JOURNAL OF Pharmaceutical Sciences

June 1964 volume 53, number 6

Review Article

1,4-Benzodiazepines

By SCOTT J. CHILDRESS and M. I. GLUCKMAN

THE DISCOVERY of chlordiazepoxide,[1] 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I) (1), which prescription surveys indicate is the most frequently prescribed new drug in the United States, has brought about a considerable amount of work on the chemistry and biological activity of 1,4-benzodiazepines. A second benzodiazepine, 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (II) (2, 3), has been marketed as diazepam.[2] Two other benzodiazepines have been given extensive clinical study: 7-nitro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (III) (LA-1) (4) and 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (IV), oxazepam (5).

These compounds have a wide spectrum of powerful effects on the central nervous system. Chlordiazepoxide and diazepam find their principal use as antianxiety agents with diazepam also recommended as a centrally acting muscle relaxant. Oxazepam is comparable to chlordiazepoxide with diminished side effects. LA-1 has been studied primarily as an anticonvulsant agent (6).

It is the purpose of this review to summarize the chemistry of the 1,4-benzodiazepines and report the structure-activity relationships that can be drawn. The literature has been covered through 1963. No attempt has been made to list clinical material. Patents have not been cited in the presence of a comparable scientific article.

Received from the Research Division, Wyeth Laboratories, Inc., Radnor, Pa.

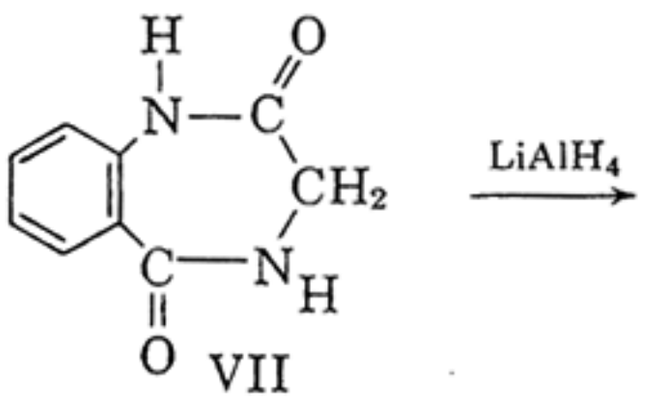
The authors are grateful to Drs. P. B. Russell, S. C. Bell, and T. S. Osdene for their comments on the manuscript.

[1] Formerly methaminodiazepoxide. Marketed as Librium by Roche Laboratories, Nutley, N. J.

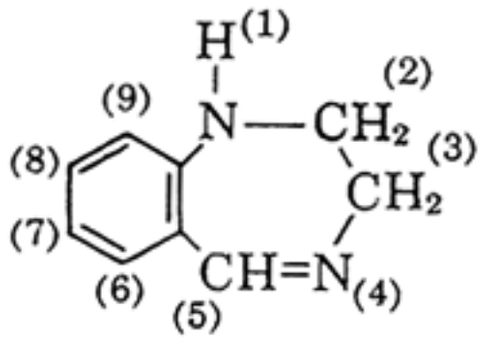
[2] Marketed as Valium by Roche Laboratories, Nutley, N. J.

1,4-BENZODIAZEPINES

Although 1,4-benzodiazepine itself has not yet been prepared, both 2,3-dihydro (V) and 2,3,-4,5-tetrahydro-1*H*-1,4-benzodiazepine (VI) have been obtained by reduction of 3,4-dihydro-2*H*-1,4-benzodiazepine-2,5-(1*H*)-dione (VII) with lithium aluminum hydride (7).

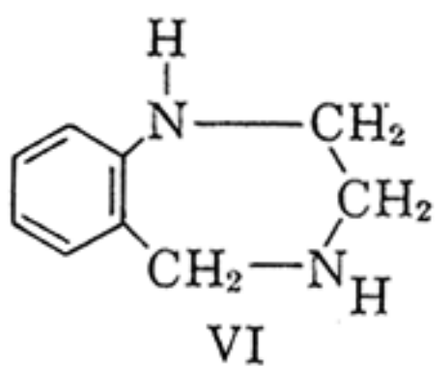


VII



V

+

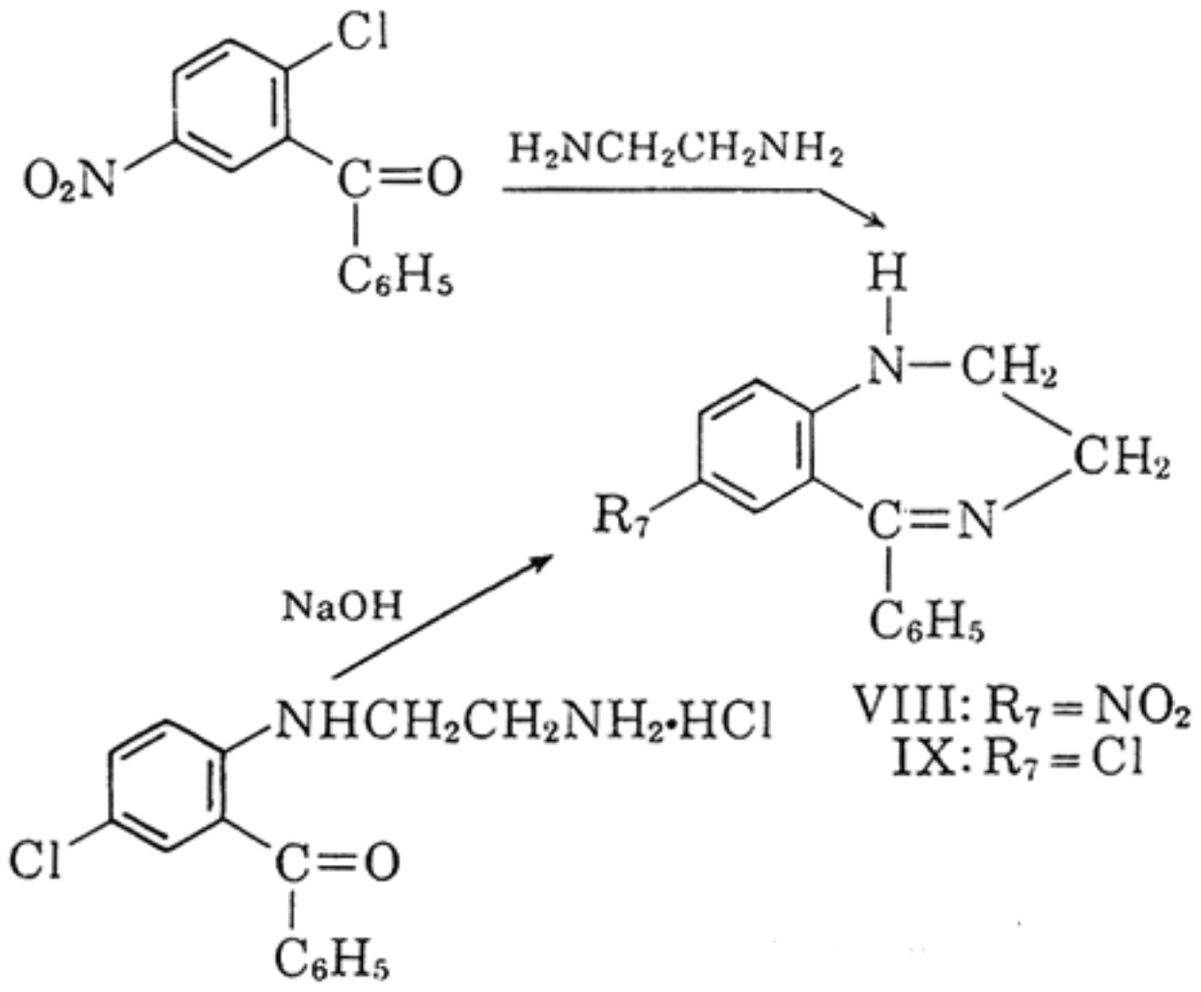


VI

Similar reduction of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones gives compounds carrying the corresponding 5-phenyl groups (8, 9). Reduction of the analogous 7-chloro-2-phenyl-3,-4-dihydro-5*H*-1,4-benzodiazepin-5-one affords 7-chloro-2-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine, the 1-double bond being reduced before the carbonyl group (10). This preparative method is obviously limited by

availability of the requisite starting materials, but this limitation is not serious in view of the many routes to benzodiazepinones.

A reductive method is not suitable for nitro substituted compounds. 7-Nitro-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine (VIII) is obtained by treatment of 2-chloro-5-nitrobenzophenone with ethylenediamine (11). Success with this method has been reported with 2,5-dichlorobenzophenone, but greater activation of the halogen to be displaced would seem to be desirable (12).



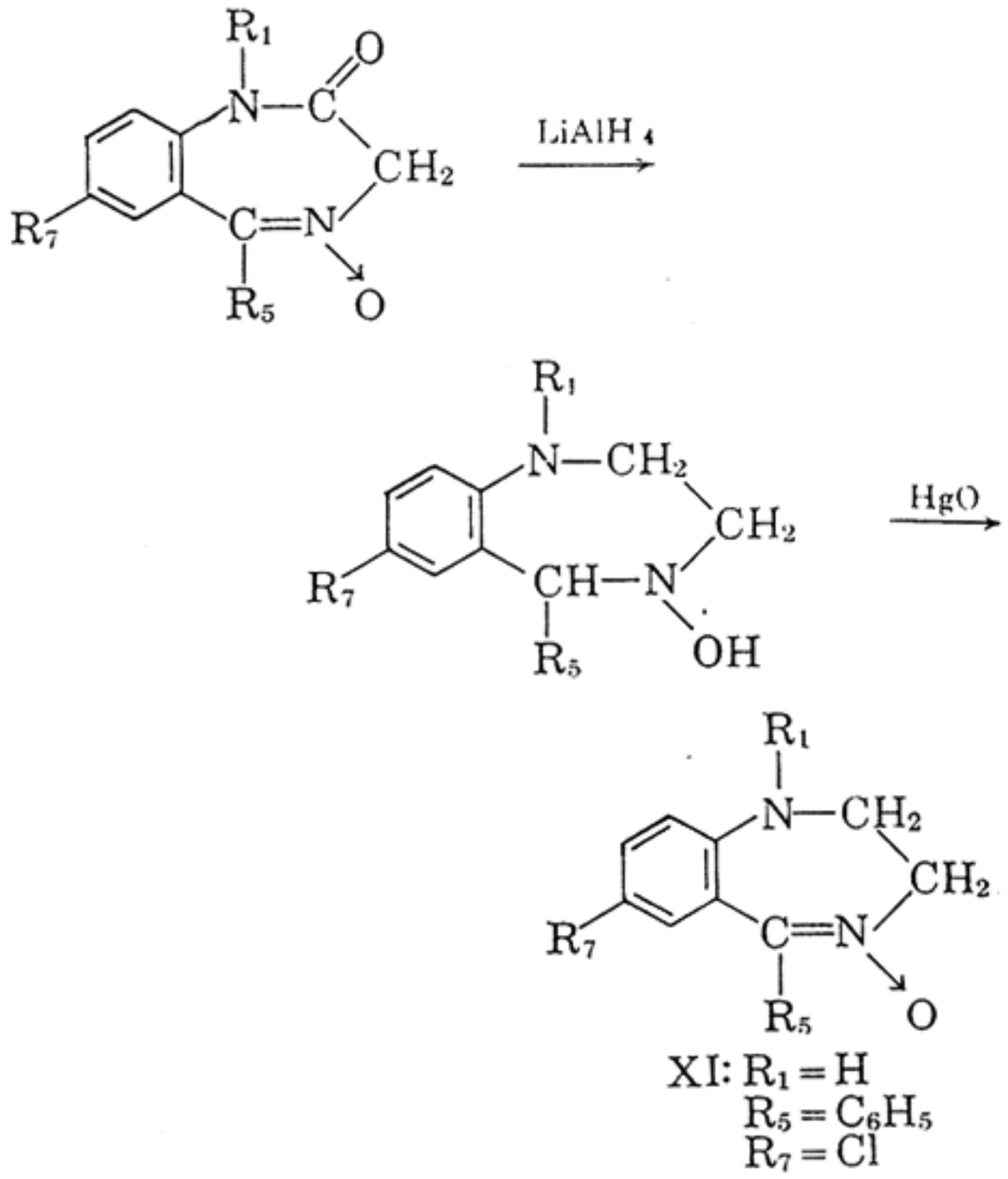
VIII: $R_7 = NO_2$
IX: $R_7 = Cl$

Desulfurization by Raney nickel of 1,3-dihydro-2*H*-1,4-benzodiazepine-2-thiones has also been reported to yield 2,3-dihydro-1*H*-1,4-benzodiazepines (13).

2 - Aminoethylamino - 5 - chlorobenzophenone, which can be prepared in a number of conventional ways, is stable only as a salt; 7-chloro - 5 - phenyl - 2,3 - dihydro - 1*H* - 1,4-benzodiazepine (IX) results upon alkalinization (9, 14).

Compound IX has been acylated and alkylated in the 1-position. The 1-alkyl compounds are obtainable directly by applying the reductive method to the appropriate 1-alkyl benzodiazepin-2-one (9).

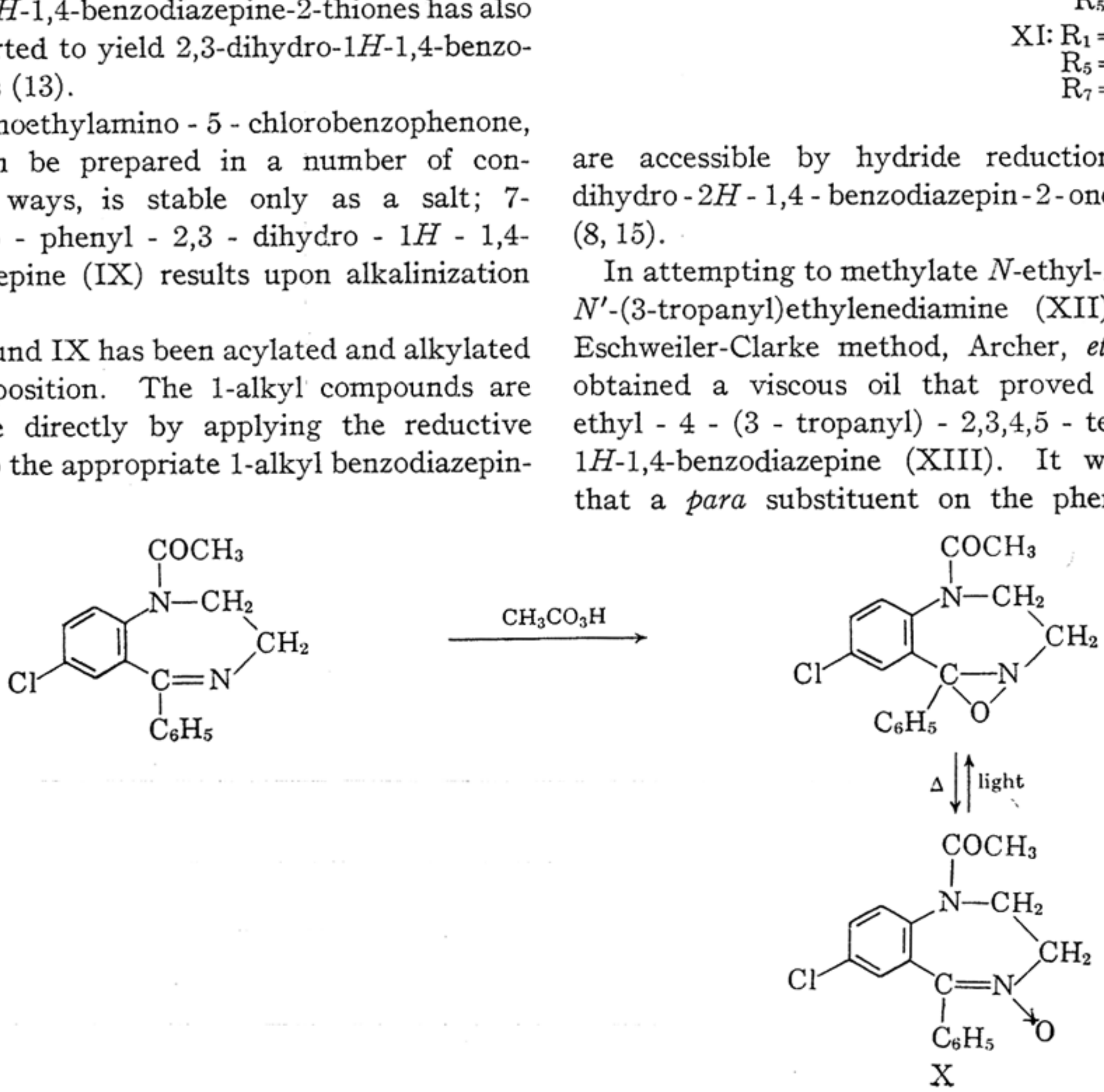
1-Acyl-2,3-dihydro-1*H*-1,4-benzodiazepines have been oxidized to the corresponding 4-oxides by peracetic acid (15). An intermediate 4,5-epoxy derivative rearranges with heat to the 4-oxide. The reverse transformation takes place upon exposure of the 4-oxide to light. An alternative source of 2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxides is the oxidation with mercuric oxide of the corresponding 4-hydroxy-2,3,4,5-tetrahydro compounds. These latter compounds



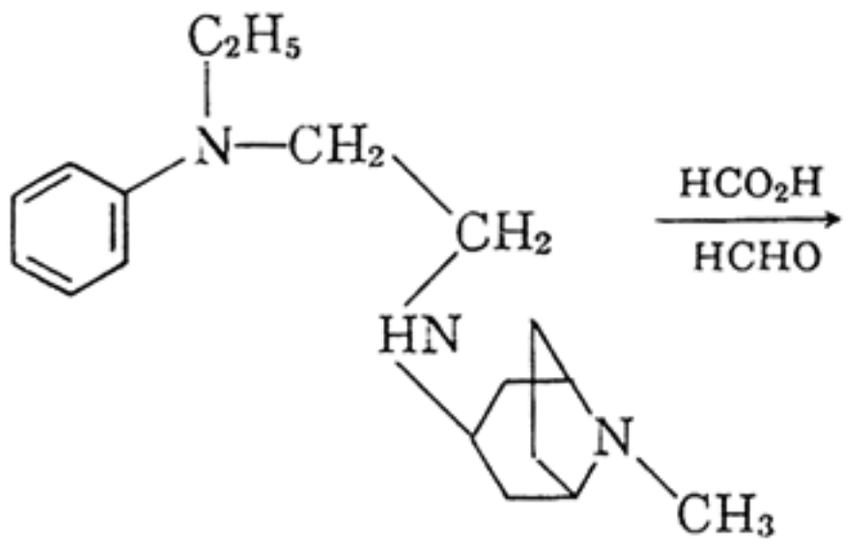
XI: $R_1 = H$
$R_5 = C_6H_5$
$R_7 = Cl$

are accessible by hydride reduction of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxides (8, 15).

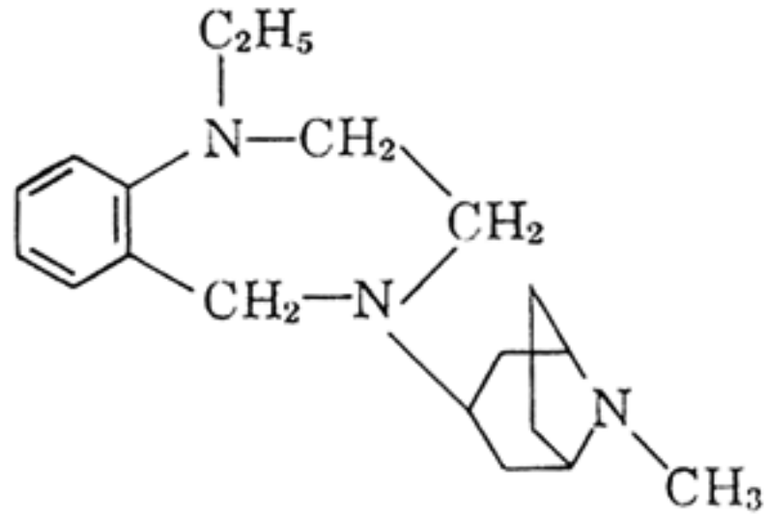
In attempting to methylate *N*-ethyl-*N*-phenyl-*N'*-(3-tropanyl)ethylenediamine (XII) by the Eschweiler-Clarke method, Archer, *et al.* (16), obtained a viscous oil that proved to be 1-ethyl - 4 - (3 - tropanyl) - 2,3,4,5 - tetrahydro-1*H*-1,4-benzodiazepine (XIII). It was shown that a *para* substituent on the phenyl group



X



XII



XIII

leads to increased yields of benzodiazepine by reducing polymer formation. Although this type of ring closure would appear to have general applicability, it has not been studied extensively. Treatment of the products with methyl iodide causes quaternization on the two nitrogen atoms in the benzodiazepine ring.

Biological Activity.—An insufficient number of 5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxides has been studied to permit conclusions about structure-activity relationships within the group. However, comparisons of the data in Table I with those of Table III (benzodiazepinones) show the corresponding compounds in the latter to be rather more active.

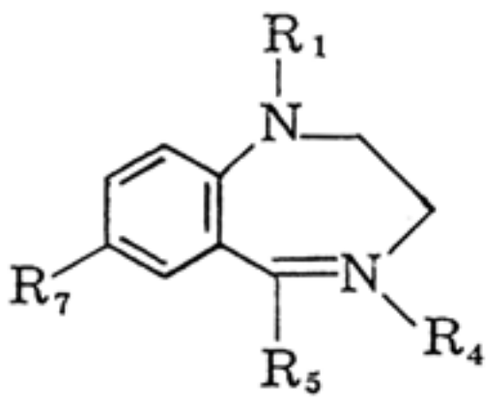
1 - Ethyl - 4 - (3 - tropanyl) - 2,3,4,5 - tetrahydro-1*H*-1,4-benzodiazepine (XIII) in the form of a bis quaternary salt is reported to have ganglionic blocking activity (16).

AMINO-1,4-BENZODIAZEPINES

In attempting to prepare 2-aminomethyl-6-chloro-4-phenylquinazoline 3-oxides by treating 6 - chloro - 2 - chloromethyl - 4 - phenylquinazoline 3-oxide (XV) (17) with the appropriate amines, Sternbach and Reeder (1) discovered the ring enlargement reaction that led to chlordiazepoxide. Although a normal reaction occurs with secondary amines to afford the expected 2-substituted aminomethyl products, with methylamine a rearrangement takes place to afford 7 - chloro - 2 - methylamino - 5 - phenyl - 3*H*-1,4-benzodiazepine 4-oxide (I) (chlordiazepoxide). The structure of I was established by spectral data and the hydrolysis of its reduction product (XVIII) to 2-amino-5-chlorobenzophenone, methylamine, and glycine. The exact tautomeric form was indicated by its acetylation to the 2-(*N*-methylacetamido) derivative. Cyanoethylation also takes place on the exocyclic nitrogen (18). Nuclear magnetic resonance data confirm the tautomeric structure—the signal from the *N*-methyl group is split into a doublet by spin-spin coupling with the proton on the nitrogen atom.

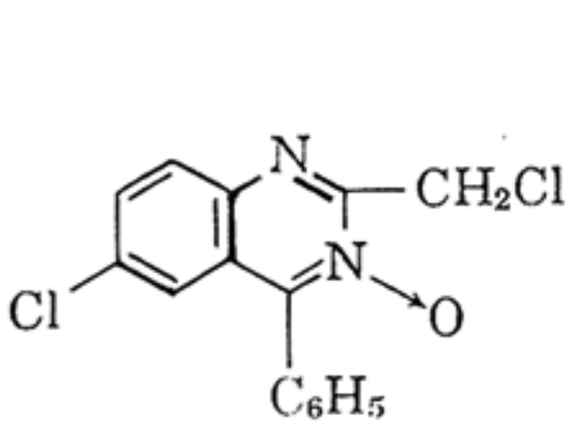
The rearrangement reaction proved to be general with ammonia and primary amines except for weak bases such as aniline which give the aminomethylquinazoline 3-oxides (19). With some amines, *e.g.*, allylamine, both the 6- and 7-membered ring products are formed (1). Electron releasing substituents in the 6- and 8-posi-

TABLE I.—STRUCTURE-ACTIVITY RELATIONSHIPS OF 2,3-DIHYDRO-1*H*-1,4-BENZODIAZEPINES[a]



Compd.	Structure R1	Structure R5	Structure R4	Structure R7	Biological Activity,[b] Mice, mg./Kg., p.o. Motor Activity Decrease, MED	Anti-pentylenetetrazol, ED50	Anti-Max. El. Shock, ED50	Anti-morphine, ED50	Ataxia at 1 hr., ED50
IX	H	C_6H_5	..	Cl	0.4	0.9	9.8	6.8	6.8
VIII	H	C_6H_5	..	NO_2	4	1.4	...	40	12
XI	H	C_6H_5	O	Cl	12.7	4	12.7	13	117
XIV	H	*o*-ClC_6H_4	O	Cl	4	4	9	7	51
X	CH_3CO	C_6H_5	O	Cl	40	78	150	250	78

[a] The test data reported in this article are those observed at Wyeth Laboratories and are used throughout to maintain consistency. Data from other laboratories are cited by reference. [b] The D.M.A. test is a subjective measure of reduction in spontaneous motor activity, and the values quoted are the minimum amount of drug required to produce such an effect. The estimate of the ataxic effect at 1 hour is based on the method of Dunham, N. W., and Miya, T. S., THIS JOURNAL, **46**, 208 (1957). The antagonism studies are modifications of those reported by Everett, G. M., and Richards, R. K., *J. Pharmacol. Exptl. Therap.*, **81**, 402(1944); Swinyard, E. A., Brown, W. C., and Goodman, L. S., *ibid.*, **106**, 319(1952); and Holten, C. H. *Acta Pharmacol. Toxicol.*, **13**, 113(1957).



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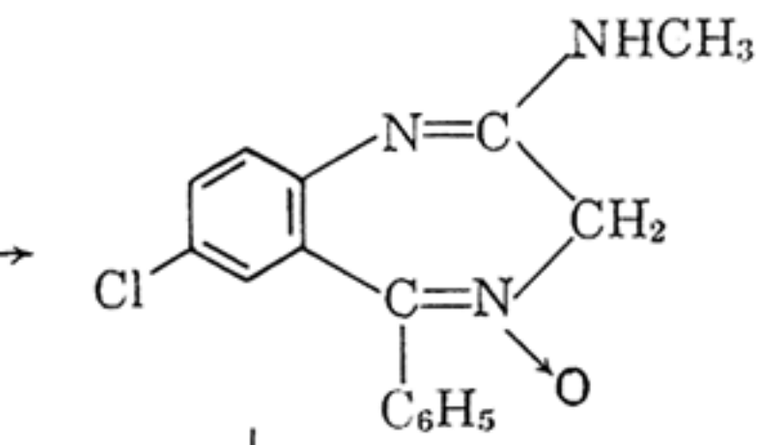
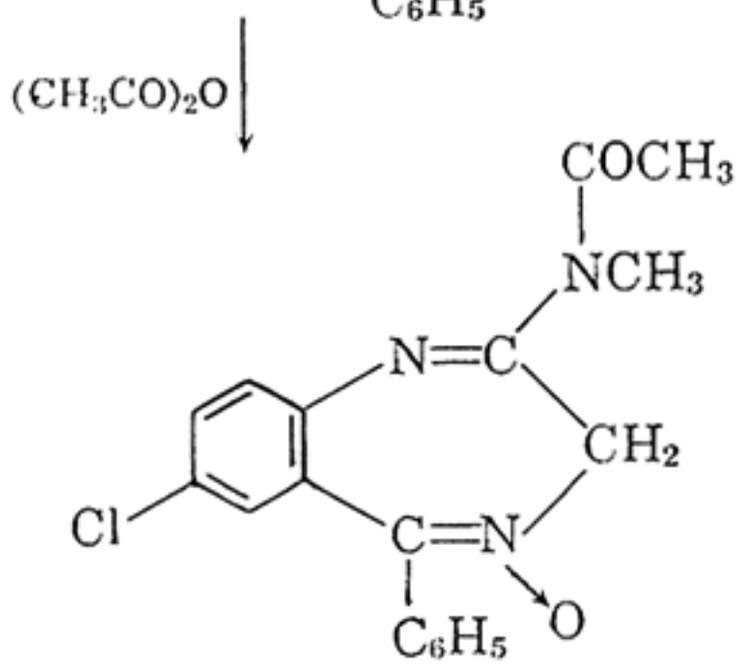
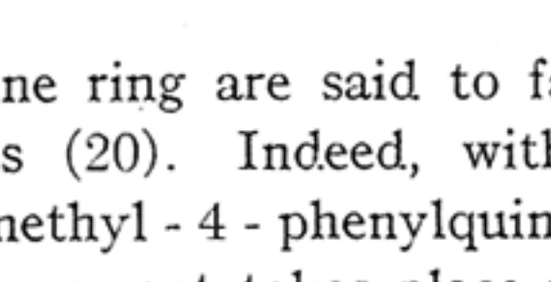


I

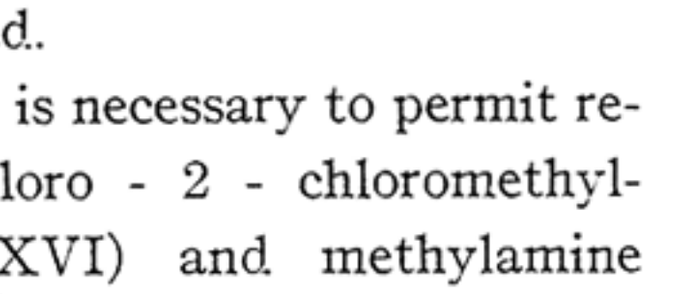


tions of the quinazoline ring are said to favor unrearranged products (20). Indeed, with 2-chloromethyl - 6,8 - dimethyl - 4 - phenylquinazoline 3-oxide no rearrangement takes place with methylamine. Once formed, aminomethylquinazoline 3-oxides appear to be stable. No report of their conversion into 7-membered ring compounds has appeared.

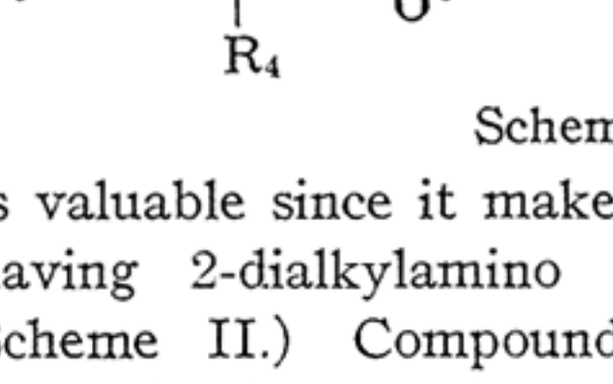
The 3-oxide function is necessary to permit rearrangement. 6 - Chloro - 2 - chloromethyl-4-phenylquinazoline (XVI) and methylamine give only 6-chloro-2-methylaminomethyl-4-phenylquinazoline (XVII) (19).



XVI



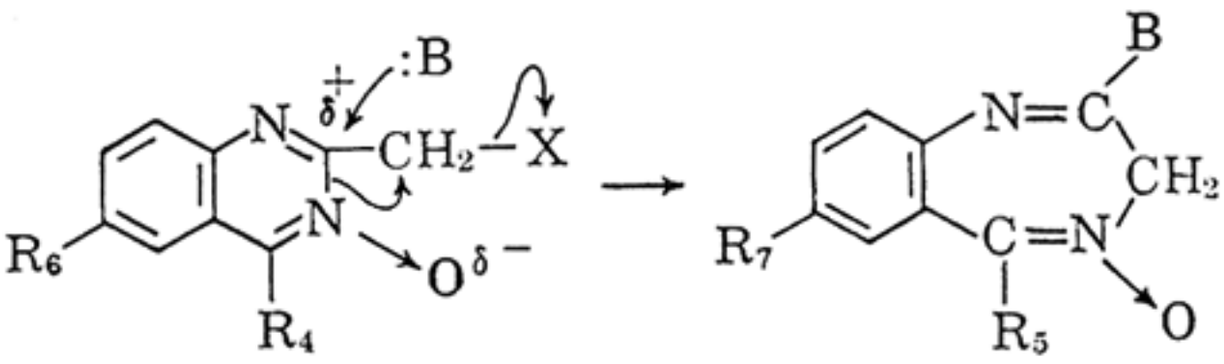
XVII



XVIII

A possible mechanism for the rearrangement involves the induction by the *N*-oxide function of a partial positive charge at C-2 which is reinforced by an electron attracting atom at C-6. Under nucleophilic attack, a concerted displacement of halide takes place through simultaneous attack of the 2,3-bonding electrons on the methylene carbon. Such a mechanism must rely on steric hindrance to explain the failure of strong secondary amines to effect rearrangement.[3] (See Scheme I.)

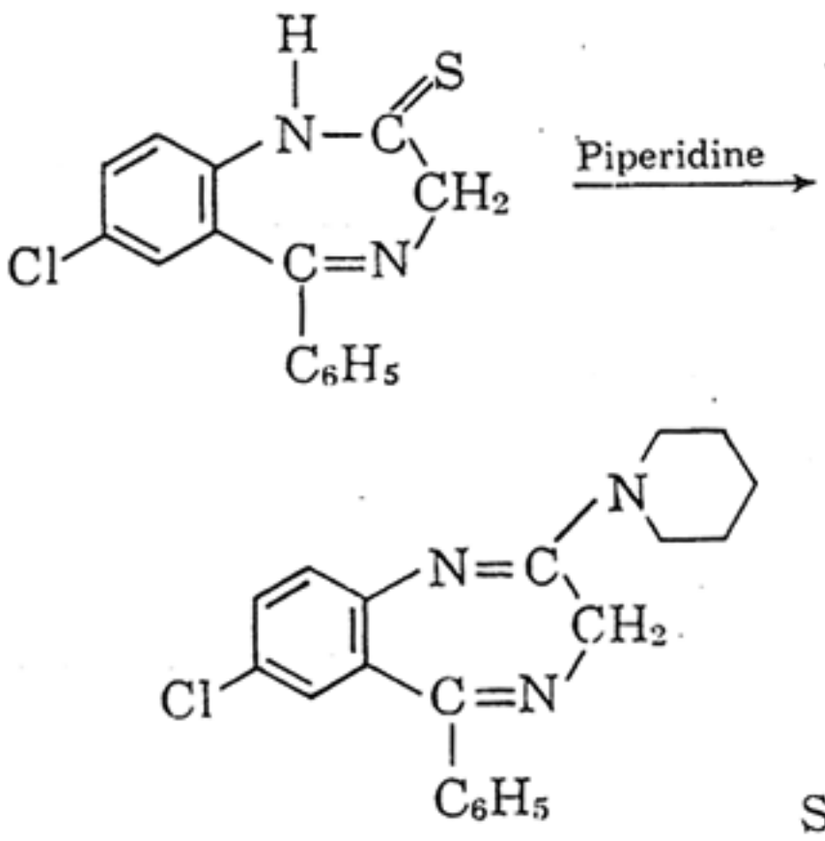
An alternative synthesis of 2-amino-5-phenyl-3*H*-1,4-benzodiazepines from the corresponding benzodiazepine-2-thiones or their *S*-methyl derivatives has been developed (13). This reaction



Scheme I

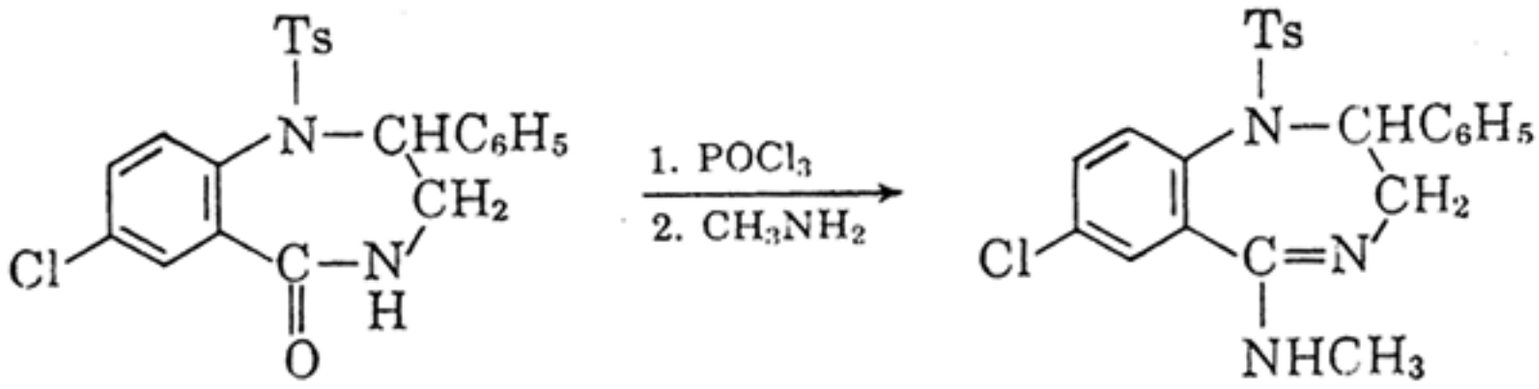
is valuable since it makes available compounds having 2-dialkylamino substitution. (See Scheme II.) Compounds substituted in the benzo ring by an amino group have been prepared by reduction of nitro compounds (21).

In the synthesis of analogs of I a variety of substituents has been employed on the benzo ring



Scheme II

[3] Note added in proof—*Cf.* Farber, S., Wuest, H. M., and Meltzer, R. I., *J. Med. Chem.*, 7, 235(1964).

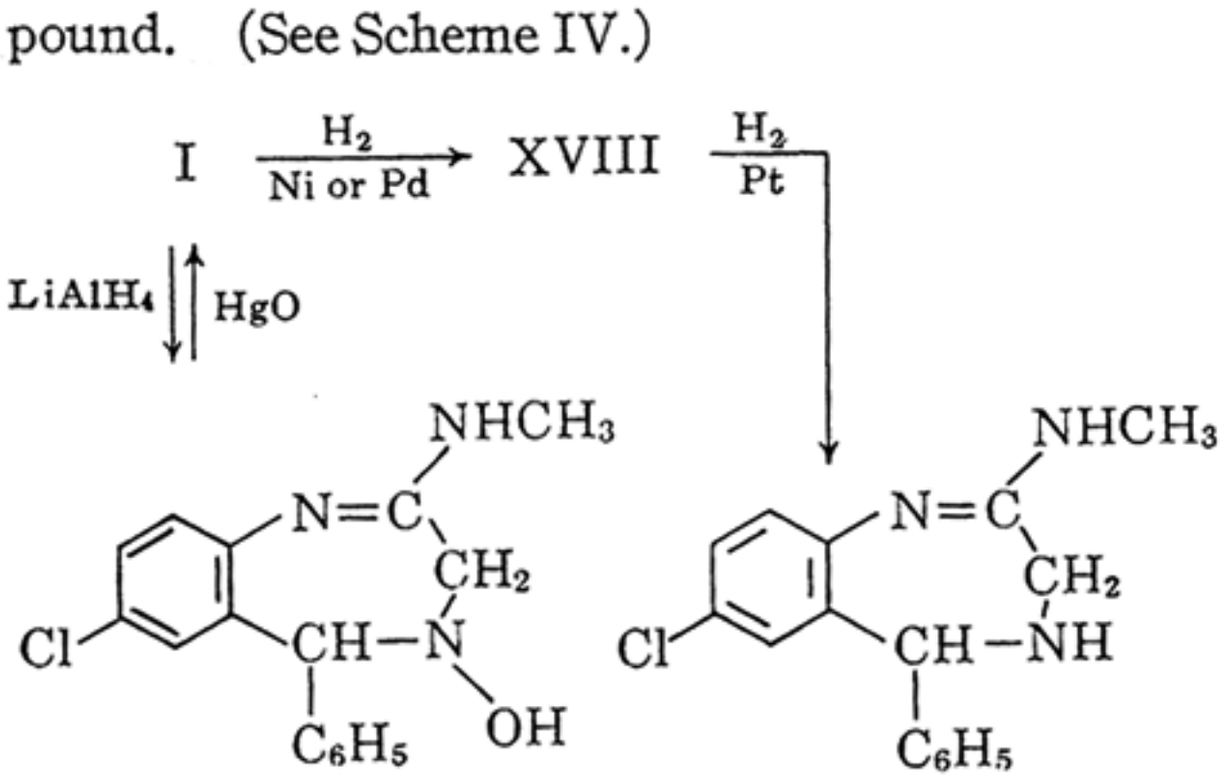


Scheme III XIX

and at the 3- and 5-positions (19, 20). These substituents largely parallel those of the benzodiazepinones (Scheme III). Compounds having the 2-amino group substituted by alkenyl, acyl, aralkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, heteroalkyl, cyanoalkyl, and iminocarbamoyl groups have been prepared.

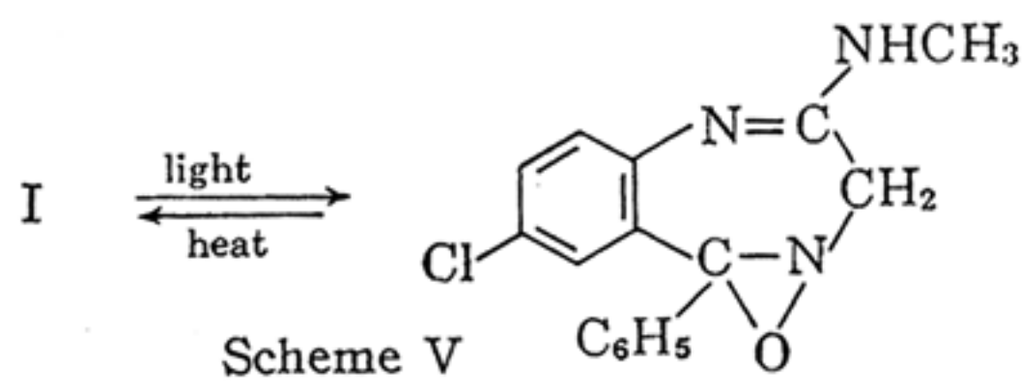
An isomer (XIX) of chlordiazepoxide has been prepared as a tosylate derivative from a related benzodiazepinone (10). Apparently the tosyl group could not be removed.

Catalytic reduction of the 2-aminobenzodiazepine 4-oxides removes the 4-oxide function (1, 19). Treatment with phosphorus trichloride brings about the same result. With platinum as catalyst, saturation of the 4,5-double bond occurs in addition to removal of the 4-oxide function. Reduction by lithium aluminum hydride gives the corresponding 4-hydroxy compound. (See Scheme IV.)



Scheme IV

Chlordiazepoxide undergoes the typical rearrangement of a nitrone in daylight, forming an oxaziridine (22). This process is reversed by heat (Scheme V.)



Scheme V

Biological Activity.—Chlordiazepoxide, the first of the useful benzodiazepines, is characterized by activity in a number of conventional pharmacological screens: antipentylenetetrazol, antielectroshock, antiemetric, antistrychnine, and antimorphine tests as well as a host of other more subjective measurements such as animal taming and muscle relaxation (ataxia) (23). Possibly the best single indicator of utility is the antipentylenetetrazol test.

Table II gives the results of certain of these pharmacological screens. Using the antipentylenetetrazol test as a guide, it is apparent that an electronegative substituent in the 7-position is of great importance. In order of decreasing potency: $Cl > CH_3 \cong H$. Other data indicate that $NO_2 > Cl$ (4) and that CF_3 is a potent substituent (24, 25). Alkyl substitution on the 2-amino group reduces potency with the possible exception of CH_3. The effect of the *N*-oxide function is variable in this series. Its removal (XVIII) reduces the activity of chlordiazepoxide but increases the activity of the 2-amino analog (XX).

A phenyl group is the most satisfactory substituent in position 5. A 2-thienyl group reduces potency. Cycloalkyl groups are still less effective (19). It seems likely that *ortho* substitution of the 5-phenyl group would increase potency as it does in the benzodiazepinone series.

Chlordiazepoxide is rapidly absorbed from the intestines and is extensively metabolized in the rat and in man. 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide (XXXI), an active compound, has been identified among the metabolites (26).

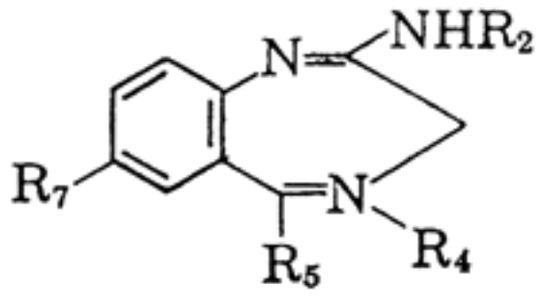
1,4-BENZODIAZEPINONES[4]

Benzodiazepin-2-ones.—Possibly the most important structures having the characteristic central nervous-system activity of chlordiazepoxide are the 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones. Because of this, more attention has been paid to their synthesis than to the preparation of other benzodiazepines. A versatile group of reactions has been assembled for preparing these compounds.

One of the simplest methods and certainly the most straightforward is the treatment of 2-(α-haloacylamido)benzophenones with ammonia (3, 27). The bromo compounds are most often used. In liquid ammonia the intermediate 2-(α-aminoacylamido)benzophenones are isolated and then cyclized by heat. In alcoholic ammonia the cyclization occurs *in situ*. The yield in the

[4] A benzodiazepin-3-one is discussed under *Hydroxybenzodiazepines*.

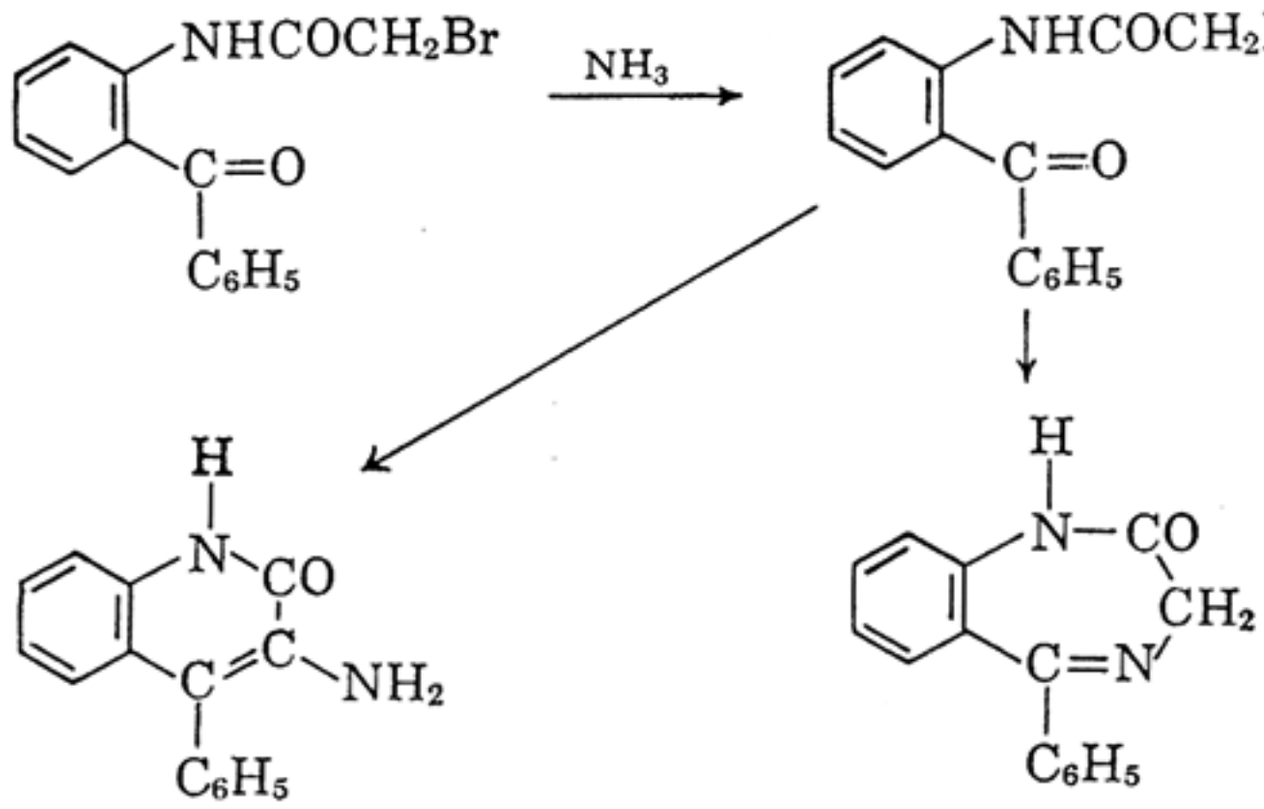
TABLE II.—STRUCTURE-ACTIVITY RELATIONSHIPS OF 2-AMINO-3*H*-1,4-BENZODIAZEPINES[a]



Compd.	Structure R_2	R_4	R_5	R_7	Biological Activity, Mice, mg./Kg., p.o. Motor Activity Decrease, MED	Anti-pentylene-tetrazol, ED_{50}	Anti-Max. El. Shock, ED_{50}	Anti-morphine, ED_{50}	Ataxia at 1 hr., ED_{50}
XX	H	..	C_6H_5	Cl	3.1	1.6	..	3.9	12.7
XXI	H	O	C_6H_5	Cl	50	3.6	..	6.7	28
XXII	CH_3	..	C_6H_5	H	12.5	>50	..	50	...
XXIII	CH_3	O	C_6H_5	H	25	>50	..	>50	...
XVIII	CH_3	..	C_6H_5	Cl	4	5.5	..	41	38
I[b]	CH_3	O	C_6H_5	Cl	4	3.7	14	14	22
XXIV	$C_6H_5CH_2$	O	C_6H_5	Cl	25	8	..	40	38
XXV	CH_3	..	C_6H_5	CH_3	50	>50	..	>50	...
XXVI	CH_3	O	C_4H_3S	Cl	50	23	..	47	...

[a] See footnotes to Table I. [b] Chlordiazepoxide.

case of 2-α-bromoacetamidobenzophenone is 85.5%. A possible competing reaction, the formation of the corresponding 2-aminomethylquinazoline, does not appear to be important, although the corresponding 3-amino-2(1*H*)-quinolones (XXVIII) have been obtained. In this



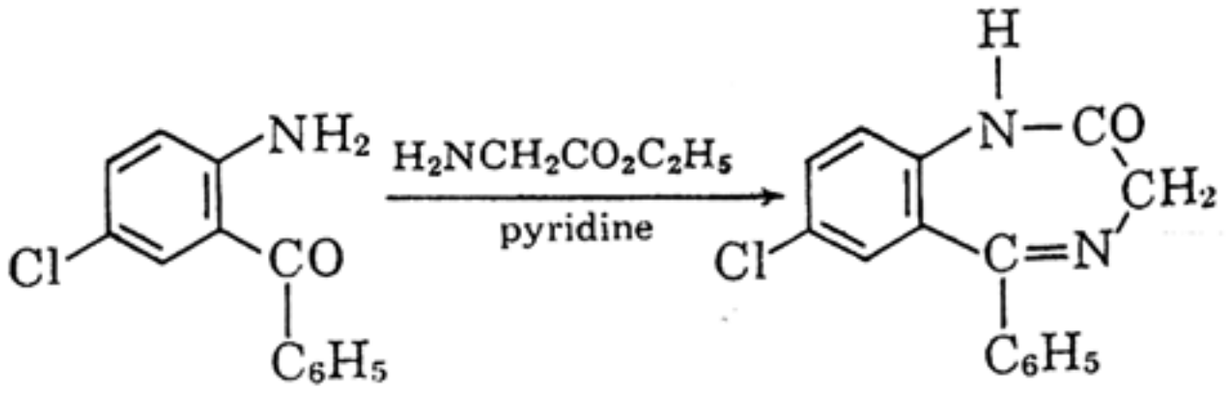
XXVIII XXVII

method the amino group of the aminobenzophenone can be substituted by an alkyl group so that a 1-alkyl product is obtained. Secondary halides can be employed to afford 3-substituted benzodiazepin-2-ones.

Because of its generality, the foregoing method is usually the first to be tried for making new benzodiazepin-2-ones.

The reaction of a 2-aminobenzophenone with an α-amino acid derivative yields 5-phenyl-1,3-dihydro - 2*H*- 1,4 - benzodiazepin - 2 - ones directly (27, 28). Typically, 2-amino-5-chlorobenzophenone and ethyl glycinate are heated in pyridine solution to afford 7-chloro-5-phenyl-1,3 - dihydro - 2*H* - 1,4 - benzodiazepin - 2 - one (XXIX) in a yield of about 50%. When there is steric hindrance from *ortho* substitution of the benzophenone, yields are lower. Both amino acids themselves, and amino acid chlorides (3) have been used in modifications of this method. In using the amino acid chloride it is clear that acylation is the first step and the intermediate aminoacylamidobenzophenone hydrochloride can be isolated. 3-Amino-2(1*H*)-quinolones (XXVIII) are formed as by-products. Whether acylation or imine formation takes place first when the ester is used has not been established. Both methods can be applied to *N*-substituted compounds. In addition to esters of glycine, esters of methionine and tyrosine have been used (27). Even a spiro compound has been made from the acid chloride prepared from 1-aminocyclopentane carboxylic acid (3).

In further variations of this method, the



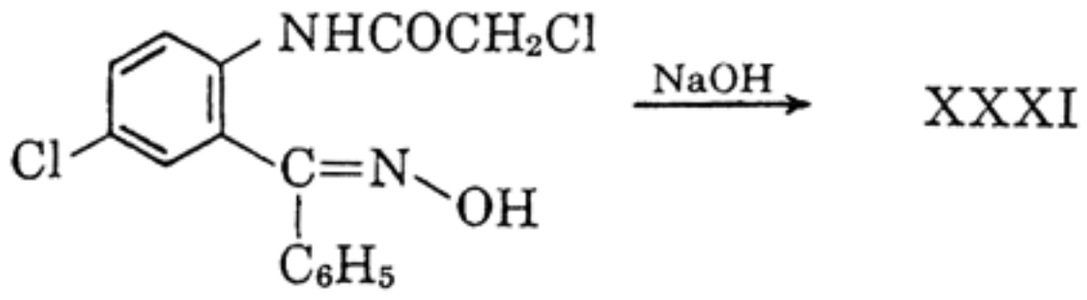
XXIX

amino acid derivative carries a protective group on the amine function. Carbobenzoxyglycine has been condensed with 2-amino-5-chlorobenzophenone by use of dicyclohexylcarbodiimide (29). Carbobenzoxyglycyl chloride reacts with the amine to form the same product (3). Since catalytic hydrogenolysis is not satisfactory, the protective group is removed by hydrogen bromide in acetic acid. The resulting intermediate is cyclized as before.

Another protective device that has been used is the trifluoroacetyl group. For example, 2-trifluoroacetamidoisobutyroyl chloride reacts with 2-amino-5-chlorobenzophenone to afford the expected intermediate, 2-(2-trifluoroacetamidoisobutyramido)-5-chlorobenzophenone (30). Mild alkaline hydrolysis and cyclization leads to 7 - chloro - 3,3 - dimethyl - 5 - phenyl - 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one. The use of a protected amino acid is to be recommended for preparing 3,3-disubstituted benzodiazepinones.

Mild acid hydrolysis (see Scheme VI) of 2-amino- or 2-acetamidobenzodiazepine 4-oxides represents yet another process leading to benzodiazepin-2-ones (2). Since there is at present only one route to the 2-aminobenzodiazepine 4-oxides that is independent of the benzodiazepin-2-ones—namely, the rearrangement by amines of the 2-chloromethylquinazoline 3-oxides (see Scheme VII)—the hydrolysis method is of limited value. This is particularly so since 2-chloromethylquinazoline 3-oxides rearrange analogously with sodium hydroxide directly to benzodiazepin-2-one 4-oxides (2, 3). A host of such reactions has been carried out and this is probably the preferred synthesis when the 4-oxides are wanted. The method can be employed with almost any substituents on the benzo ring and no limits are known for the 4-substituent. By use of a compound having a 2-(1-chloroethyl) side chain, 7 - chloro - 3 - methyl - 5 - phenyl - 1,3 - dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide (XXXVI) has been made in ethanolic solution (3). A by-product in this reaction is 7-chloro-2-ethoxy-3-methyl-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide. Benzodiazepin-2-ones prepared in this fashion will always have hydrogen in the 1-position. This is not a serious limitation, for alkylation at this position is easy. Diazepam (II) can be made in this way.

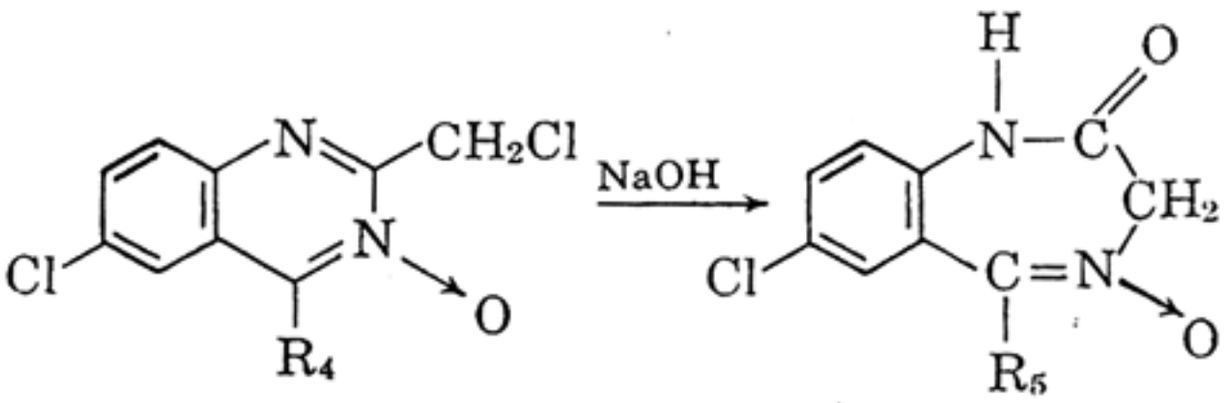
The oxime of 2-chloroacetamido-5-chlorobenzophenone having its hydroxyl group *anti* to the substituted phenyl ring undergoes self alkylation in base to yield the benzodiazepin-2-one 4-oxide, XXXI (2). The reaction is of academic interest



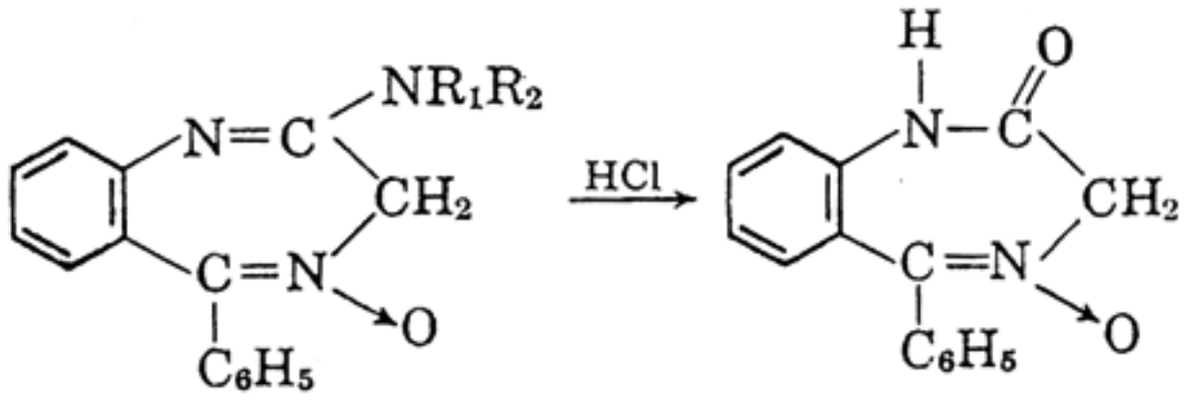
only in view of the several more useful syntheses.

The synthesis of benzodiazepin-2-ones by these methods is limited only by the availability of the required amino benzophenones. Considerable work has been done on methods for the preparation of these intermediates (31). The variations have resulted in benzodiazepinones having hydrogen (3, 27), halogen (2, 3), alkyl (3, 27), alkoxy (27), nitro (4), amino (32), trifluoromethyl (24, 25), carboalkoxy (33), carbamoyl, and cyano groups on the benzo moiety. There is mention in patent literature (32) of alkylthio, alkylsulfinyl, alkylsulfonyl, acylamido, and hydroxylalkylthio groups on this ring.

A phenyl group or a substituted phenyl group is most common at position 5, but compounds having methyl, cyclohexyl, thienyl (3), pyrryl, furyl (34), and pyridyl (35) groups have been prepared. Many of these compounds have been alkylated (2, 3) in the 1-position by alkyl, alkenyl (2), alkynyl (36), aralkyl, and cyanoalkyl (37) groups.



Scheme VII



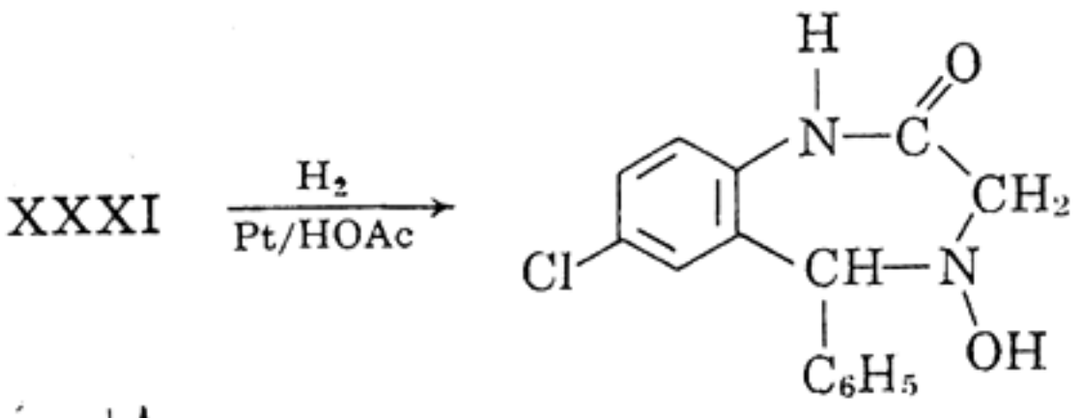
R_1 = H, alkyl
R_2 = H, acetyl

XXX

Scheme VI

Groups placed in the 3-position include hydrogen, alkyl, alkoxyalkyl, alkylthioalkyl, aryl, and hydroxyaralkyl (2, 3, 27).

Catalytic hydrogenation of 1,4-benzodiazepin-2-one 4-oxides with palladium removes the 4-oxide function and may also remove a 7-chloro substituent (3). Hydrogenation using platinum in acetic acid is said to effect the conversion of benzodiazepin-2-one 4-oxides to the corresponding 4-hydroxy-4,5-dihydro compounds (XXXVII). The same treatment applied to a benzodiazepinone having no *N*-oxide leads to saturation of the 4,5-double bond (2). Phosphorus trichloride is the most selective reagent



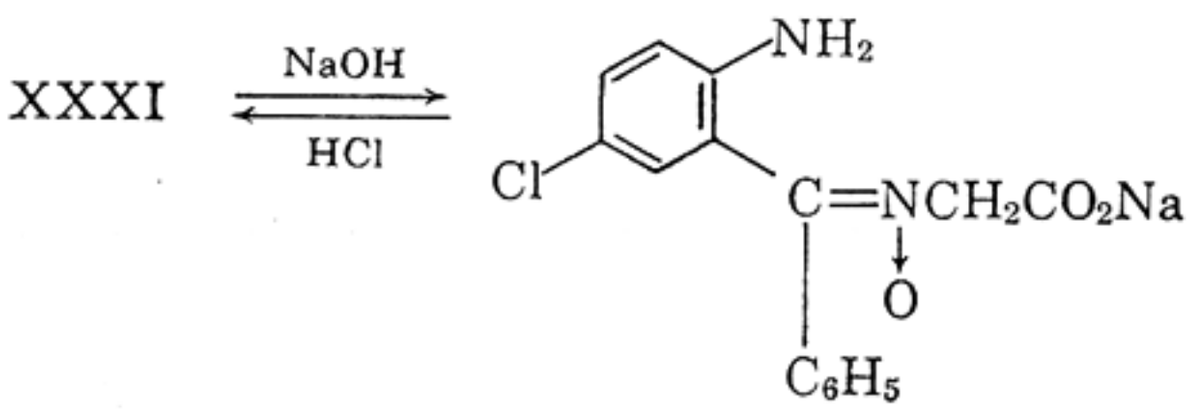
XXXVII

XXXVIII

for deoxygenating the 4-oxides. Peroxides serve to convert 1,4-benzodiazepin-2-ones into their 4-oxides; this reaction can be a useful alternative synthesis.

Oxaziridine formation from XXXI under ultraviolet irradiation has been observed as in the case of chlordiazepoxide (38).

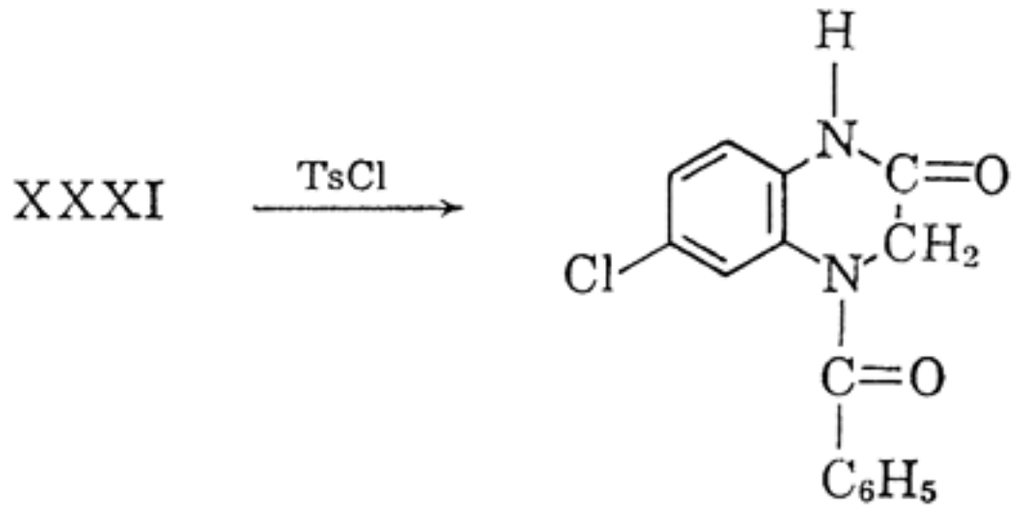
1,4-Benzodiazepin-2-ones and their 4-oxides are unstable in alkali, cleavage occurring between the 1- and 2-positions to afford benzophenone imines or nitrones, respectively. With the nitrones recyclization takes place in acid. With



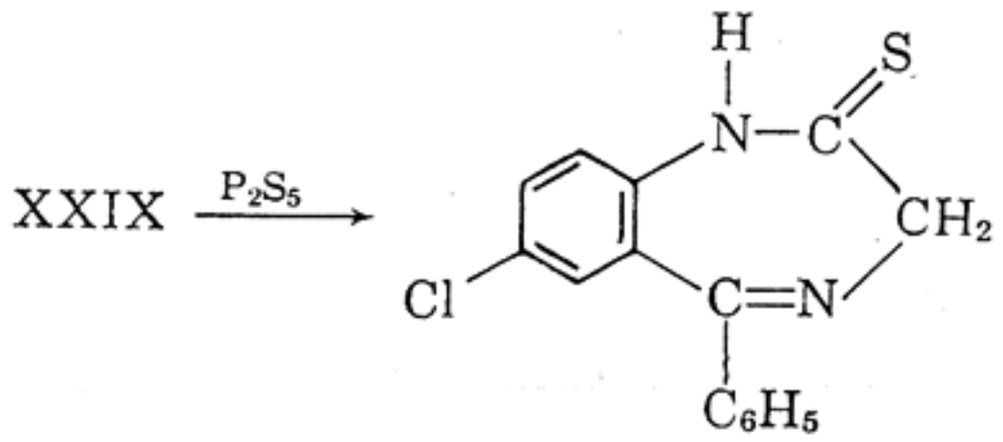
the imines regeneration of the benzodiazepinones is much less ready; hydrolysis of the imine bond predominates.

The nitration of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones by means of potassium nitrate and sulfuric acid has been shown to lead to 7-nitro derivatives (4). The entry of a second nitro group takes place in the *meta* position of the 5-phenyl ring (39). An earlier report (40) had placed the second nitro group in the 9-position.

Beckmann rearrangement occurs when benzodiazepin-2-one 4-oxides are allowed to react with toluenesulfonyl chloride (41).

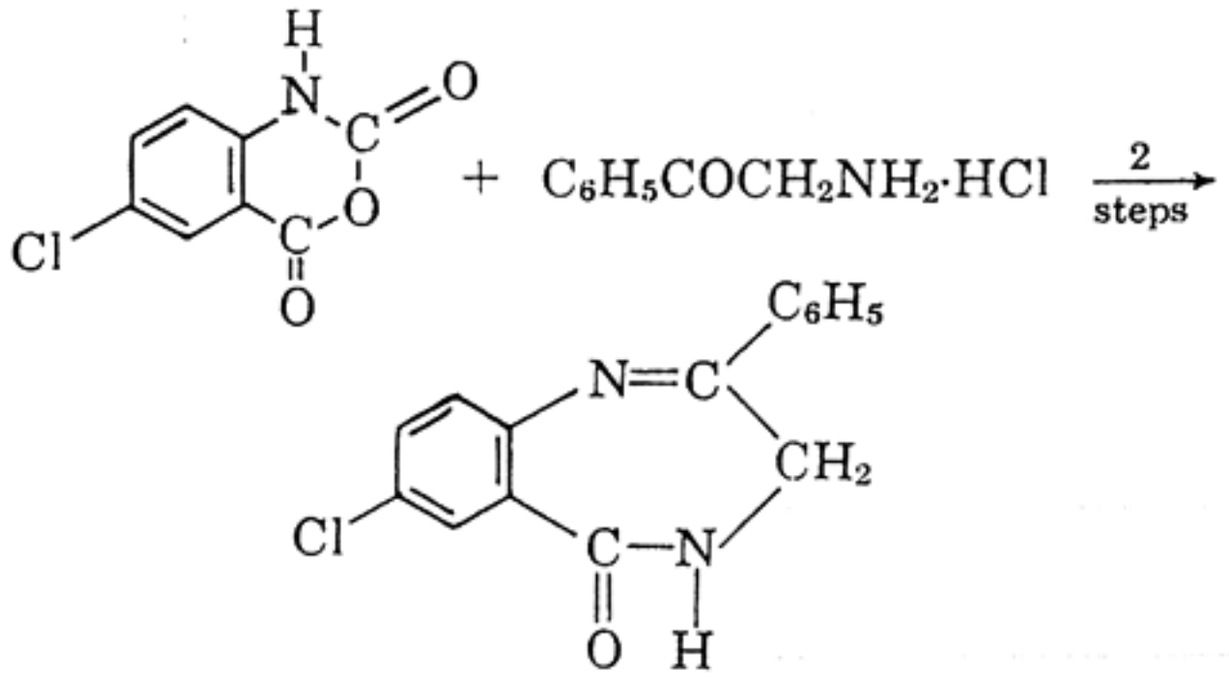


The carbonyl groups of benzodiazepin-2-ones (and benzodiazepin-5-ones) are readily converted to thione groups by phosphorus pentasulfide (10, 13, 42).



XXXIX

Benzodiazepin-5-ones.—Some isomers of the pharmacologically active benzodiazepin-2-ones have been made by different procedures (10). 7 - Chloro - 2 - phenyl - 3,4 - dihydro - 5*H*-1,4-benzodiazepin-5-one (XL) is obtained from the reaction of α-aminoacetophenone hydrochloride with 5-chloroisatoic anhydride by way of 2-amino-5-chloro-*N*-phenacylbenzamide as an intermediate. Reduction with a limited amount



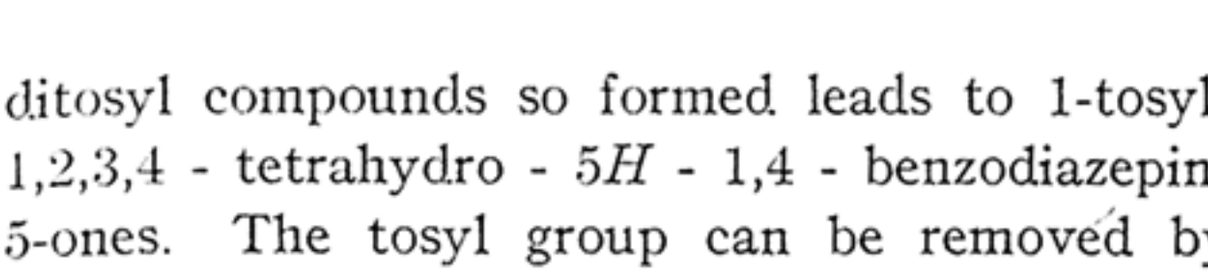
XL

of lithium aluminum hydride gives the corresponding 1,2,3,4-tetrahydro compound. The carbonyl group is attacked only by more strenuous treatment with hydride.

Tosylation of 2-amino-*N*-(2-hydroxyethyl)-benzamides and subsequent heating of the *N*,*O*-

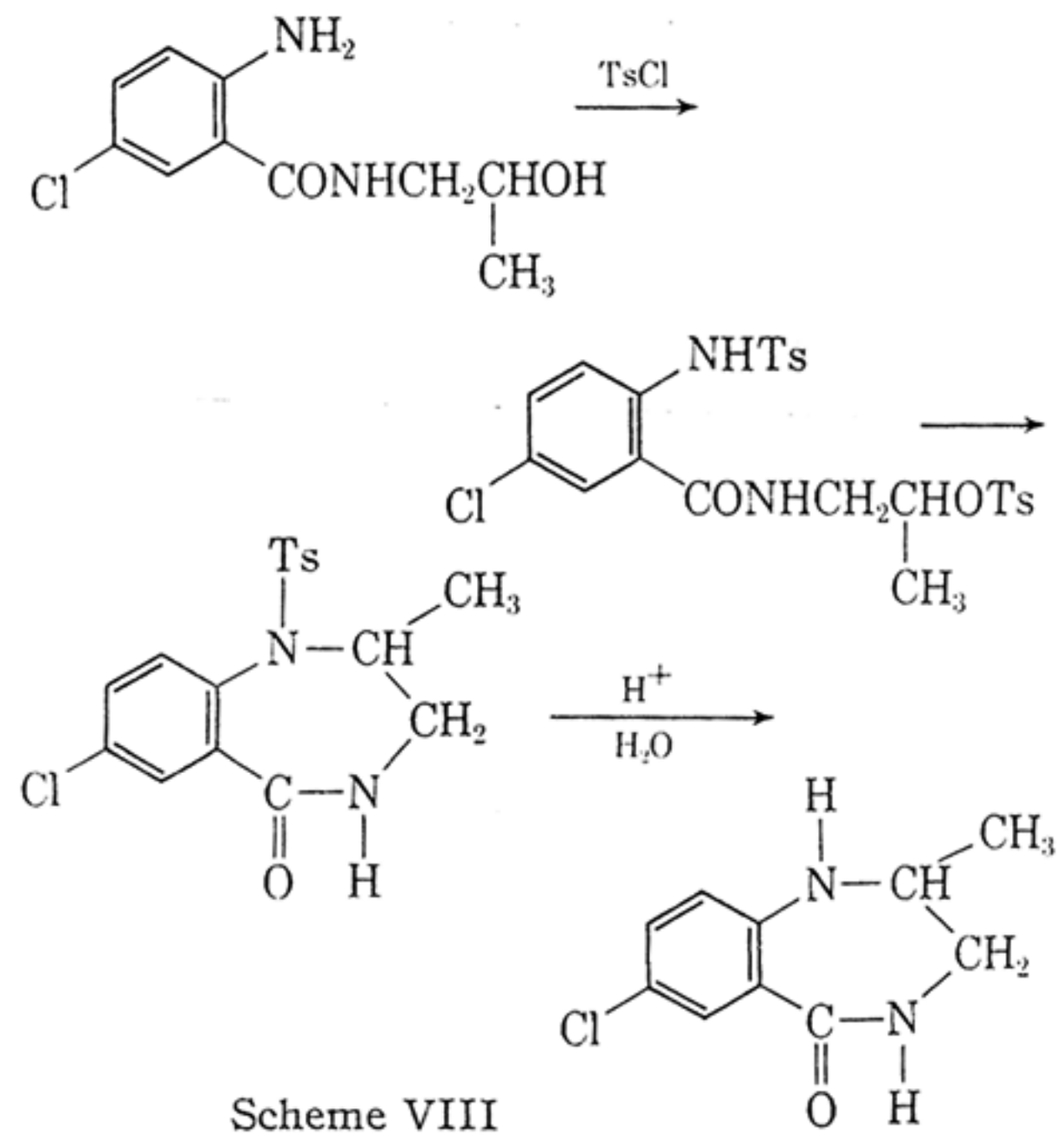
ditosyl compounds so formed leads to 1-tosyl-1,2,3,4 - tetrahydro - 5*H* - 1,4 - benzodiazepin-5-ones. The tosyl group can be removed by acid hydrolysis. In most cases, the intermediate ditosyl derivatives cannot be obtained pure since they tend to cyclize spontaneously. (See Scheme VIII.)

A modified approach avoids the necessity for removing the tosyl group. 2-Amino-5-chloro-*N*-hydroxyethylbenzamide treated with thionyl chloride and then with sodium carbonate solution affords 7-chloro-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (XLI). Reaction of 2-anilino - *N* - (2 - hydroxyethyl)benzamide with methanesulfonyl chloride affords 1-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one.



XLI

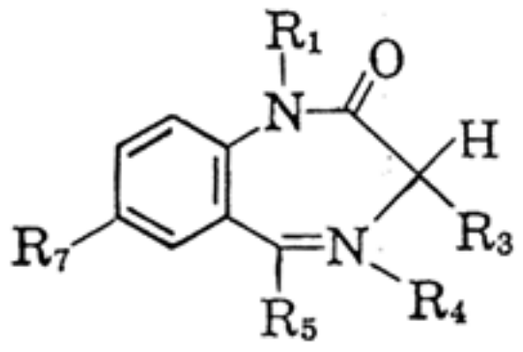
Biological Activity.—Benzodiazepin-2-ones are in general more potent than the corresponding 2-amino analogs. Again, for high potency, an electronegative substituent at position 7 is required. Most of the data of Table III are for compounds having 7-Cl substitution, but other data (4) indicate that $NO_2 > Cl$ and that CF_3 (24) is an effective replacement for Cl. Some excitation in the mouse has been observed with nitro compounds (43).



Scheme VIII

Alkylation at the 1-position is possible in this series and methylation of XXIX, giving II, results in an increase in the ataxic effect. Ataxia is a crude measure of muscle relaxation, an effect for which diazepam (II) is recommended. A decrease in potency is observed with methylation at position 3. The effect of an *N*-oxide function

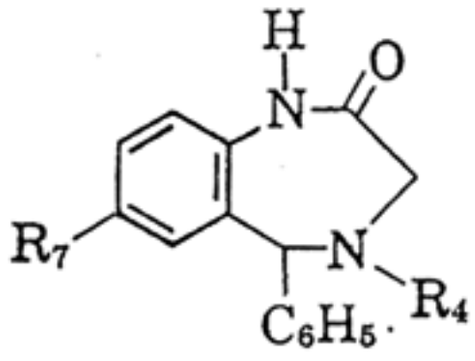
TABLE III.—STRUCTURE-ACTIVITY RELATIONSHIPS OF 1,3-DIHYDRO-2*H*-1,4-BENZODIAZEPIN-2-ONES[a]



	Structure					Biological Activity, Mice, mg./Kg., p.o.				
Compd.	R_1	R_3	R_4	R_5	R_7	Motor Activity Decrease, MED	Anti-pentylene-tetrazol, ED_{50}	Anti-Max. El. Shock, ED_{50}	Anti-morphine, ED_{50}	Ataxia at 1 hr., ED_{50}
XXVII	H	H	..	C_6H_5	H	50	36	...	>50	92[b]
XXX	H	H	O	C_6H_5	H	400	>50	...	>50	>100
XLII	H	H	..	C_6H_5	CH_3	50	>50	...	>50	>100
XLIII	H	H	O	C_6H_5	CH_3	50	38	...	>50	>100
XXIX	H	H	..	C_6H_5	Cl	6.2	0.9	...	2.3	11
XXXI	H	H	O	C_6H_5	Cl	6.2	2.0	...	12.8	48
II[c]	CH_3	H	..	C_6H_5	Cl	0.4	0.9	3.4	4.1	4.6
XLIV	C_2H_5	H	..	C_6H_5	Cl	3.1	1.0	9.4	4.2	19
XXXIII	CH_3	H	O	C_6H_5	Cl	25	2.2	...	26	48
XLV	H	CH_3	..	C_6H_5	Cl	25	6.5	...	15	54[b]
XXXVI	H	CH_3	O	C_6H_5	Cl	25	3.1	...	20	...
XLVI	H	H	..	*o*-ClC_6H_4	Cl	0.4	0.1	4.7	1.2	7.4
XXXII	H	H	O	*o*-ClC_6H_4	Cl	1.3	2.0	>40	6	>40
XXXIV	CH_3	H	..	*o*-ClC_6H_4	Cl	0.4	0.1	4	2.8	7
XXXV	CH_3	H	O	*o*-ClC_6H_4	Cl	4	0.65	15	5.2	3.2
XLVII	H	H	O	2-C_4H_3S	Cl	25	20	...	29	>100

[a] See footnotes to Table I. [b] At 1/2 hr. [c] Diazepam.

TABLE IV.—STRUCTURE-ACTIVITY RELATIONSHIPS OF 1,3,4,5-TETRAHYDRO-2*H*-1,4-BENZODIAZEPIN-2-ONES[a]



Compd.	Structure R_4	Structure R_7	Biological Activity, Mice, mg./Kg., p.o. Motor Activity Decrease, MED	Anti-pentylene-tetrazole, ED_{50}	Anti-Max. El. Shock ED_{50}	Anti-morphine, ED_{50}	Ataxia at 1 hr., ED_{50}
XLVIII	H	H	100	29	..	>50	>100
XXXVIII	H	Cl	...	5.2	13	44	29
XLIX	CH_3	Cl	100	8	..	18	>100

[a] See footnotes to Table I.

is variable, but in most of the cases its presence decreases potency.

The most active compounds of Table III contain a 5-*o*-chlorophenyl group. Other negative substituents at this location also increase activity. Placement at the *meta* and *para* positions is less effective in this respect. In Table IV, one can see that saturation of the 4,5-bond of XXIX (Table III), affording XXXVIII, leads to a reduction in activity.

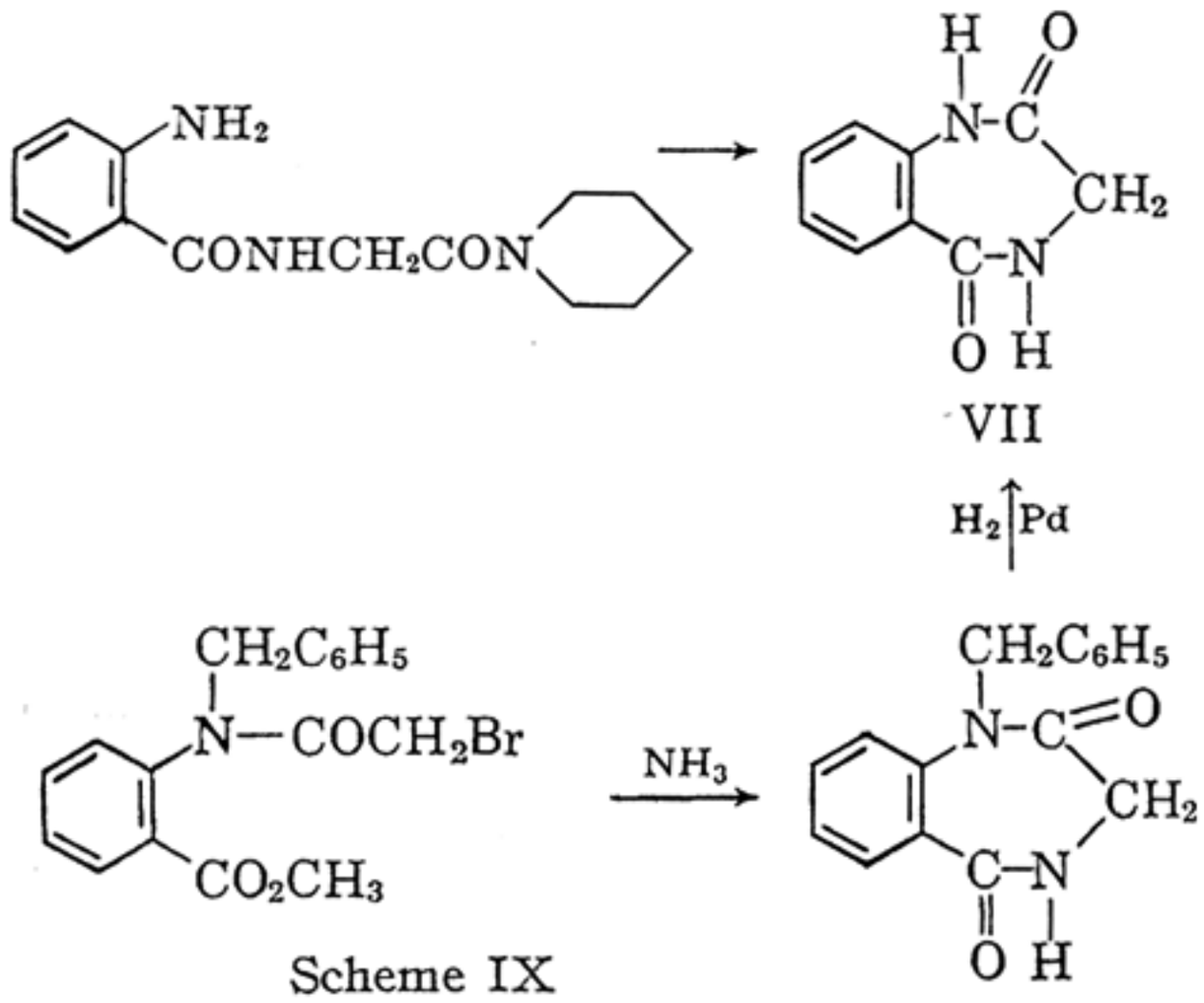
Diazepam has been studied extensively, and its pharmacology has been reported (44). Direct comparisons of diazepam and chlordiazepoxide have been made that show diazepam five to ten times as potent as chlordiazepoxide. These two compounds have also been compared with LA-1 (III) and XXXI in a Sidman avoidance situation (45). The nitro compound (III) was found to be the most potent of the four and to have the best ratio of activity to side effects. Strangely, XXXI was inactive.

The benzodiazepin-5-ones do not have activity of the chlordiazepoxide type.

1,4-BENZODIAZEPINEDIONES[5]

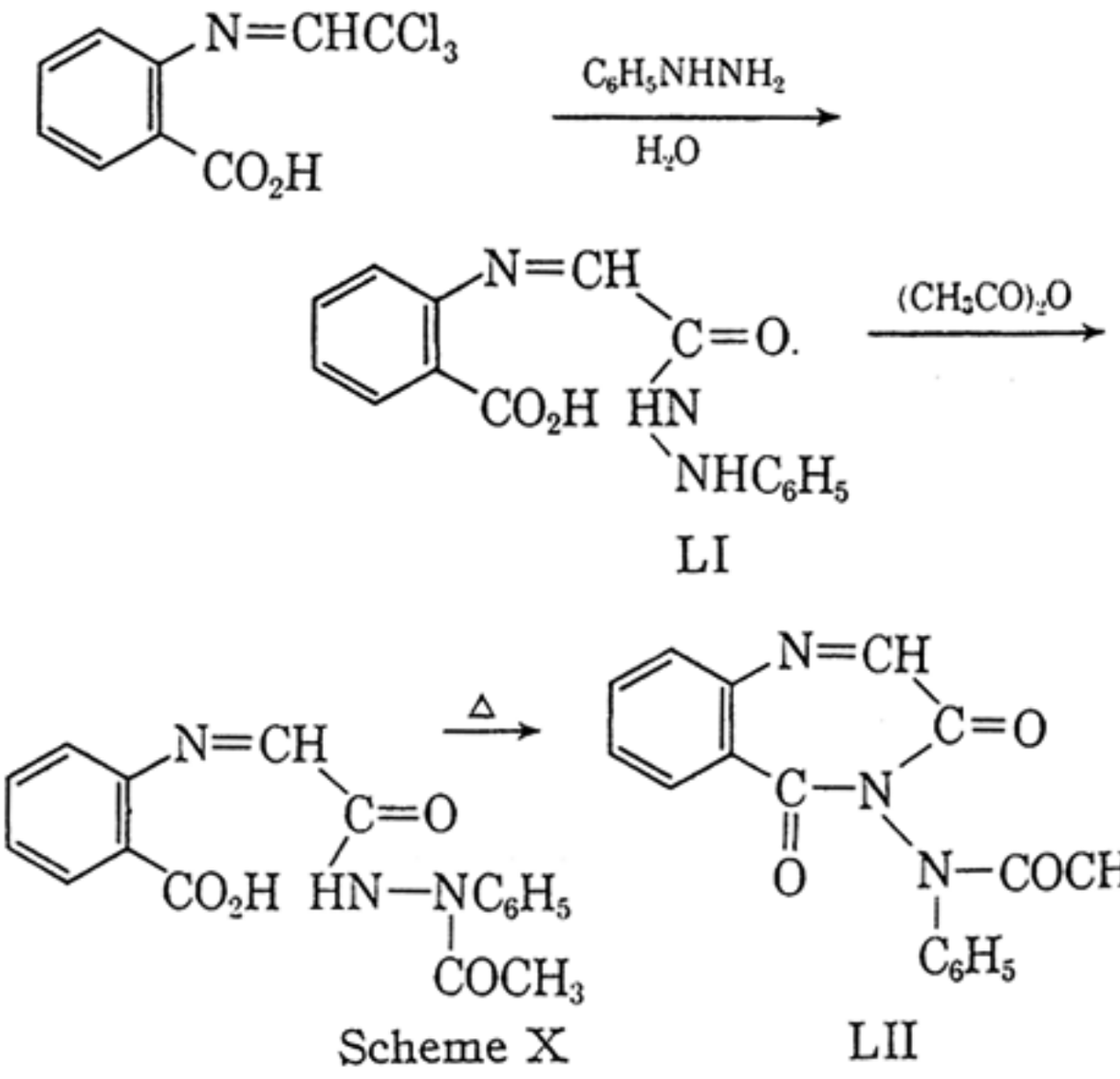
3,4 - Dihydro - 2*H* - 1,4 - benzodiazepine-2,5-(1*H*)-dione (VII) can be made from *o*-aminohippurylpiperidine by heating in basic solution (7). The same compound is prepared by catalytic debenzylation of the 1-benzyl derivative (L), itself obtainable from 2-(*N*-benzyl-α-bromoacetamido)benzoic acid methyl ester by treatment with ammonia. (See Scheme IX.) Heating in alcoholic methylamine converts VII into the *N*-methylamide of *o*-aminohippuric acid.

The chloral derivative of anthranilic acid reacts with phenylhydrazine to give LI, which, in turn, is acetylated and cyclized by heating to afford 4 - (*N* - phenylacetamido) - 3*H* - 1,4-benzodiazepine - 3,5 - (4*H*) - dione (LII). (See Scheme X.) Compound LII is the earliest known 1,4-benzodiazepine, having been prepared in 1904 by Gärtner (46).



VII

Scheme IX



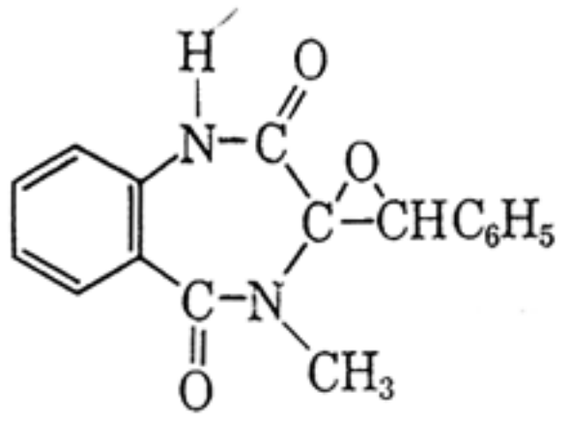
LI

Scheme X

LII

Mohammed and Luckner, in a preliminary communication (47), have proposed structure LIII for the mold metabolite, cyclopenin. The evidence so far given for this structure is not completely convincing.

[5] Benzodiazepine-2,3-diones are discussed under *Hydroxybenzodiazepines*.

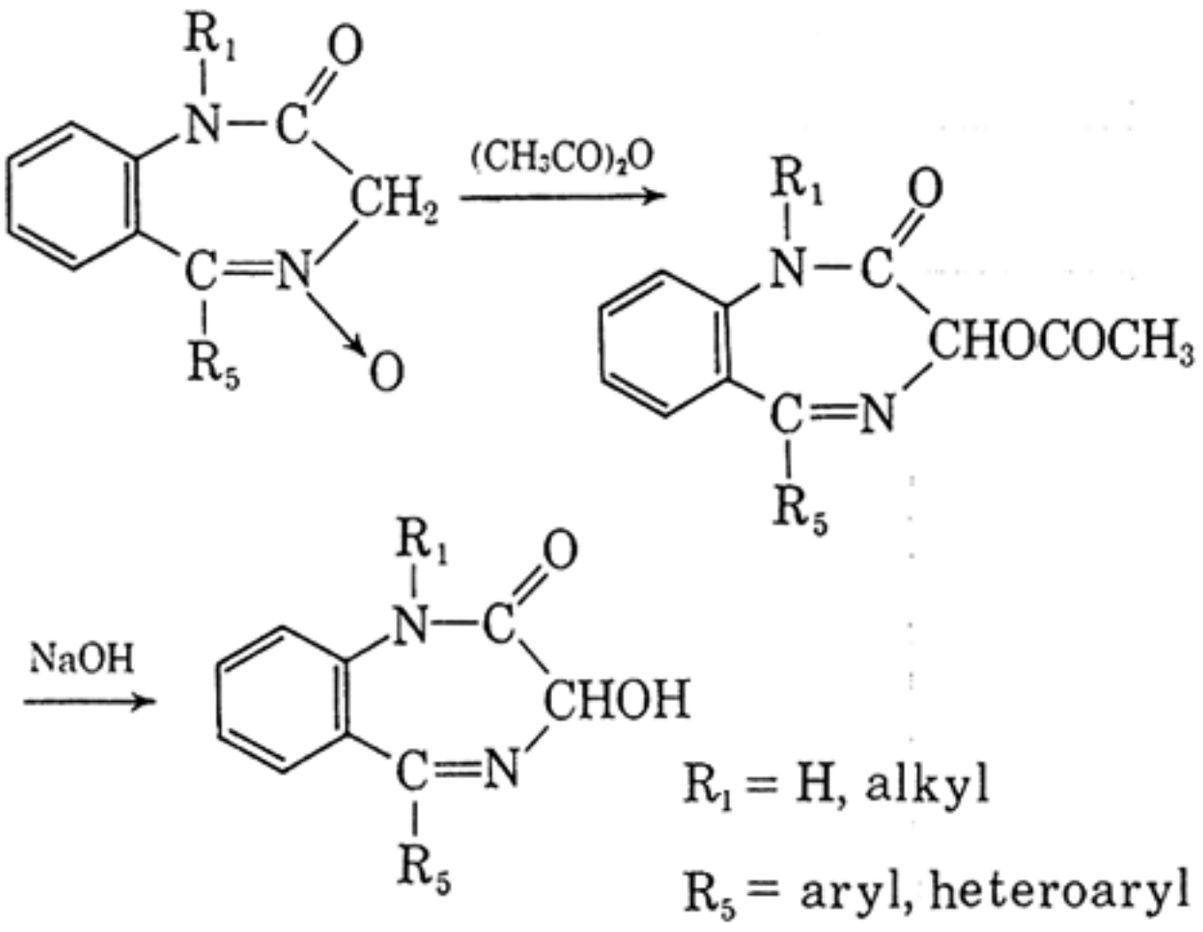


LIII

No biological activity has been reported for the benzodiazepinediones.

HYDROXY-1,4-BENZODIAZEPINES[6]

3 - Hydroxybenzodiazepin - 2 - ones.—5-Aryl - 1,3 - dihydro - 2*H* - 1,4-benzodiazepin-2-one 4-oxides, upon treatment with acylating agents such as acetic anhydride, undergo Polonovski-type rearrangements to afford 3-acyloxy-5-aryl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (5). The acyl groups are easily hydrolyzed to yield the corresponding 3-hydroxy compounds. (See Scheme XI.) The structure of the rearranged compounds has been confirmed by replacement

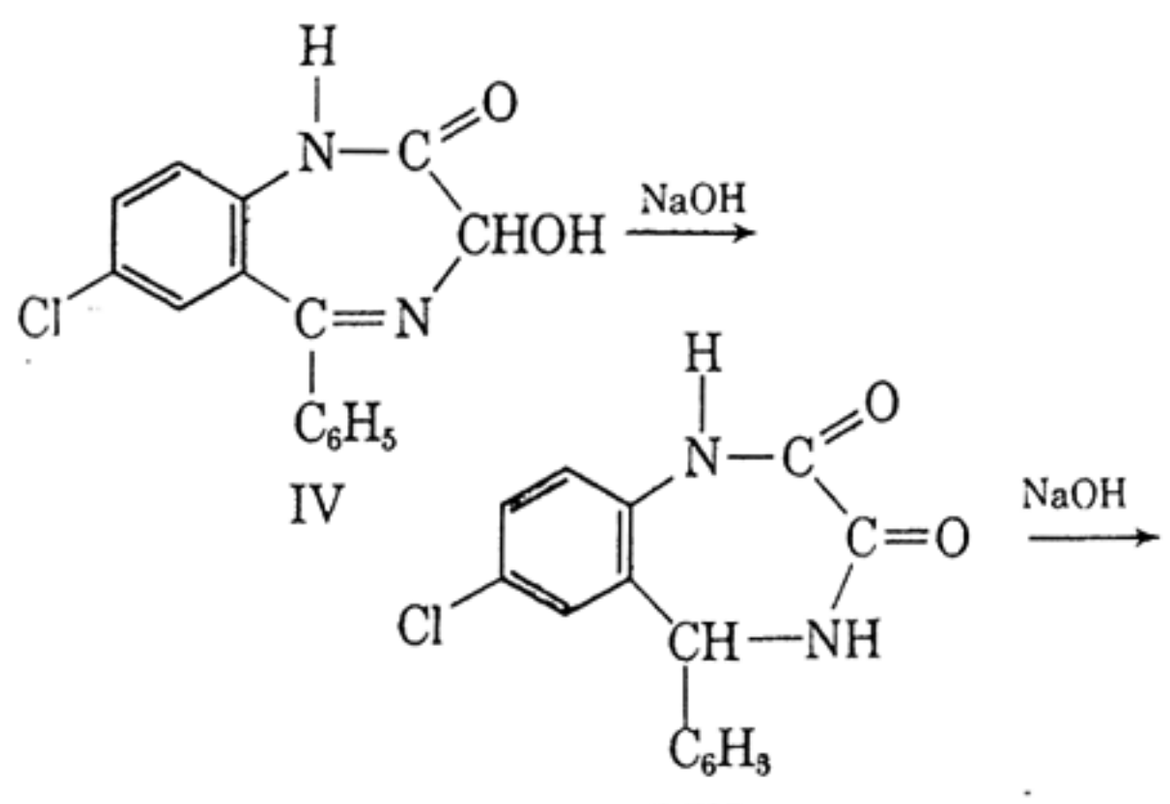


Scheme XI

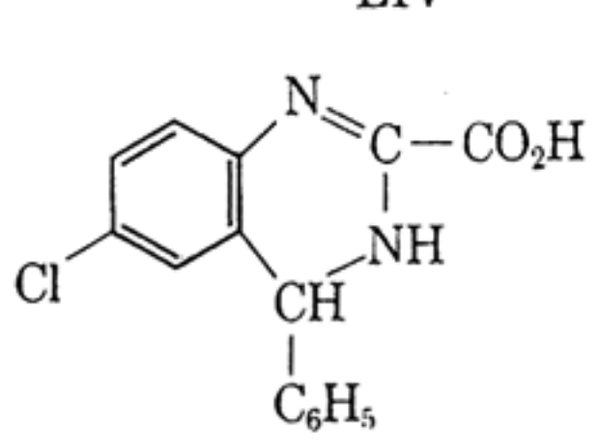
of the hydroxy group by chloride followed by catalytic removal of the chlorine, giving compounds of known structure. N.M.R. data further indicate the 3-position for the hydroxy group by the spin-spin coupling of the hydroxy proton with the 3-hydrogen.

Although 3-hydroxybenzodiazepin-2-ones are stable as solids or in neutral solution, the imino-carbinol structure leads to a number of rearrangements on treatment with acid or base. For example, 7-chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (IV) is changed into 7-chloro-5-phenyl-4,5-dihydro-2*H*-1,4-benzodiazepin-2,3(1*H*)-dione (LIV) with warm sodium hydroxide. More vigorous treatment results in 6 - chloro - 4 - phenyl - 3,4 - dihydroquinazoline-2-carboxylic acid (LV). (See Scheme XII.) Parallel rearrangements take place with the 1-methyl analog (LVI), except that the final

[6] 4-Hydroxybenzodiazepines are treated along with the corresponding oxidation products, the 4-oxides.



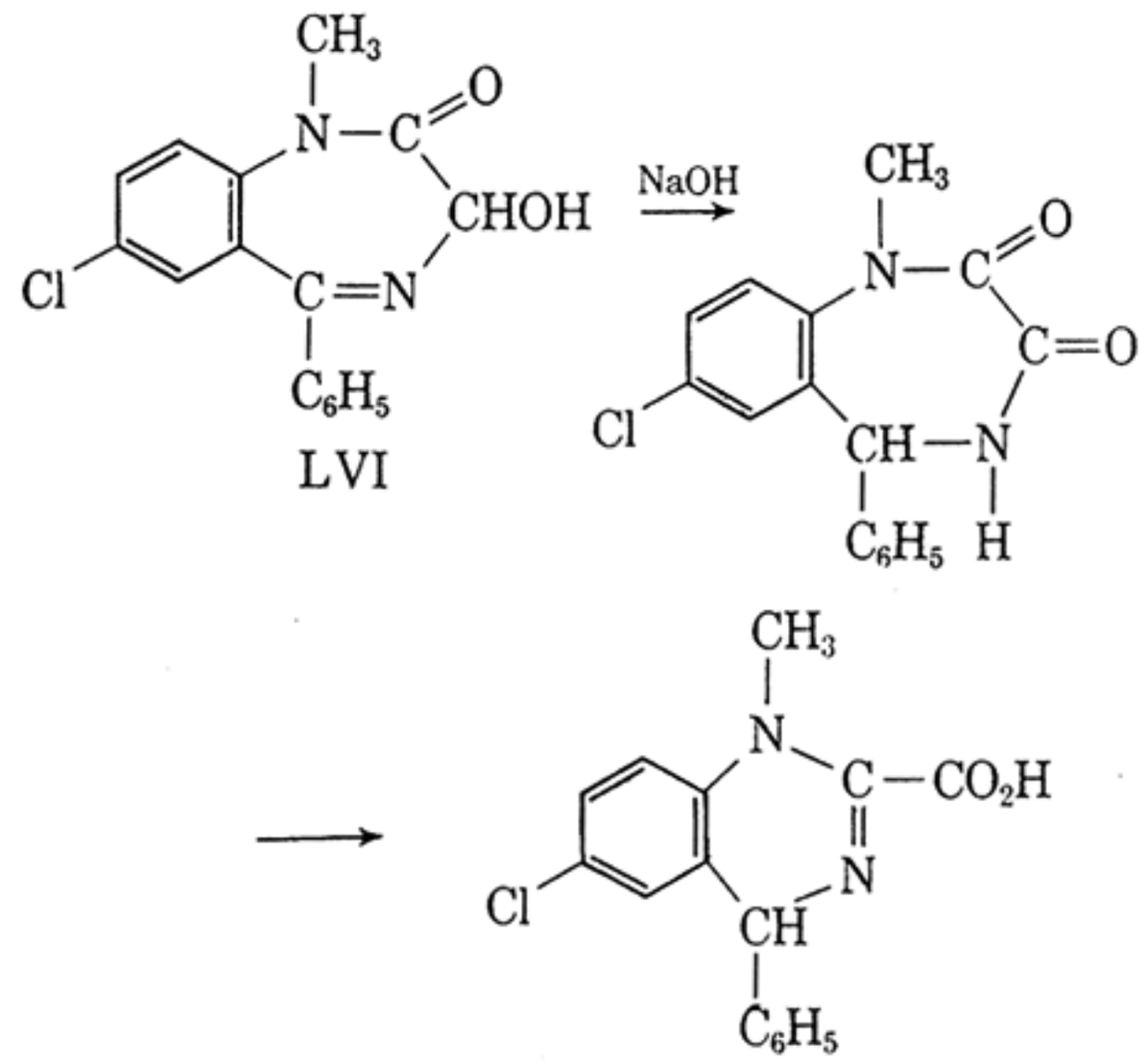
LIV



LV

Scheme XII

quinazoline (LVII) is a 1,4-dihydro rather than a 3,4-dihydro form (38). (See Scheme XIII.)

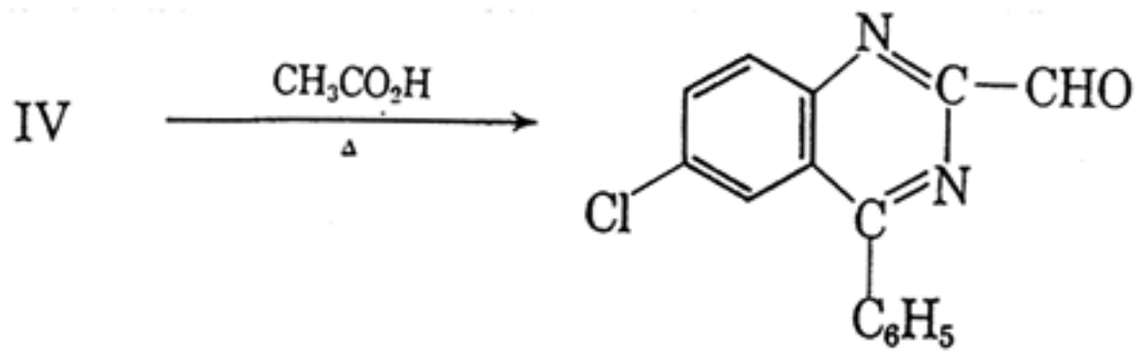


LVI

LVII

Scheme XIII

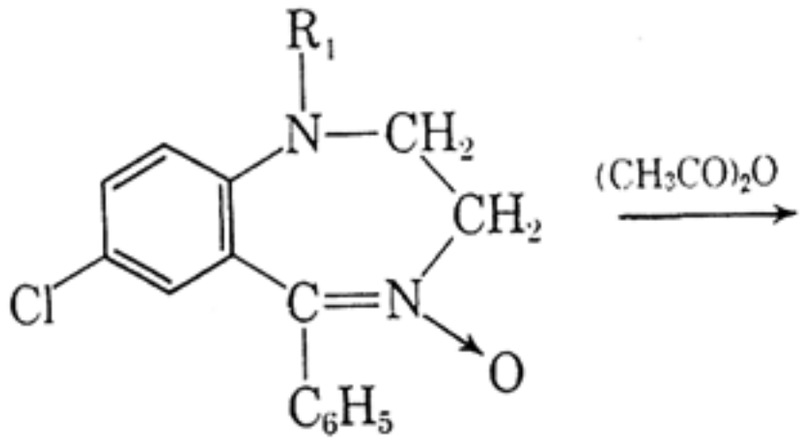
Compound IV rearranges in hot acetic acid, resulting in 6-chloro-4-phenylquinazoline-2-carboxaldehyde (LVIII) (41). Hydrazine causes the same rearrangement, the final product being the corresponding hydrazone. Primary amines give aldimines under similar conditions. Com-



LVIII

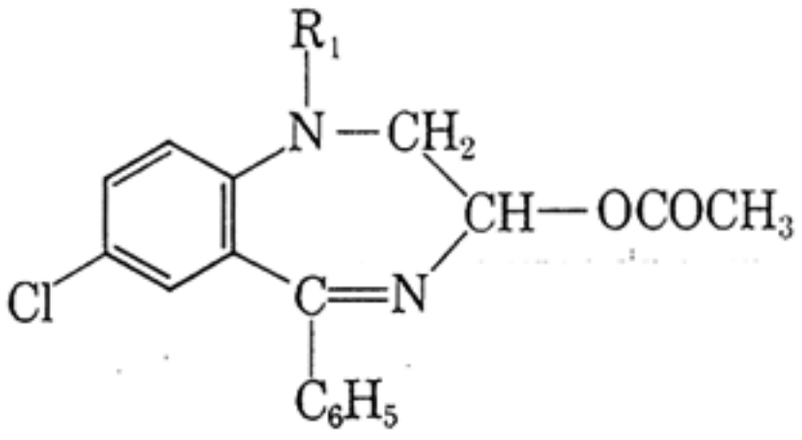
pound IV is easily converted into 7-chloro-3-ethoxy - 5 - phenyl - 1,3 - dihydro - 2*H* - 1,4-benzodiazepin-2-one (LIX) by way of the 3-chloro derivative (5).

3 - Hydroxybenzodiazepines.—The 2-oxo function is not required to permit the Polonovski rearrangements of the 4-oxides (48). 1-Acetyl-7-chloro - 5 - phenyl - 2,3 - dihydro - 1*H* - 1,4-benzodiazepine 4-oxide (LX) or its 1-methyl analog (LXI) rearranges as does IV, giving the 3-acetoxy-(LXII) and (LXIII) and, subsequently, the 3-hydroxy compounds (LXIV and LXV).



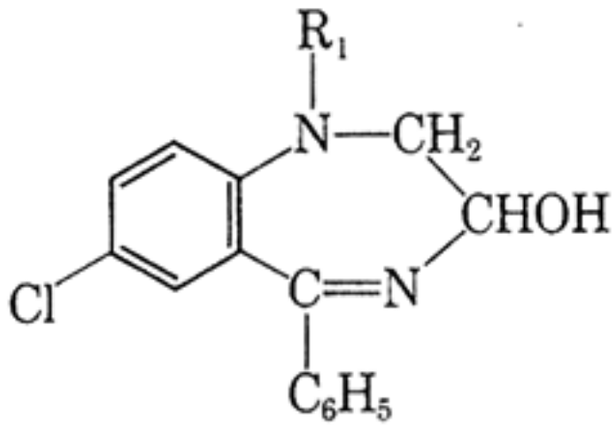
LX: $R_1 = CH_3CO$

LXI: $R_1 = CH_3$



LXII: $R_1 = CH_3CO$

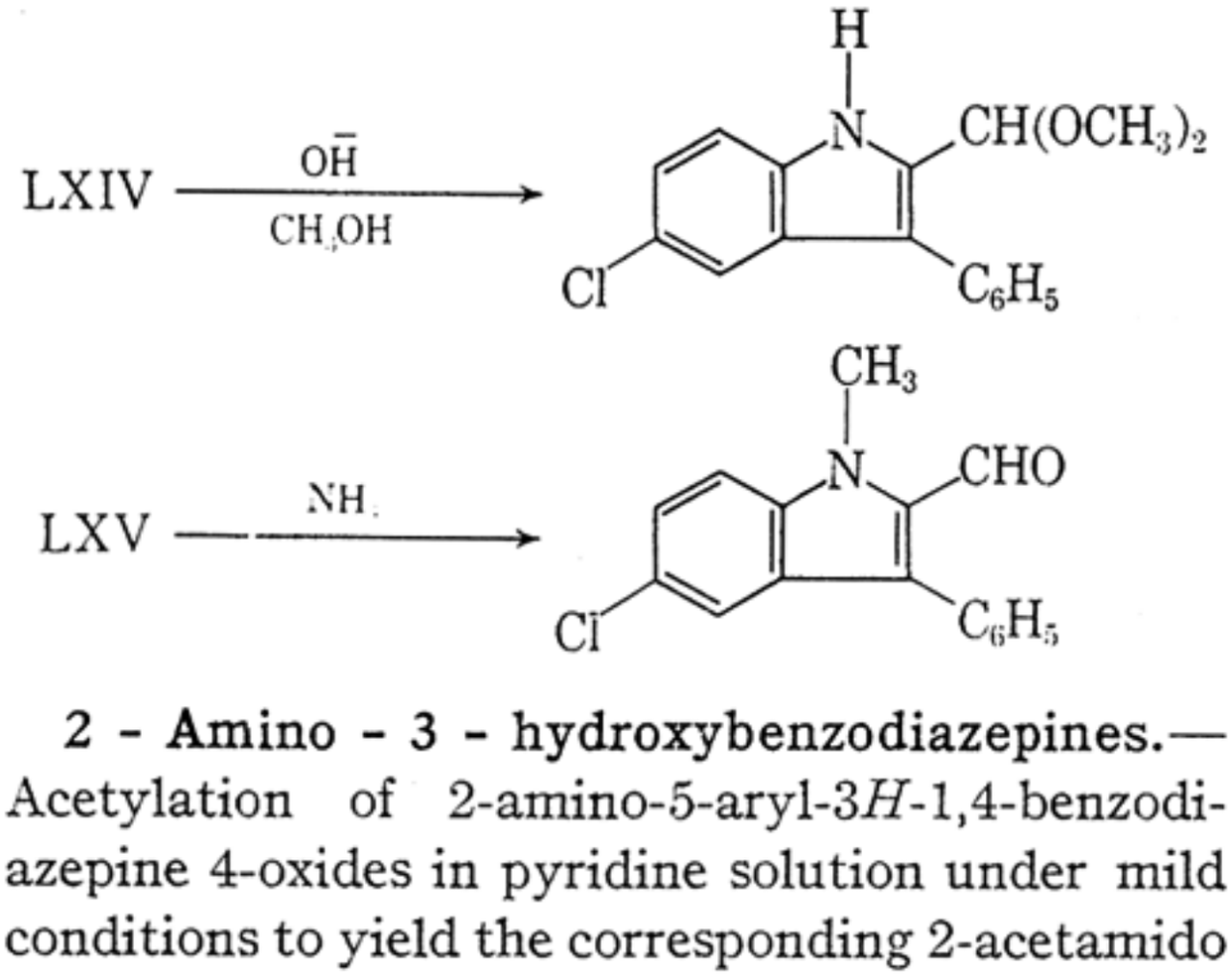
LXIII: $R_1 = CH_3$



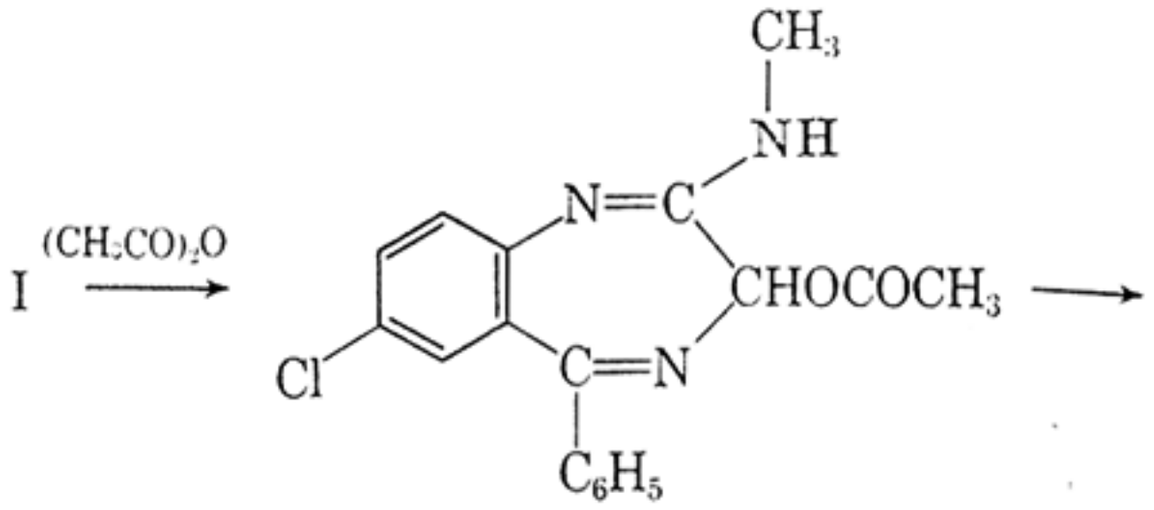
LXIV: $R_1 = CH_3CO$

LXV: $R_1 = CH_3$

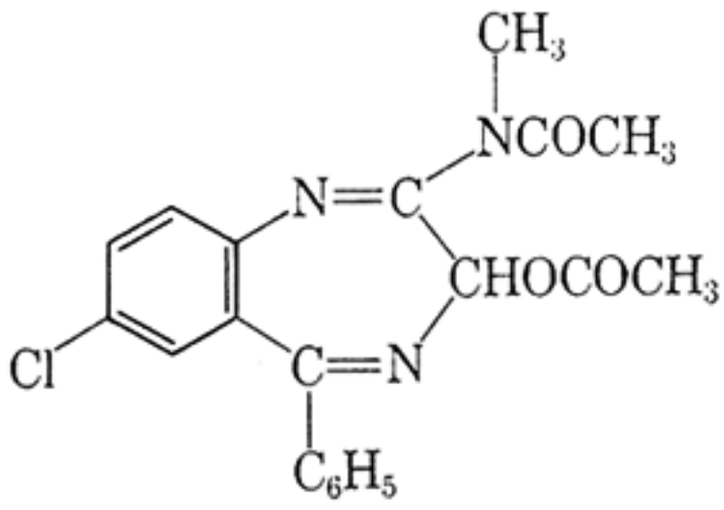
Alkaline conditions cause compounds LXIV and LXV to undergo ring contraction, furnishing indole derivatives.



2 - Amino - 3 - hydroxybenzodiazepines.—Acetylation of 2-amino-5-aryl-3*H*-1,4-benzodiazepine 4-oxides in pyridine solution under mild conditions to yield the corresponding 2-acetamido compounds has already been discussed. More vigorous acetylation in the absence of pyridine brings about a Polonovski-type rearrangement (49). For example, I is converted into 3-acetoxy - 2 - (*N* - methylacetamido) - 7 - chloro-5-phenyl-3*H*-1,4-benzodiazepine (LXVI) with acetic anhydride on the steam bath. The isolation of LXVII indicates that the rearrangement takes place before acetylation of the methylamino group.



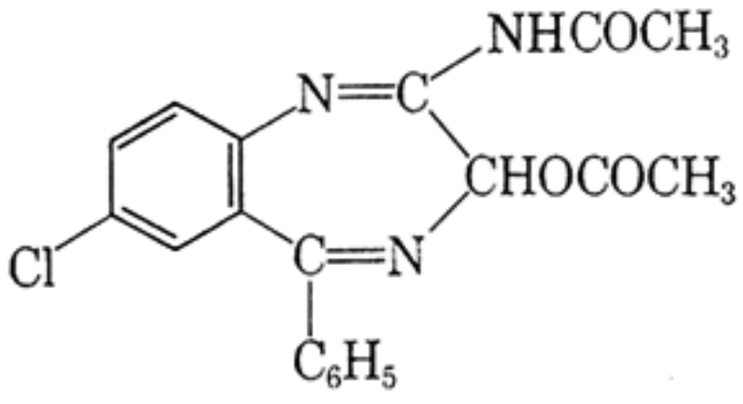
LXVII



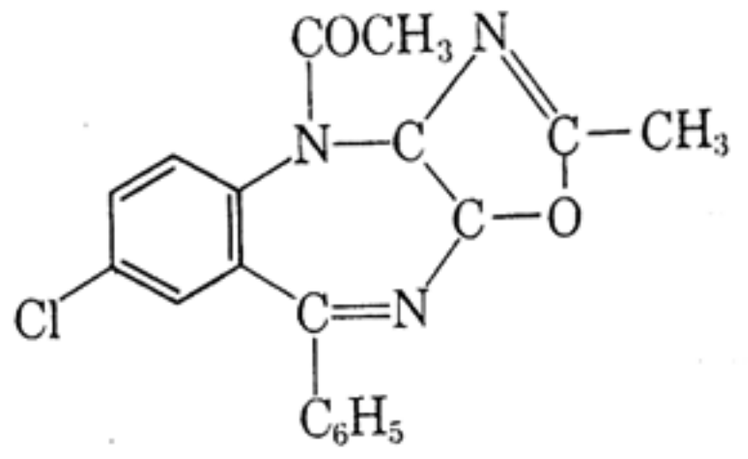
LXVI

With an unsubstituted 2-amino group, diacetylation (LXVIII) occurs and two by-products (LXIX and LXX) are formed. The formation of 2-acetamido-7-chloro-5-phenyl-3*H*-

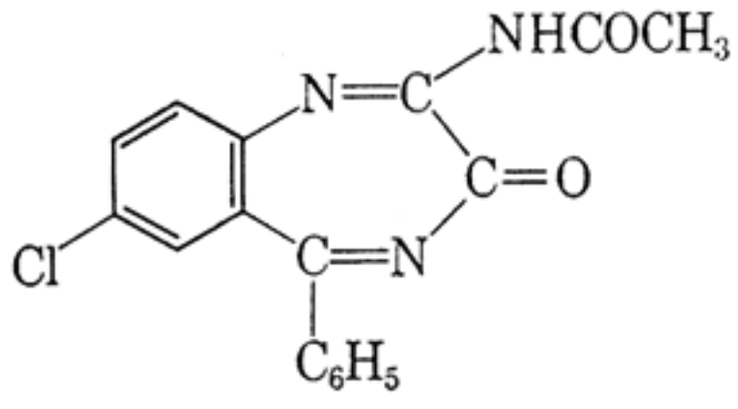
XXI + $(CH_3CO)_2O$ ⟶



LXVIII



LXIX



LXX

1,4-benzodiazepin-3-one (LXX) is especially

difficult to account for. With LXX, a ring contraction takes place in hot acetic acid to afford *N* - acetyl - 6 - chloro - 4 - phenylquinazoline-2-carboxamide.

Both acetyl groups of LXVIII are removed in base yielding the corresponding 2-amino-3-hydroxy product (LXXI). Mild acid hydrolysis converts the diacetyl compound into 3-acetoxy-7-chloro - 5 - phenyl - 1,3 - dihydro - 2*H*- 1,4-benzodiazepin-2-one (LXXII).

Other Hydroxy Compounds.—7-Hydroxy-5-phenyl - 1,3 - dihydro - 2*H* - 1,4 - benzodiazepin-2-one has been prepared in the standard way by reaction of 2-amino-4-hydroxybenzophenone with glycine ethyl ester (27).

Biological Activity.—A group of compounds containing a 3-hydroxy group or a functional derivative thereof is listed in Table V. The general pattern of influences of the 1,5, and 7-position substituents seen in Tables II and III exists here.

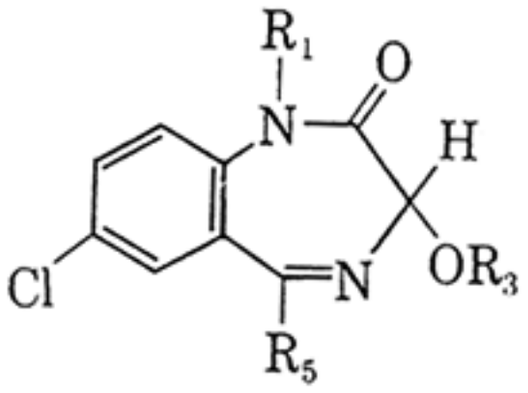
The 3-hydroxy group is a more effective substituent than an acetoxy or an ethoxy group. Particularly interesting compounds are LXXIII and LXXIV, whose ataxic doses are high in relation to their antipentylenetetrazol activity.

2-Amino-3-hydroxy compounds (Table VI) are much less potent than the corresponding 2-oxo-3-hydroxy products.

Oxazepam has been compared directly with chlordiazepoxide and diazepam in an induced conflict situation (50) which measures anti-anxiety effects. Diazepam was the most potent of the three compounds, with oxazepam and chlordiazepoxide approximately equipotent. Oxazepam had the most favorable ratio of activity to side effects.

The 3-hydroxy group is effective in reducing toxicity. The acute LD_{50} values in mice (p.o.) for oxazepam, diazepam, and chlordiazepoxide are >5000, 720, and 620 mg./Kg., respectively (44, 51). Possibly this reduced toxicity results from the ease of conjugation and subsequent elimination of oxazepam as a glucuronide. This metabolic product has been found in the dog (52).

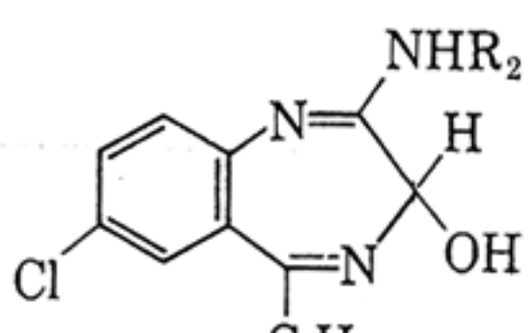
TABLE V.—STRUCTURE-ACTIVITY RELATIONSHIPS OF 3-OXY-1,3-DIHYDRO-2*H*-1,4-BENZODIAZEPIN-2-ONES[a]



Compd.	Structure R_1	Structure R_3	Structure R_5	Biological Activity, Mice, mg./Kg., p.o.: Motor Activity Decrease, MED	Anti-pentylene-tetrazol, ED_{50}	Anti-Max. El. Shock, ED_{50}	Anti-morphine, ED_{50}	Ataxia at 1 hr., ED_{50}
IV[b]	H	H	C_6H_5	1.6	0.9	1.3	3.1	5.0
LVI	CH_3	H	C_6H_5	1.3	0.7	2.6	1.5	5.0
LXXII	H	CH_3CO	C_6H_5	1.6	2.6	...	7.5	7.1
LIX	H	C_2H_5	C_6H_5	25	5.7	...	21	56
LXXIII	H	H	*o*-ClC_6H_4	0.1	0.07	2.0	0.24	16
LXXIV	CH_3	H	*o*-ClC_6H_4	0.4	0.09	2.4	0.25	33
LXXV	H	CH_3CO	*o*-ClC_6H_4	1.0	0.26	3.7	0.12	30

[a] See footnotes to Table I. [b] Oxazepam.

TABLE VI.—STRUCTURE-ACTIVITY RELATIONSHIPS OF 2-AMINO-3-HYDROXY-3*H*-1,4-BENZODIAZEPINES[a]

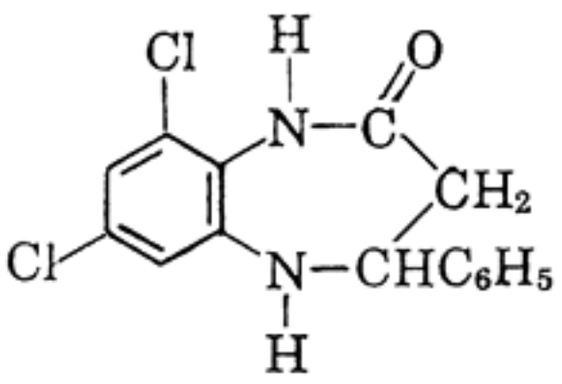


Compd.	Structure R_2	Biological Activity, Mice, mg./Kg., p.o.: Motor Activity Decrease, MED	Anti-pentylene-tetrazol, ED_{50}	Anti-Max. El. shock, ED_{50}	Anti-morphine, ED_{50}	Ataxia at 1 hr., ED_{50}
LXXI	H	4	25	40	120	>40
LXXVI	CH_3	127	31	28	>40	>40

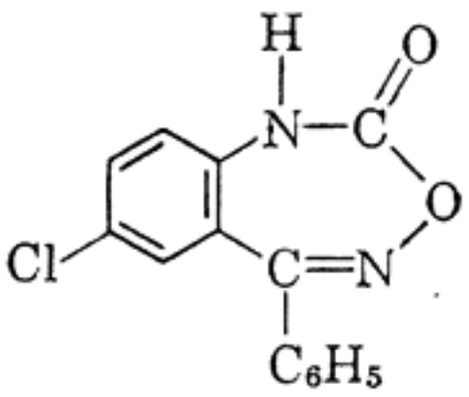
[a] See footnotes to Table I.

MISCELLANEOUS COMPOUNDS

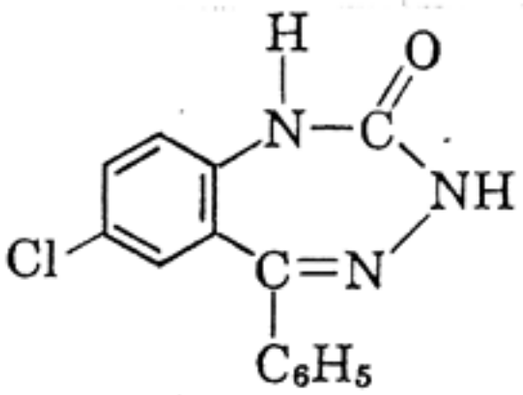
Several compounds that are not 1,4-benzodiazepines but that are analogs of active 1,4-benzodiazepines have been synthesized and are helpful in establishing the structural requirements for activity. Included are 7,9-dichloro-4-phenyl - 1,3,4,5 - tetrahydro - 2*H* - 1,5 - benzodiazepin-2-one (LXXVII) (53), 7-chloro-5-phenyl 3,1,4-benzoxadiazepin-2(1*H*)-one (LXXVIII) (54), 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,3,4-benzotriazepin-2-one (LXXIX) (55), and 7-chloro - 1 - methyl - 5 - phenyl - 3,5 - dihydro-4,1-benzoxazepin-2(1*H*)-one (LXXX) (56). No activity results are reported for the first of these compounds. The last three do not have activity of the same type as chlordiazepoxide.



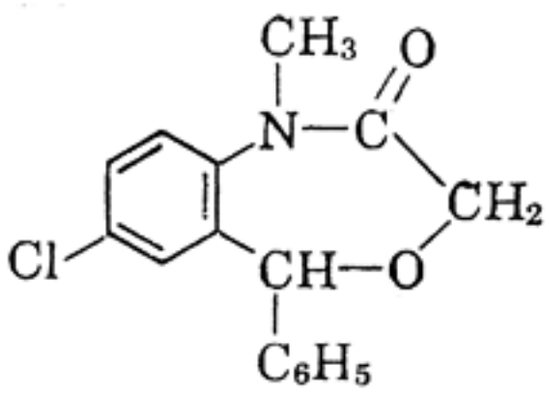
LXXVII



LXXVIII



LXXIX



LXXX

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