychiatry to use in surgical procedures for producing analgesia is underway.[39,40] The appearance of several clinical studies[41] on the psychiatric use of trifluperidol indicates the prospect of its future availability for treatment of schizophrenia. There are some reports of its especial value in paranoid schizophrenia.[42]

Pharmacological and clinical data on compound XIV[43] show it to resemble haloperidol except for the addition of an antireserpine effect. A homolog of XIV (XV)[44] has also been studied but was found to have troublesome side-effects. Both of these products are somewhat related to XVI[45] which, although having an effective antipsychotic action, caused cataracts and disturbances of cholesterol balance.

A group of fluorobutyrophenones derived from 4-aminopiperidines has been described.[46] The treatment of 1-benzyl-4-t-aminopiperidine-4-nitriles with Grignard reagents effected displacement of the cyano group whereas organo-lithium reagents reacted with the cyano function to afford ketones. Subsequent debenzylation and alkylation gave the corresponding fluorobutyro-phenones. These compounds are less active than haloperidol in apomorphine antagonism but are more potent in countering morphine-induced mania in cats. The most potent of these preparations is XVII.

A strong neuroleptic of long duration related to the butyrophenones has recently been reported.[47] Compound XVIII antagonizes the effect of apomorphine for as long as 100 hours.
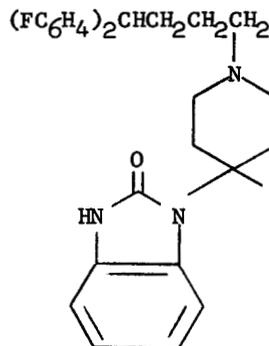
F〈〉-COCH$_2$CH$_2$CH$_2$N〈〉R$_1$R$_2$
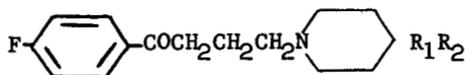
XIV: R$_1$= -CH$_3$; R$_2$= -H

XV: R$_1$=R$_2$= -CH$_3$

XVI: R$_1$R$_2$= -CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-

XVII: R$_1$= -COC$_2$H$_5$; R$_2$= -N〈〉

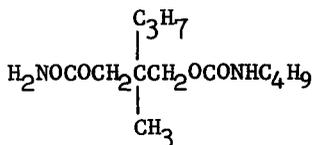(FC$_6$H$_4$)$_2$CHCH$_2$CH$_2$CH$_2$

XVIII

Carbamates - A new carbamate, tybamate (XIX)[48] closely resembling mepro-
bamate in structure and in activity was marketed during 1965. Its potency is
comparable to meprobamate in many tests, yet it has only one-third the potency
of meprobamate in the antipentylenetetrazole test. However, in contrast to
meprobamate, it antagonises the effect of LSD on the electroencephalogram and
has an antiserotonin action. Convulsions are not seen in dogs receiving
tybamate upon abrupt withdrawal of the drug, whereas convulsions do result
upon withdrawal of meprobamate.[49] In the dog tybamate is metabolized by
hydroxylation and/or N-dealkylation.[50] Hydroxytybamate is the principal
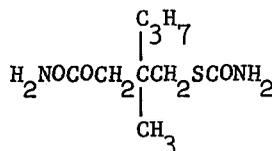metabolite found in the urine.

Several clinical studies have appeared demonstrating effectiveness
against anxiety.[51,52] One report[53] suggested mild stimulant properties, but
in a study with alcoholics no separation from placebo could be made.[54]

A series of meprobamate analogs was prepared containing silicon in place
of the quaternary carbon atom.[55] Each silicon compound is approximately
equivalent to its carbon analog in the rotarod test and in acute toxicity. A
monothiol analog (XX) of meprobamate is also comparable to meprobamate in
potency and toxicity.[56]

A chemical review of the carbamates has been written by Adams and Baron[57]
with some attention to biological activity.

$$H_2NOCOCH_2\overset{\overset{\displaystyle C_3H_7}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}CH_2OCONHC_4H_9$$

XIX

$$H_2NOCOCH_2\overset{\overset{\displaystyle C_3H_7}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}CH_2SCONH_2$$
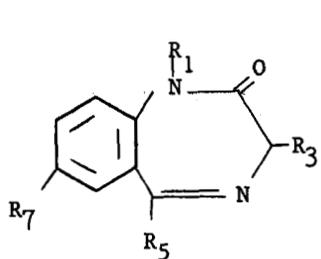
XX

Benzodiazepines - The introduction of oxazepam in 1965 brought to three the number of 1,4-benzodiazepines commercially available in the United States. The animal studies of oxazepam (XXI)[16,58,59] particularly the anticonvulsant and conflict tests, suggested its use as an anti-anxiety agent and clinical studies[60,61] indicated its efficacy for this purpose. Its potency appears to lie between chlordiazepoxide and diazepam. The compound has also been examined as a water-soluble hemisuccinate ester, sodium salt.[62]

In the form of its glucuronide, oxazepam is the principal excretion product in the dog and man of diazepam (XXII) which is also hydroxylated to some extent without N-demethylation.[63,64] In the circulating serum, the most prominent metabolite of diazepam is the unhydroxylated compound XXIII. There is an indication of the presence of further phenolic metabolites whose precise structures are unknown. The metabolism of chlordiazepoxide in the dog and man results principally in the production of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide, but in the rat basic compounds as yet unidentified are produced.[65] Some opening of the lactam ring was observed, but no alteration of the aromatic rings or reduction of the N-oxide function was detected.

Nitrazepam (XXIV)[66,67] has been introduced in Europe and is being promoted as a hypnotic but its activity profile suggests it would be effective against anxiety. A clinical report on a related compound (XXV)[68] indicates a resemblance to diazepam.

Some additions to the list of benzodiazepinones having functional substituents have been made. French workers succeeded in preparing 3-carboalkoxy-benzodiazepinones, e.g. XXVI,[69] by transimidation of the appropriate 2-aminobenzophenone imines with α-aminomalonic esters followed by cyclization. The benzodiazepine esters so obtained were converted to amides and also hydrolyzed to salts of the corresponding carboxylic acids. The ease of decarboxylation upon acidification of these salts suggests that the decarboxylation products may be responsible for the high biological activity. Although the esters and amides have typical benzodiazepine profiles they are not so potent as the carboxylic acid salts which compare favorably with diazepam.
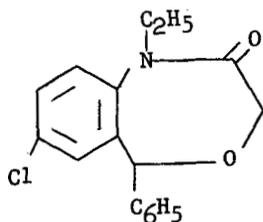
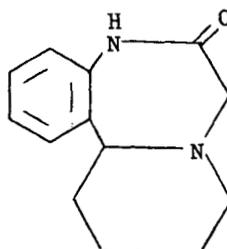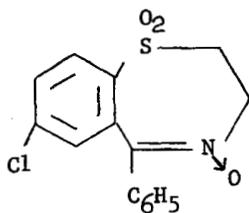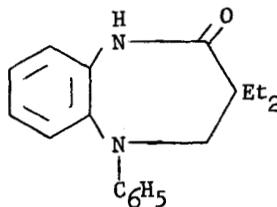|	R_1	R_3	R_5	R_7
XXI:	H	OH	C_6H_5	Cl
XXII:	CH_3	H	C_6H_5	Cl
XXIII:	H	H	C_6H_5	Cl
XXIV:	H	H	C_6H_5	NO_2
XXV:	CH_3	H	$\underline{o}\text{-}FC_6H_4$	Cl
XXVI:	H	CO_2Et	C_6H_5	Cl
XXVII:	$CH_2CH_2N(C_6H_5)_2$	H	$\underline{o}\text{-}FC_6H_4$	Cl
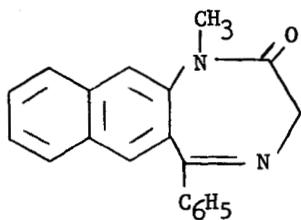
XXVIII
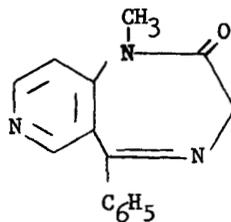
XXIX

XXX

XXXI

XXXII

XXXIII

3-Acetamidobenzodiazepines were prepared by cyclization of 2-(2-acetamido-2-aminoacetamido)benzophenones.[70] A novel elimination of acetic acid from the appropriate 2-(N-acetoxyacetamido)acetamidobenzophenone afforded the intermediate. It was possible to hydrolyze the acetamidobenzodiazepines to the corresponding 3-amino compounds and convert these products into 3-hydroxy compounds by treatment with nitrous acid. The amino and acetamido compounds are merely reported to be active.[71]

Stempel, et al.,[72] achieved a direct synthesis of a 3-chlorobenzodiazepinone 4-oxide by base treatment of 6-chloro-2-dichloromethyl-4-phenylquinazoline 3-oxide. The course of this ring enlargement, which was responsible for the original discovery of chlordiazepoxide, was clarified by the isolation of an intermediate, 2-dichloroacetamido-5-chlorobenzophenone oxime (anti), which slowly cyclized. Cyclization of the monochloroacetyl analog is too fast to permit its isolation. The 3-chloro substituent of the benzodiazepine product reacted conventionally with nucleophiles following removal of the N-oxide function.

A number of benzodiazepinones with functional substituents in the 1-position has been published along with test data.[73] The general structure-activity requirements already described for the benzodiazepines obtain for the 1-aminoalkyl types. The importance of an o-fluoro substituent on the 5-phenyl ring in increasing the potency of the compounds is clear. Compound XXVII is one of the most potent of the group, but it is slightly less potent than diazepam. The activity of the related 1-aminobenzodiazepines prepared by use of chloramine was not given.[74]

Compounds containing a fused naphthalene ring (XXVIII)[75] and a fused pyridine ring (XXIX)[76] have been disclosed. The former types are inactive and the latter are less active than diazepam. Further examples of compounds related to active benzodiazepines, but for which test data are missing, include XXX,[77] XXXI,[78] XXXII[79] and XXXIII.[80]

Miscellaneous Compounds - Investigations on several compounds that do not fall into the above groups were reported. The pharmacology of trimetozine (XXXIV)[81] indicates it to be a tranquillizer without hypnotic or anticonvulsant properties. Compound XXXV[82] has sedative properties approximating chlorpromazine but does not produce catalepsy and ataxia. A disruptive effect on conditioned behavior at very low dosage is seen with the adrenolytic compound XXXVI.[83] Compound XXXVII[84] is less effective than meprobamate against anxiety and it has been shown that poor absorption is not the explanation.[85] The tranquillizing potency of XXXVIII[86] is approximately equivalent to meprobamate.

Taborsky, et al.,[87] have studied the effect of 1-methylation on a group of psychoactive indoles. In general, the effects on behavior of the methylated and unmethylated pairs are similar.

Compound XXXIX,[88] which resembles tetrabenazine in structure, has both stimulant and depressant properties. It blocks conditioned avoidance in rats but the required dose is at least five times that of chlorpromazine. Replacement of the p-chlorophenyl groups by an alkyl or aralkyl group leads to inactive products. A good clinical response in schizophrenics has been noted. A group of 17-haloyohimbanes[89] was examined by observation of the effects on