THE CHEMISTRY OF BENZODIAZEPINES

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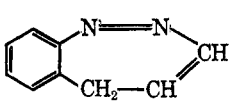
CONTENTS

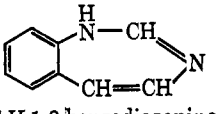
I. INTRODUCTION

A. GENERAL INTRODUCTION

Benzodiazepines are bicyclic heterocyclic compounds having a benzene nucleus fused to a seven-membered ring containing two nitrogen atoms. The following six formulas represent the basic ring structures of benzodiazepines considered in this review.

Since the syntheses and reactions of the six classes of benzodiazepines differ considerably, they have been described separately and will be found under the appropriate class headings.


5*H*-1,2-benzodiazepine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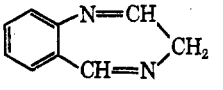
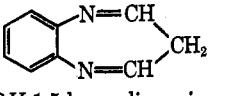
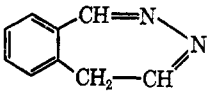
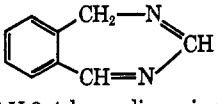

3*H*-1,4-benzodiazepine

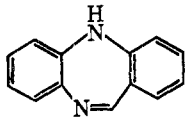

3*H*-1,5-benzodiazepine


5*H*-2,3-benzodiazepine


1*H*-2,4-benzodiazepine

B. SCOPE OF REVIEW

The present review covers the literature through 1967. The above six classes of benzodiazepines are described, together with their various substituted or reduced forms. No attempt has been made to survey compounds having a second ring fused to the diazepine portion of the molecule; *e.g.*, dibenzodiazepines (**1**), pyridobenzodiazepines (**2**), and naphthodiazepines (**3**) will not be discussed. Compounds such as the pyridodiazepine **4** and the quinoxalinodiazepine **5** will likewise not be included. Products obtained by simple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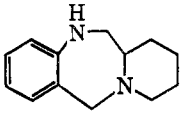
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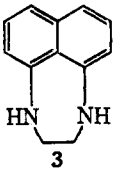
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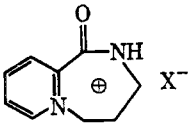
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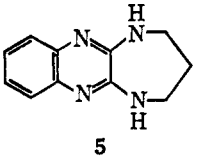
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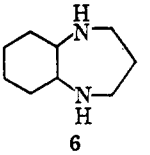
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transformations, *e.g.*, reduction as in **6**, are considered in this article.

The 1,4-benzodiazepines form the most extensively explored group in this series, largely owing to the discovery[1-4] of their interesting biological activity, which has led to the introduction of four drugs (section I.E). The 1,5-benzodiazepines have been thoroughly studied during a period of several decades, largely because of their relatively easy synthesis from common starting materials. The other four groups of benzodiazepines have so far failed to attract very much interest.

C. OTHER REVIEWS PUBLISHED

Review articles by the following authors have appeared in the years and languages indicated: Vaĭsman,[5] 1,5-benzodiazepines (1940, Russian); De Stevens,[6] 1,3-benzodiazepines (1962; English); Childress and Gluckman,[2] 1,4-benzodiazepines, chemistry and pharmacology (1964, English); Sternbach, Randall, and Gustafson,[1] 1,4-benzodiazepines, chemistry, pharmacology, and clinical investigations (1964, English); Nawojski,[7] 1,3- and 2,3-benzodiazepines (1964, Polish); Nawojski,[8] 1,4- and 1,5-benzodiazepines (1965, Polish); Popp and Noble,[9] diazepines and benzodiazepines (1967, English); Moore and Mitchell,[10] diazepines and benzodiazepines (1967, English); Sternbach and Randall,[3] 1,4-benzodiazepines, chemistry and pharmacology (1966, English); Sternbach, Randall, Banziger, and Lehr,[4] 1,4-benzodiazepines, chemistry and pharmacology (1968, English).

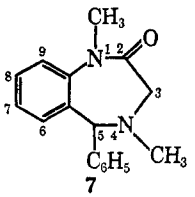
D. NOMENCLATURE

Modern *Chemical Abstracts* nomenclature[11] has been used throughout this review, and older names of compounds have been appropriately changed to conform with this system.

Benzodiazepines are numbered as shown in formula **7**, starting at the position adjacent to the carbocyclic ring, regardless of the positions of the nitrogen atoms. The latter are specified by prefixed numbers, as shown in section A; *e.g.*, **7** is a 1,4-benzodiazepine and **8** is a 2,4-benzodiazepine. The term benzodiazepine implies a maximum degree of unsaturation, *i.e.*, a total of three double bonds in the seven-membered ring. The position of the odd hydrogen atom (even if occupied by another mono- or divalent substituent) is indicated by the term 1*H*, 2*H*, 3*H*, etc., as shown in section A. In dihydro- and tetrahydrobenzodiazepines the odd hydrogen is given the lowest possible number. This is, however, complicated by the fact that first consideration is given to the position of a functional group which is expressed as a suffix to the name of the compound; *e.g.*, **7** is a 1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one (indicated *H* assigned to the position of the 2-one group),

(1) L. H. Sternbach, L. O. Randall, and S. Gustafson, "Psychopharmacological Agents," Vol. 1–4, Academic Press, New York, N. Y., 1964, p 137.
(2) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).
(3) L. H. Sternbach and L. O. Randall, "CNS Drugs, a Symposium held at the Regional Research Laboratory, Hyderabad, India," CSIR, New Delhi, India, 1966, p 53.
(4) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lehr, "Medicinal Research Series," Vol. 2, "Drugs Affecting the Central Nervous System," A. Burger, Ed., Marcel Dekker Inc., New York, N. Y., 1968, p 237.
(5) S. B. Vaĭsman, *Tr. Inst. Khim. Khar'kov Gosudarst. Univ.*, **5**, 57 (1940); *Chem. Abstr.*, **38**, 750 (1944).
(6) G. De Stevens, *Record Chem. Progr.*, **23**, 105 (1962).
(7) A. Nawojski, *Wiadomosci Chemi.*, **12**, 673 (1964).
(8) A. Nawojski, *Wiadomosci Chemi.*, **19**, 75 (1965).
(9) F. D. Popp and A. C. Noble, *Advan. Heterocyclic Chem.*, **8**, 21 (1967).
(10) J. A. Moore and E. Mitchell, "Heterocyclic Compounds," Vol. 9, John Wiley and Sons, Inc., New York, N. Y., 1967, p 224.
(11) "The Naming and Indexing of Chemical Compounds by Chemical Abstracts," Introduction to Subject Index of *Chem. Abstr.*, **56** (1962).

but **8** is a 2,3,4,5-tetrahydro-1*H*-2,4-benzodiazepine (indicated *H* given the lowest possible numerical value in the absence of a substituent named as a suffix).



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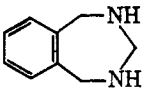

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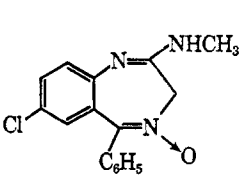
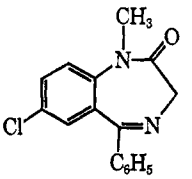
E. DRUGS

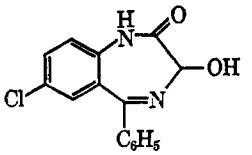
Among the large number of benzodiazepines that have been synthesized, only members of the 1,4-benzodiazepine group have shown sufficient pharmacological and clinical activity to warrant introduction as new drugs. The four compounds below are the active ingredients of the presently marketed psychosedative and tranquilizing agents: (A) Librium®, (B) Valium®, (C) Serax®, and (D) Mogadon®; their generic names are shown under the formulas. The metabolism of these



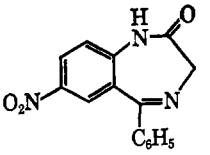
A, chlordiazepoxide



B, diazepam



C, oxazepam



D, nitrazepam

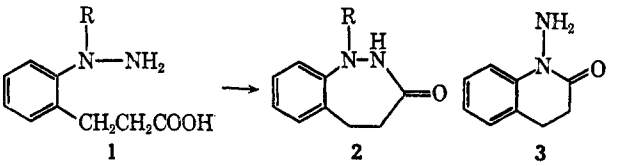
compounds has been extensively studied,[12-17] and methods for their analytical detection and determination have been reported.[18-25]

(12) B. A. Koechlin, M. A. Schwartz, G. Krol, and W. Oberhansli, *J. Pharmacol. Exptl. Therap.*, **148**, 399 (1965).
(13) H. W. Ruelius, J. M. Lee, and H. E. Alburn, *Arch. Biochem. Biophys.*, **111**, 376 (1965).
(14) M. A. Schwartz, B. A. Koechlin, E. Postma, S. Palmer, and G. Krol, *J. Pharmacol. Exptl. Therap.*, **149**, 423 (1965).
(15) M. A. Schwartz and E. Postma, *J. Pharm. Sci.*, **55**, 1358 (1966).
(16) M. A. Schwartz, P. Bommer, and F. M. Vane, *Arch. Biochem. Biophys.*, **121**, 508 (1967).
(17) S. S. Walkenstein, R. Wiser, C. H. Gudmundsen, H. B. Kimmel, and R. A. Corradino, *J. Pharm. Sci.*, **53**, 1181 (1964).
(18) H. Oelschlaeger and H. Volke, *Collection Czech. Chem. Commun.*, **31**, 1264 (1966).
(19) J. A. F. De Silva, B. A. Koechlin, and G. Bader, *J. Pharm. Sci.*, **55**, 692 (1966).
(20) H. Oelschlaeger, J. Volke, G. T. Lim, and U. Frank, *Arzneimittel-Forsch.*, **16**, 82 (1966).
(21) H. Oelschlaeger, J. Volke, K. Hoffmann, and E. Kurek, *Arch. Pharm.*, **300**, 250 (1967).
(22) O. Pribilla, *Arzneimittel-Forsch.*, **15**, 1148 (1965).
(23) J. Rieder, *ibid.*, **15**, 1134 (1965).
(24) B. Z. Senkowski, M. S. Levin, J. R. Urbigkit, and E. G. Wollish, *Anal. Chem.*, **36**, 1991 (1964).
(25) H. Waldmann, C. van Planta, B. Senkowski, and E. G. Wollish submitted for publication.

II. 1,2-BENZODIAZEPINES

A. SYNTHESIS

Cyclization of the *o*-hydrazinophenylpropionic acid (**1**, R = ethyl) gave[26] 1-ethyl-1,2,4,5-tetrahydro-3*H*-1,2-benzodiazepin-3-one (**2**, R = ethyl) in 60–70% yield. An attempt to prepare **2** (R = H) from **1**



1 **2** **3**

(R = H) yielded only the aminoquinolone **3**.

Treatment of the diketone **4** with hydrazine gave[27] the corresponding azine, 5,5a,6,7,8,9-hexahydro-3-phenyl-4*H*-1,2-benzodiazepine (**5**) in 86% yield.

4 **5**

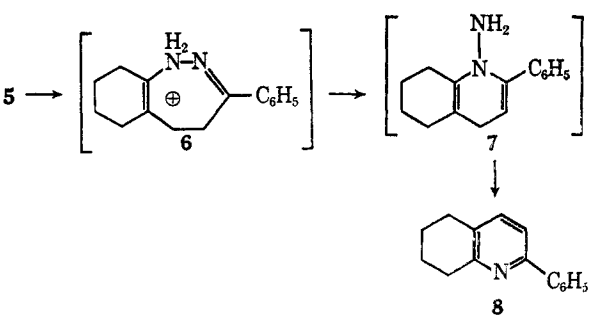
B. REACTIONS

1. *Hydrolysis*

The benzodiazepin-3-one **2** was stable to alkali but was readily hydrolyzed by hot hydrochloric acid to give[26] compound **1**. Compound **3** remained unaffected under these conditions.

2. *Ring Contraction*

Diazepine **5** was converted[27] into 2-phenyl-5,6,7,8-tetrahydroquinoline (**8**) by treatment with hydrogen chloride at 235°, in the absence of solvent, or in ethanolic or aqueous solution. The mechanism of this ring contraction has been discussed[28] and proceeds by isomerization of the protonated species **6** to the aminodihydropyridine **7**, which readily aromatizes, by loss of ammonia, to give **8**.



6 **7** **8**

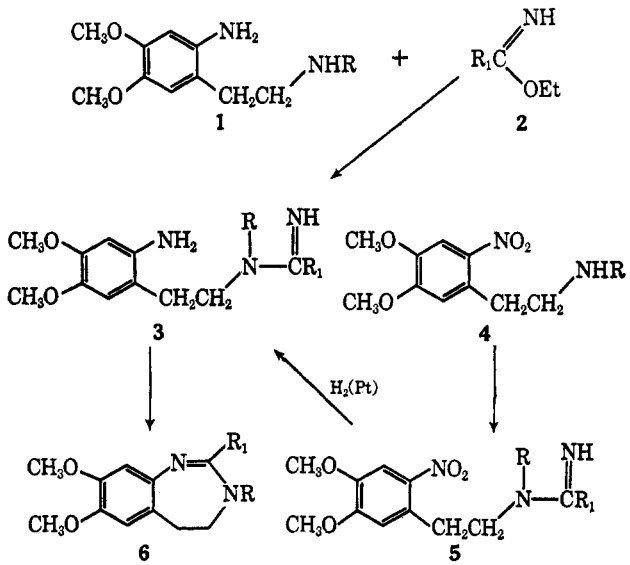
(26) E. Fischer and H. Kuzel, *Ann.*, **221**, 261 (1883).
(27) N. S. Gill, K. B. James, F. Lions, and K. T. Potts, *J. Am. Chem. Soc.*, **74**, 4923 (1952).
(28) F. R. Brody and P. R. Ruby, "The Chemistry of Heterocyclic Compounds, Pyridine and Its Derivatives," Part I, Interscience Publishers, New York, N. Y., 1960, p 268.

III. 1,3-BENZODIAZEPINES

A. SYNTHESIS

1. 1,3-Benzodiazepines

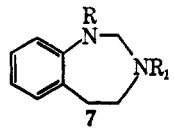
A general synthesis for 4,5-dihydro-3*H*-1,3-benzodiazepines (**6**) involved condensation[29] of *o*-aminophenethylamines **1** with imidates **2**, which led to mixtures containing the amidine **3** and the benzodiazepine **6**. Better yields of **3** were obtained by use of the



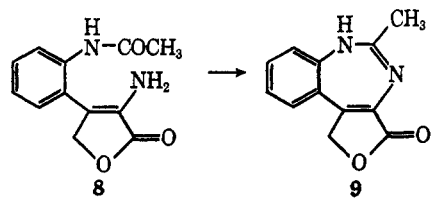
R = H or CH_3; R_1 = alkyl or aryl

2-nitrophenethylamine **4** in the condensation reaction. Catalytic reduction of the nitro group in the intermediate **5** gave **3**, which was cyclized to **6** in refluxing toluene or ethanol.

Reduction of benzodiazepin-4-ones **12** (R = H or $C_6H_5CH_2$; R_1 = CH_3) with lithium aluminum hydride gave[30,31] unstable 2,3,4,5-tetrahydro-1*H*-1,3-benzodiazepines **7**.

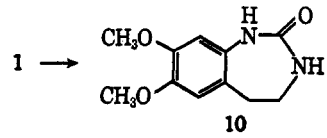


Intramolecular condensation of **8** in dilute hydrochloric acid yielded a red hydrochloride, to which the structure 5-hydroxymethyl-2-methyl-1*H*-1,3-benzodiazepine-4-carboxylic acid γ-lactone (**9**) was assigned.[32]

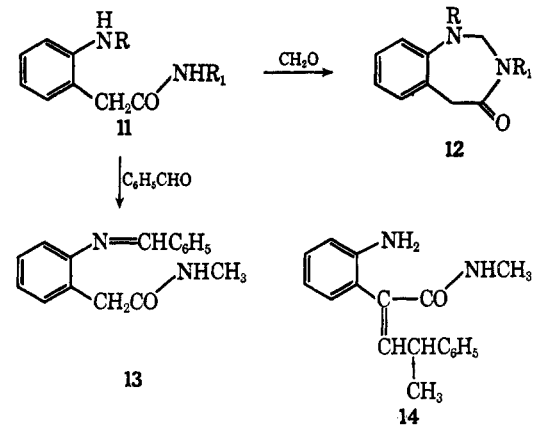


2. 1,3-Benzodiazepinones

The 1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one **10** was made[29] by treatment of *o*-aminophenethylamine **1** (R = H) with N,N′-carbonyldiimidazole.

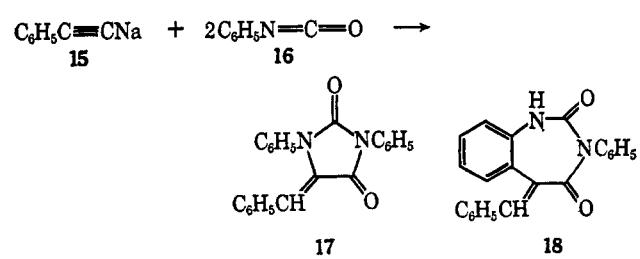


Condensation of *o*-aminophenylacetamides **11** with formaldehyde gave[30,31] the 1,2,3,5-tetrahydro-4*H*-1,3-benzodiazepin-4-ones **12**. Reaction of **11** (R = H; R_1 = CH_3) with benzaldehyde gave the benzylidene



derivative **13**, whereas condensation of the same amide with α-phenylpropionaldehyde resulted in formation of the α-phenylpropylidene amide **14**. Compound **13** was reduced with sodium borohydride to **11** (R = $C_6H_5CH_2$; R_1 = CH_3), and both this compound and **14** were condensed with formaldehyde to give compounds of type **12**.

Treatment of sodium phenylacetylide (**15**) with two molar proportions of phenyl isocyanate (**16**) gave[33] two isomeric products **17** and **18**. Compound **17** was identified with an authentic sample; the 5-benzyl-

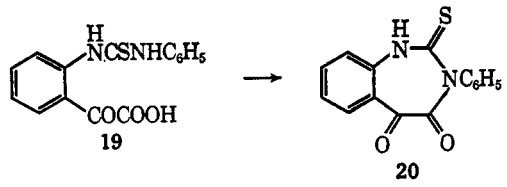


idene-3-phenyl-5*H*-1,3-benzodiazepine-2,4-(1*H*,3*H*)-dione structure ascribed to the yellow compound **18** was based on correct analyses, molecular weight deter-

(29) H. R. Rodriguez, B. Zitko, and G. De Stevens, *J. Org. Chem.*, **33**, 670 (1968). The present authors wish to thank Dr. Rodriguez for making available a prepublication copy of this paper.
(30) G. De Stevens, *Record Chem. Progr.*, **23**, 105 (1962).
(31) G. De Stevens and M. Dughi, *J. Am. Chem. Soc.*, **83**, 3087 (1961).
(32) H. Plieninger and J. Nogradi, *Ber.*, **88**, 1965 (1955).
(33) C. W. Bird, *J. Chem. Soc.*, 5762 (1965).

mination, and interpretation of nmr, infrared, and ultraviolet spectra. Catalytic reduction of **18** over palladium–charcoal gave a colorless dihydro derivative, presumably by saturation of the ethylenic double bond.

Heating the α-keto acid **19** with acetic anhydride gave a compound to which structure **20** was assigned.[34]



B. REACTIONS

1. *Reduction*

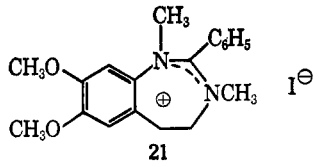
The reduction of 1,3-benzodiazepin-4-ones with lithium aluminum hydride has been described (section A.1). Debenzylation of **12** (R = $C_6H_5CH_2$; R_1 = CH_3) with hydrogen over palladium gave[31] compound **12** (R = H; R_1 = CH_3).

2. *Alkylation*

Compounds **12** (R = H or $C_6H_5CH_2$; R_1 = H) reacted with formaldehyde to yield[30] 3-hydroxymethyl derivatives (**12**, R_1 = CH_2OH).

Methylation of **9** gave a monomethyl methyl sulfate of unidentified structure;[32] it would seem probable that quaternization at position 3 had occurred.

Methylation of the dihydrobenzodiazepine **6** (R = H; R_1 = C_6H_5) with *n*-butyllithium and methyl *p*-toluenesulfonate afforded[29] the 3-methyl derivative **6** (R = CH_3; R_1 = C_6H_5). Treatment of **6** (R = H; R_1 = C_6H_5) with methyl iodide gave[29] the 1,3-dimethylbenzodiazepinium iodide **21**.



3. *Hydrolysis*

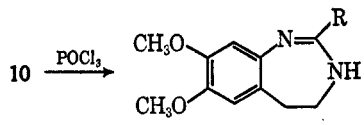
The 1,3-benzodiazepin-4-one **12** (R = H; R_1 = CH_3) was readily hydrolyzed in hot dilute hydrochloric acid to give an amorphous product, thought[30] to be an oxindole polymer. The 1,3-benzodiazepine **7** (R = H; R_1 = CH_3) could only be isolated as a maleate salt;[30] the free base decomposed spontaneously. Mineral acid salts of this compound could not be prepared. These properties emphasize the acetal-like properties of the >NCH_2N< grouping.

(34) T. N. Ghosh, *J. Indian Chem. Soc.*, **10**, 583 (1933); *Chem. Abstr.*, **28**, 2009 (1934).

The 1,3-benzodiazepine **9** was readily hydrolyzed to the aminoacetanilide **8** by heating in water.[32] More vigorous treatment with acid or alkali gave polymers.

4. *Amination*

Treatment of the tetrahydrobenzodiazepin-2-one **10** with phosphorus oxychloride gave[29] a mixture containing **22** and **23**. Reaction of either product with ammonia yielded the 2-amino-1,3-benzodiazepine **24**.



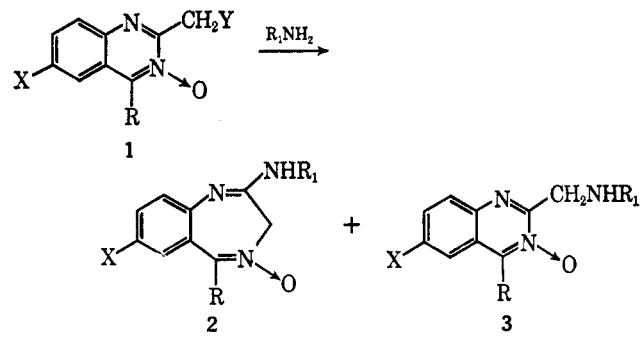
22, R = $OPOCl_2$
23, R = Cl
24, R = NH_2

IV. 1,4-BENZODIAZEPINES

A. 2-AMINO-1,4-BENZODIAZEPINES

1. *Synthesis*

This group of compounds was one of the most extensively explored, in view of the pharmacological activity discovered in 2-aminobenzodiazepine 4-oxides (**2**). The most widely used route to these compounds was the ring enlargement of quinazoline 3-oxides **1**, when treated with ammonia or primary aliphatic amines [35–38] or hydrazine.[39,40] Compounds **2** could be reductively deoxygenated if desired (section A.2.a).

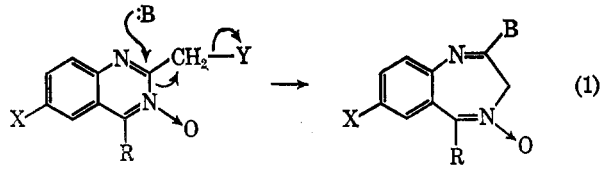


The ring enlargement has been reported for variously substituted quinazoline 3-oxides **1**, *e.g.*, R = phenyl or substituted phenyl,[35–37,41] 2- or 4-pyridyl,[42] 2-thienyl,[37]

(35) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).
(36) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *ibid.*, **26**, 4488 (1961).
(37) S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).
(38) In some cases the isomeric 2-aminomethylquinazoline 3-oxide (**3**) was also formed.
(39) M. E. Derieg, R. I. Fryer, and L. H. Sternbach, *J. Chem. Soc.*, *C*, 1103 (1968).
(40) Methylhydrazine or 1,1-dimethylhydrazine reacted differently with **1**, to give[39] hydrazones of the quinazolinecarboxaldehyde **27**.
(41) G. N. Walker, *J. Org. Chem.*, **27**, 1929 (1962).
(42) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

alkyl,[43] cyclohexyl,[37] and hydrogen;[44] X = chlorine,[35-37] bromine,[36] hydrogen,[36,37] methyl,[36,37] trifluoromethyl,[45,46] nitro,[47] methoxycarbonyl,[48] and alkylthio.[49] These substituents were usually, but not always, in the 6 position of the quinazoline, as shown. The leaving group Y was generally chlorine,[35-37] although the ring enlargement of bromomethyl-[35] and methylsulfonyloxymethylquinazoline[50] 3-oxides has also been described. Weakly basic aromatic amines (*e.g.*, aniline) did not[37] yield benzodiazepine 4-oxides **2**, and only two secondary amines, dimethylamine[51] and pyrrolidine,[52] have been reported to cause ring enlargement to compounds of type **2**, having a tertiary amino group in position 2. In all other cases described, secondary amines resulted in formation of compounds **3** only.[35,37] The ratios of **3** and **2** formed appear to depend on the nature of the reactants, *e.g.*, when X was an electron-releasing substituent in formula **1**, formation of **3** was favored,[36] and two such substituents in 2-chloromethyl-6,8-dimethyl-4-phenylquinazoline 3-oxide further hindered ring enlargement on treatment with methylamine.[36]

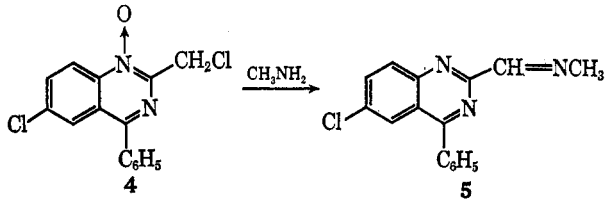
A mechanism for the ring enlargement has been suggested[1,53] (eq 1), which involves nucleophilic attack by a base B at the 2 position of the quinazoline nucleus, which carries a partial positive charge due to the inductive effect of the N-oxide grouping. That the N-oxide function is necessary for the ring enlargement has been



shown,[54] since the 6-chloro-2-chloromethyl-4-phenylquinazoline (**1**, R = C_6H_5; X = Y = Cl, no N-oxide grouping) gave only the simple displacement product, 6-chloro-2-methylaminomethyl-4-phenylquinazoline, when treated[37] with methylamine under the usual conditions for ring enlargement of compounds **1**.

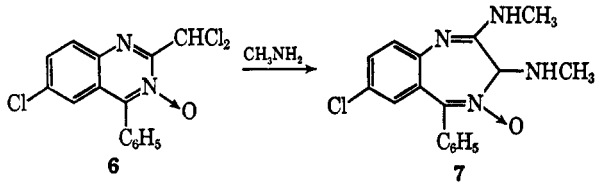
Aminomethylquinazoline 3-oxides are stable under the conditions of the ring enlargement and therefore are not intermediates.[43,55]

A 2-chloromethylquinazoline 1-oxide **4** behaved differently; reaction with methylamine resulted[56] only in formation of the 2-methyliminomethylquinazoline **5**.



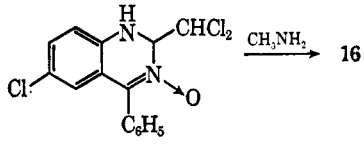
4 **5**

Treatment of a dichloromethylquinazoline 3-oxide **6** with methylamine resulted[57] in ring enlargement to yield the 2,3-bis(methylamino)benzodiazepine **7**.



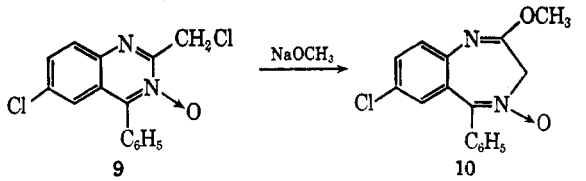
6 **7**

The dichloromethyl-1,2-dihydroquinazoline 3-oxide **8** underwent ring enlargement to the aminobenzodiazepine 4-oxide **16**, when treated[58] with methylamine.



8

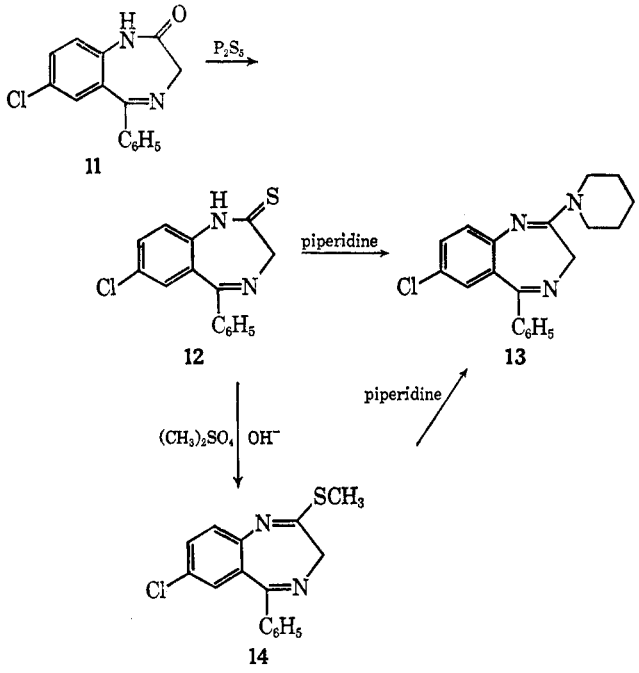
Quinazoline 3-oxides **1** underwent ring enlargement to 2-methoxybenzodiazepine 3-oxides on treatment[59] with sodium methoxide in methanol; *e.g.*, **9** gave **10** which, on reaction with methylamine, formed **16**. Compound **10** was obtained[60] by treatment of the lactam **20** with diazomethane in methanol–ether.



9 **10**

(43) H. S. Broadbent, R. C. Anderson, M. C. J. Kuchar, and P. D. Ziemer, Abstracts of the First International Congress of Heterocyclic Chemistry, Albuquerque, N. Mex., 1967.
(44) Aktiengeselskabet Grindstedvaerket, Netherlands Patent 6,608,039; *Chem. Abstr.*, **66**, 105006 (1967).
(45) G. Saucy and L. H. Sternbach, *Helv. Chim. Acta*, **45**, 2226 (1962).
(46) M. Gordon, I. Pachter, and J. W. Wilson, *Arzneimittel-Forsch.*, **13**, 802 (1963).
(47) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).
(48) L. H. Sternbach, G. Saucy, F. A. Smith, M. Müller, and J. Lee, *Helv. Chim. Acta*, **46**, 1720 (1963).
(49) O. Keller, N. Steiger, and L. H. Sternbach, U. S. Patent 3,121,075; *Chem. Abstr.*, **61**, 5672 (1964).
(50) H. M. Wuest, U. S. Patent, 3,189,602; *Chem. Abstr.*, **63**, 7026 (1965).
(51) S. Farber, H. M. Wuest, and R. I. Meltzer, *J. Med. Chem.*, **7**, 235 (1964).
(52) Hoffmann-La Roche, Netherlands Patent 6,413,180; *Chem. Abstr.*, **63**, 14890 (1965).
(53) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).
(54) M. C. J. Kuchar, Ph.D. Thesis, Brigham Young University; University Microfilms, Order No. 64-6643, 277 pp; *Dissertation Abstr.*, **25**, 1572 (1964).
(55) M. C. J. Kuchar, ref 54, p 218.
(56) L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964).
(57) Hoffmann-La Roche, Netherlands Patent 6,603,736; *Chem. Abstr.*, **66**, 76044 (1967).
(58) Hoffmann-La Roche, Netherlands Patent 6,512,614: *Chem. Abstr.*, **66**, 55533 (1967).
(59) Hoffmann-La Roche, Netherlands Patent 6,412,484; *Chem. Abstr.*, **63**, 13298 (1965).
(60) Hoffmann-La Roche, Netherlands Patent 6,412,300; *Chem. Abstr.*, **64**, 6671 (1966).

2-Aminobenzodiazepine 4-oxides have been converted into the corresponding desoxy derivatives by reduction with phosphorus trichloride or by catalytic hydrogenation (section A.2.a). An alternative general route to 2-aminobenzodiazepines is illustrated by conversion[61] of the benzodiazepin-2-one **11** into the corresponding thione **12**, by treatment with phosphorus pentasulfide and subsequent reaction with piperidine to give **13**. The last reaction was facilitated[61] by methylation of **12** to **14**, which reacted very readily with amines. This method was most useful for the synthesis of those 2-aminobenzodiazepines which were not easily obtained by the ring enlargement of quinazoline 3-oxides.



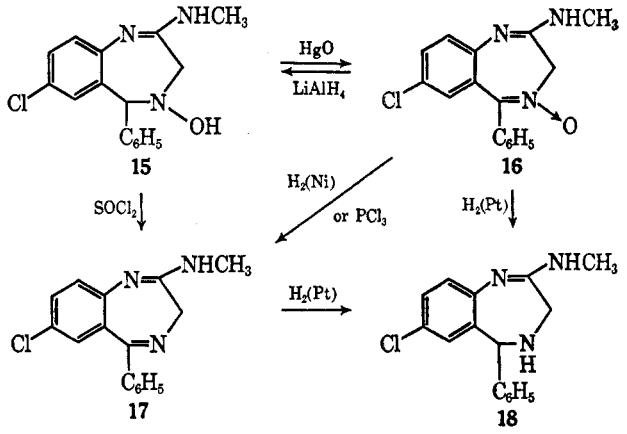
11 12 13 14

2. *Reactions*

a. Reduction

The N-oxide grouping of compound **16** was reduced to a hydroxylamine function as in **15**, by treatment with lithium aluminum hydride;[35] the reaction was reversed by oxidation of **15** with mercuric oxide.

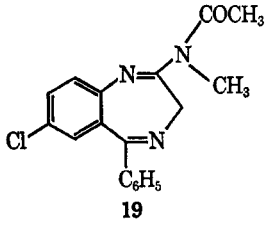
Catalytic hydrogenation of **16** over a Raney nickel catalyst, or reduction with phosphorus trichloride, resulted[35] in deoxygenation to give **17**. The latter compound was also obtained[35] by dehydration of **15** with thionyl chloride. Catalytic hydrogenation of **16** or **17** over platinum yielded[35] **18**, whereas use of a palladium catalyst resulted in concomitant hydrogenolysis to give the 7-deschloro analog of **18**. An attempt to reduce the 1,2-imine function in **18**, by catalytic hydrogenation over platinum, was unsuccessful;[62] electrolytic reduction of **18** resulted[62] in ring contraction to give 6-chloro-3,4-dihydro-2-methyl-4-phenylquinazoline in 80% yield.



15 16 17 18

b. Oxidation

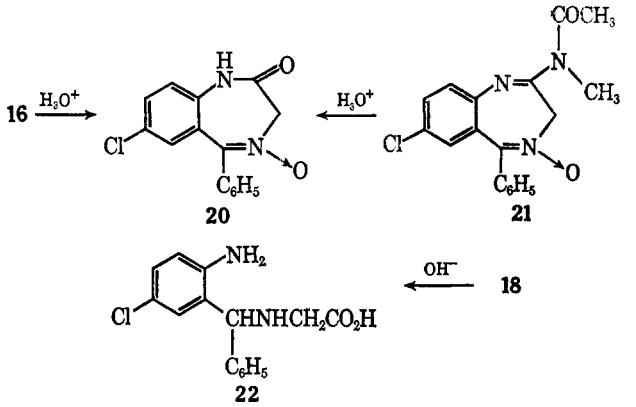
Compound **19** has been converted into the corresponding 4-N-oxide **21** by treatment[63] with peracetic acid in methylene chloride. The oxidation of the 4-hydroxy compound **15** to the nitrone **16** has been discussed (section A.2.a).



19

c. Hydrolysis

Mild acid hydrolysis of **16**, or of the corresponding acetyl derivative **21**, afforded[64] the benzodiazepin-2-one 4-oxide **20**. Mild alkaline hydrolysis of **21** gave[64] compound **16**. Vigorous acid hydrolysis of **17** afforded[35] 2-amino-5-chlorobenzophenone, glycine, and methylamine. Hydrolysis of the 4,5-dihydro compound **18**,



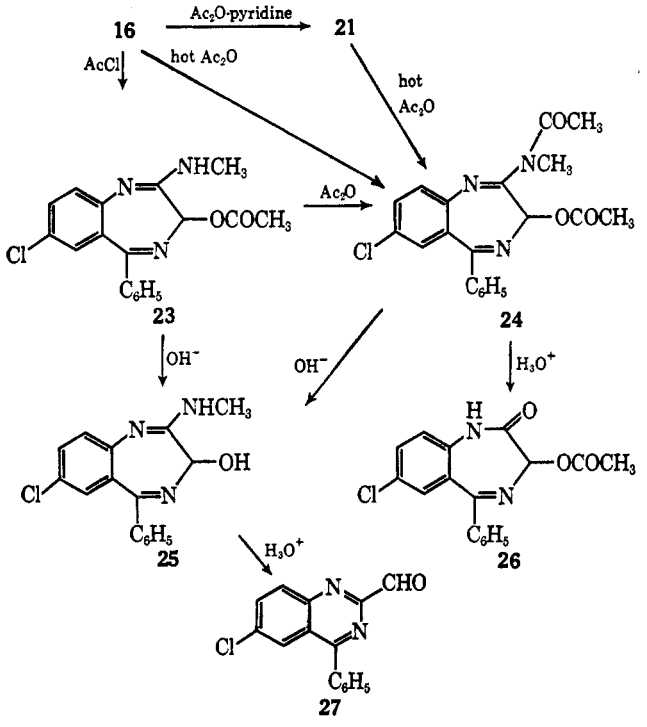
20 21 22

(61) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, 29, 231 (1964).
(62) H. Oelschlaeger and H. Hoffmann, *Arch. Pharm.*, 300, 817 (1967)
(63) Hoffmann-La Roche, Netherlands Patent, 6,514,541; *Chem. Abstr.*, 65, 10602 (1966).
(64) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, 26, 4936 (1961).

in refluxing aqueous methanolic barium hydroxide solution, yielded[35] the amino acid **22**, together with methylamine.

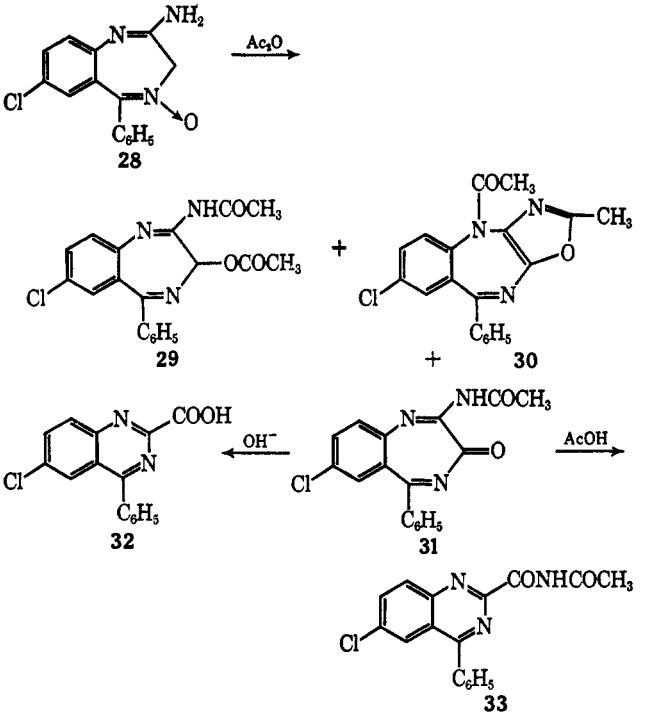
d. Acylation

Acetylation of compound **16** afforded three different products, depending on the reaction conditions.[56,65] Treatment of **16** with acetic anhydride in pyridine at room temperature gave[36,56] the N-acetyl derivative **21**. The reaction of **16** with acetyl chloride in dimethylformamide,[56] or heating it with acetic anhydride,[65] resulted in a Polonovsky-type rearrangement to the 3-acetoxy compound **23**. Longer heating of **16**, **21**, or **23** with acetic anhydride yielded[56,65] the diacetyl derivative **24**.

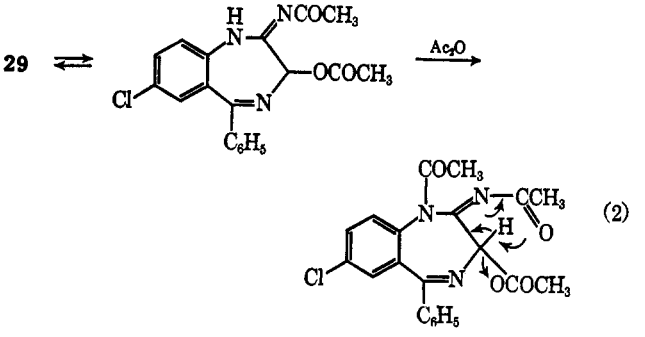


The acetyl groups in **24** could be removed in two stages; hydrolysis with 1 mole of sodium hydroxide gave[56] compound **23**, whereas treatment of **23** with a further mole of base (or of **24** with 2 moles of base) afforded the 3-hydroxybenzodiazepine **25**. Acid hydrolysis[56] of **24** gave **26** (section A.2.c), whereas compounds **23** and **25**, on treatment with acid, underwent a ring contraction[56] to yield the quinazoline aldehyde **27**.

Treament[65] of the 2-aminobenzodiazepine 4-oxide **28** with acetic anhydride gave, in addition to the diacetyl compound **29**, two other products **30** and **31**. Monoacetyl derivatives corresponding to **21** and **23** were not described. The proposed mechanism[65] for the formation of **30** involved acetylation of a tautomer of **29**, and cyclization of the oxazole ring by elimination of



acetic acid (eq 2). The benzodiazepin-3-one **31** underwent ring contractions[65] to the quinazolines **32** and **33** on treatment with sodium hydroxide and acetic acid,



(2)

respectively. The formation of **31** from **28** has not been explained and clearly involves an oxidation step.

Treatment of **16** with propionic and butyric anhydrides gave[56] homologs of **21** and **23**; benzoyl chloride afforded only an O-benzoyl derivative analogous to compound **23**.

e. Alkylation

Methylation of compounds **16** and **17** with sodium hydride and methyl iodide gave[51] the dimethyl derivatives **34** and **35**, respectively.[66,67]

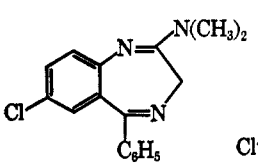
Cyanoethylation of **16**, by treatment with acrylonitrile and Triton B in dimethylformamide, also occurred on the side chain to give[68] **36**.

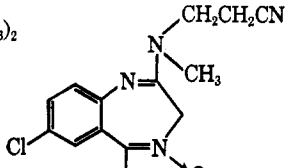
(65) S. C. Bell, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **28**, 3010 (1963).

(66) Compound **35** has also been obtained[67] by reaction of the thionamide **12** with dimethylamine, and compound **34** was synthesized[59] from the imino ether **10** and dimethylamine.

(67) G. A. Archer, L. H. Sternbach, and M. Müller, Belgian Patent 634,438; *Chem. Abstr.*, **61**, 4382 (1964).

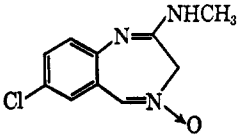
(68) E. Reeder and L. H. Sternbach, U. S. Patent, 3,051,701; *Chem. Abstr.*, **57**, 16641 (1962).


34 (4-oxide)
35


36

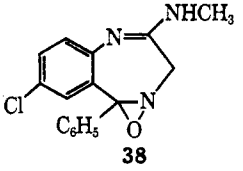
f. Grignard reactions

Addition of phenylmagnesium bromide to **37** afforded[44] the 5-phenyl-4-hydroxybenzodiazepine **15**.


37

g. Photoisomerization

Exposure of a dilute 2-propanol solution of **16** to daylight gave[69] the oxaziridine **38** in 65% yield. The isomerization was reversed, almost quantitatively, by heating **38** briefly at its melting point, or preferably, by refluxing it in 2-propanol solution. Treatment of **38** with dilute hydrochloric acid at room temperature also


38

resulted in reconversion into **16**.

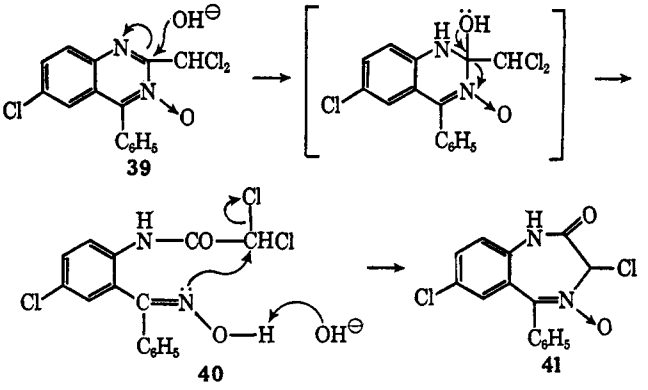
B. 1,4-BENZODIAZEPIN-2-ONES

1. Synthesis

Benzodiazepin-2-one 4-oxides (*e.g.*, **20**) have been obtained by ring enlargement of quinazoline 3-oxides (*e.g.*, **9**) on treatment with aqueous sodium hydroxide. The N-oxide oxygen could readily be removed to yield benzodiazepin-2-ones (section B.2.a).

The requirement for the N-oxide function in **9** to allow rearrangement to **20** has been shown;[70] treatment of 6-chloro-2-chloromethyl-4-phenylquinazoline with ethanolic sodium hydroxide gave only the product of displacement, 6-chloro-2-ethoxymethyl-4-phenylquinazoline.

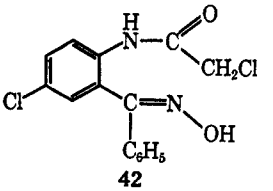
The mechanism of the ring enlargement of 2-halomethylquinazoline 3-oxides (*e.g.*, **9** to **20**) has been elucidated by a study[71] of the transformation of the dichloromethylquinazoline oxide **39** into the benzodiazepinone 4-oxide **41**. Treatment of **39** with an excess of sodium hydroxide gave **41** in almost quantitative yield. Interruption of the reaction enabled isolation of the dichloroacetamido *anti*-oxime **40**. Further treatment of **40** with base gave **41** in good yield. The suggested mechanism[71] for the rearrangement involved nucleophilic attack by hydroxyl ion at position 2 in compound **39**, followed by ring opening to *anti*-oxime **40**, and then an intramolecular alkylation to give **41**. In the case of **9**, the ring enlargement to **20** was so


39

40

41

rapid that the presumed intermediate chloroacetamido *anti*-oxime **42** could not be detected.[71] It had, however, been shown[64] that **42** could be readily cyclized to **20** under the conditions used in this reaction.


42

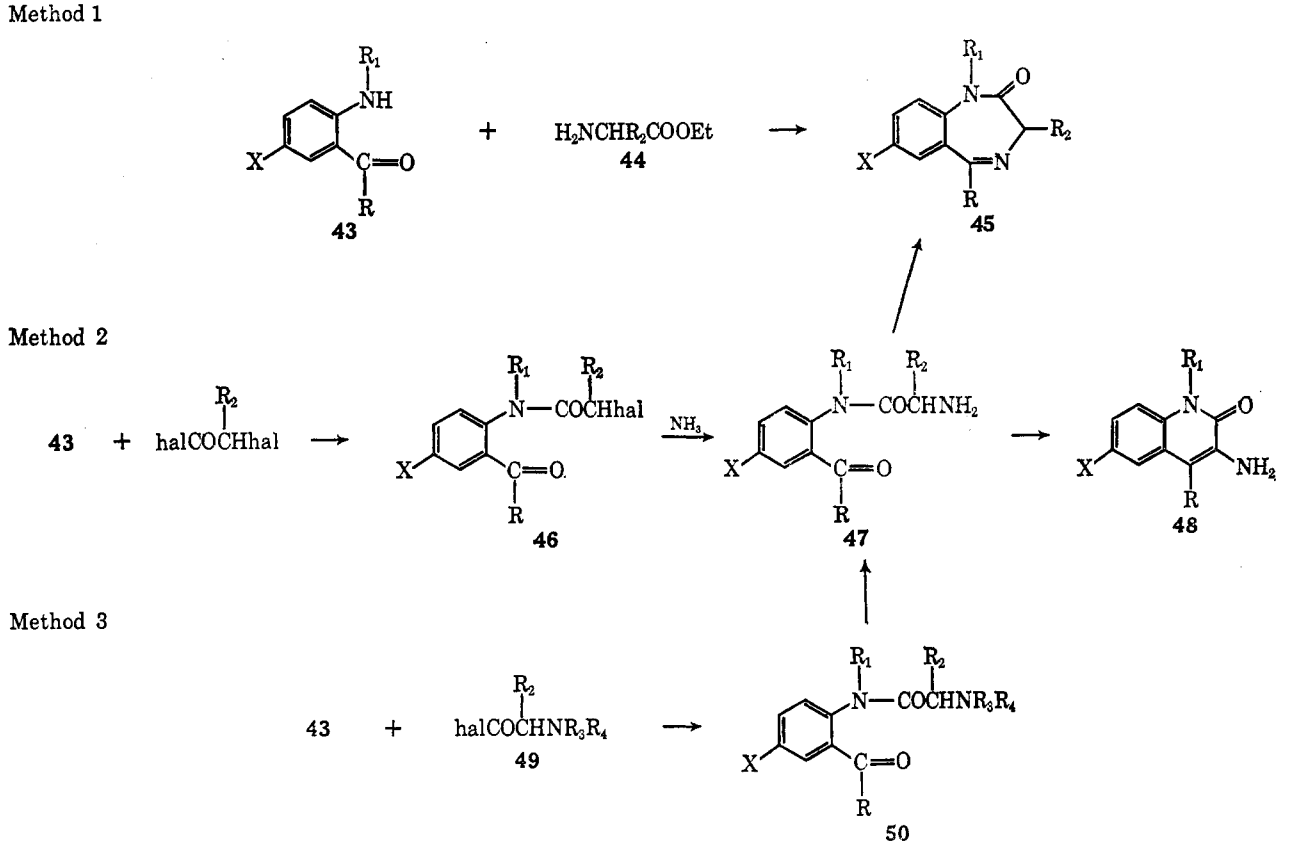
The rearrangement of the 1,2-dihydroquinazoline 3-oxide **8** to the benzodiazepinone 4-oxide **20**, on base treatment, has been described.[58] Compound **20** was also obtained[64] by acid hydrolysis of the 2-methylamino or 2-(N-methylacetamido) derivatives **16** and **21**, respectively (section A.2.c).

Benzodiazepin-2-ones **45** can be readily obtained by removal of the N-oxide oxygen from the 4-oxides just discussed (see section B.2.a).[72,73] Since compounds of this type showed pronounced psychotropic properties, a number of other methods for their synthesis were developed. The three principal synthetic routes, using 2-aminobenzophenones **43** as starting materials, are outlined in Scheme I.

In method 1, the aminobenzophenone **43** was treated with a glycine ester **44**, giving [74] the benzodiazepin-2-one **45** directly. The three-step method 2 was gener-

(69) L. H. Sternbach, B. A. Koechlin, and E. Reeder, *J. Org. Chem.*, **27**, 4671 (1962).
(70) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *ibid.*, **27**, 562 (1962).
(71) A. Stempel, E. Reeder, and L. H. Sternbach, *ibid.*, **30**, 4267 (1965).
(72) The molecular structure of 7-chloro-5-(2,4-dichlorophenyl)-1,3,4,5-tetrahydro-1,4-dimethyl-2H-1,4-benzodiazepin-2-one has been proven by X-ray crystallographic analysis.[73]
(73) J. Karle and I. L. Karle, *J. Am. Chem. Soc.*, **89**, 804 (1967).
(74) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

SCHEME I



ally more versatile and afforded higher yields; in this procedure,[70,74] haloacetylation of **43** gave the haloacetamide **46** which, on treatment with ammonia, yielded the aminoacetamide **47**, which readily cyclized to the benzodiazepin-2-one **45**. In many cases the intermediates were not isolated. In some of these syntheses, when R_2 in **47** was H, aminoquinolones **48** were obtained[70,74,75] as by-products.

Method 3 used a protected amino acid deivative **49** to acylate the aminobenzophenone **43** to **50**. Among the reagents **49** that have been described for this purpose are carbobenzoxyglycine,[76] carbobenzoxyglycyl chloride,[70,76] carbobenzoxyglycine anhydride,[76] and phthalimidoacetyl chloride;[77,78] removal of the protecting group gave **47**, and ultimately the benzodiazepin-2-one **45**. This synthesis has also been achieved with free amino acids,[74] and amino acid chlorides,[70] as acylating agents.

Benzodiazepin-2-ones having R_1 other than H have usually been made by alkylation of the compounds in which R_1 is H; *e.g.*, compounds having R_1 = alkyl,[64,70] benzyl,[64] alkenyl,[64] alkynyl,[79] hydroxyalkyl,[80] alkoxyalkyl,[80] dialkylaminoalkyl,[81] $-CH_2CONR_2$,[82] $-CH_2COOR$,[82] and $-CH_2COR$[82] have been described and were generally made by treatment of compounds **45** (R_1 = H) with sodium methoxide, followed by the appropriate alkyl halide or sulfate.

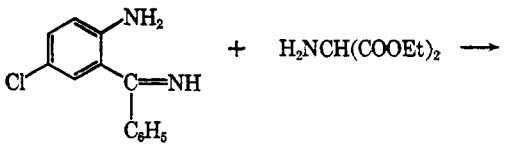
Compounds **45** have been prepared, in which R = alkyl,[70,83] phenyl or substituted phenyl,[64,70,74] cyclohexyl,[70,83-87] 2-thienyl,[70] 2- or 4-pyridyl,[42] 2-furyl,[88] or 2-pyrryl.[88] Conversion of a 5-cyclohexylbenzodiazepin-2-one into a cyclohexenyl analog is described in section B.2.i.

(75) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).
(76) A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962).
(77) Delmar, Netherlands Patent 6,500,446; *Chem. Abstr.*, **64**, 5120 (1966).
(78) F. H. McMillan and I. Pattison, French Patent 1,394,287; *Chem. Abstr.*, **63**, 8387 (1965).
(79) E. Reeder and L. H. Sternbach, French Patent, 1,343,085; *Chem. Abstr.*, **60**, 9298 (1964).
(80) Hoffman-La Roche, Netherlands Patent, 6,510,539; *Chem. Abstr.*, **65**, 732 (1966).
(81) L. H. Sternbach, G. A. Archer, J. V. Earley, R. I. Fryer, E. Reeder, N. Wasyliw, L. O. Randall, and R. Banziger, *J. Med. Chem.*, **8**, 815 (1965).
(82) G. A. Archer and L. H. Sternbach, U. S. Patent 3,236,838; *Chem. Abstr.*, **63**, 1808 (1965).
(83) J. Schmitt, French Patent 1,391,752; *Chem. Abstr.*, **63**, 4316 (1965).
(84) L. Berger and L. H. Sternbach, U. S. Patent 3,268,586; *Chem. Abstr.*, **66**, 37970 (1967).
(85) L. Berger and L. H. Sternbach, U. S. Patent 3,179,656; *Chem. Abstr.*, **63**, 11591 (1965).
(86) J. Schmitt, P. Comoy, M. Suquet, J. Boitard, J. LeMeur, J.-J. Basselier, M. Brunaud, and J. Salle, *Chim. Therap.*, **2**, 254 (1967).
(87) L. Berger and L. H. Sternbach, U. S. Patent 3,338,886 (1967).
(88) L. Berger, A. Stempel, L. H. Sternbach, E. Wenis, R. I. Fryer, and R. A. Schmidt, Belgian Patent 619,101; *Chem. Abstr.*, **59**, 10092 (1963).

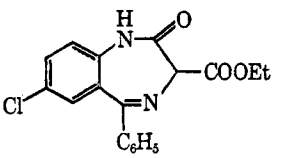
The substituent X in compound **45** (usually, but not always, in the 7 position) has been widely varied and includes hydrogen,[70,74] halogen,[64,70,74] alkyl,[70,74], alkoxy,[74] cyano,[48] carbamoyl,[48] carbomethoxy,[48] nitro,[47,89] amino,[47] trifluoromethyl,[45,46] alkylthio,[49,90] and dialkylamino.[91]

In addition, some analogous naphtho-[92] and pyrido-diazepinones[93] have been described.

Compounds with a substituent R_2 in the 3 position of **45** have been prepared by any of the above methods; *e.g.*, compounds **45** having R_2 = H,[64,70,74] alkyl,[70,74] aryl,[70,74] alkoxyalkyl,[74] alkylthioalkyl,[74] dialkyl,[70] and carbalkoxy[94] have been reported. The last type of compound **53** has also been obtained[95] by a modification of method 1, *i.e.*, by treatment of the imine **51** (prepared from the corresponding nitrile and phenylmagnesium bromide) with an aminomalonic ester derivative **52**. The carboxylate function in **53** could be removed[95] by hydrolysis and decarboxylation.



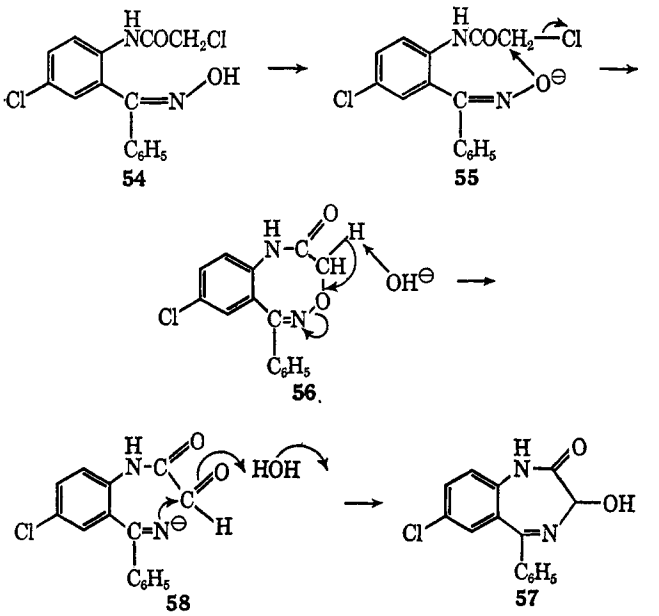
51 **52**



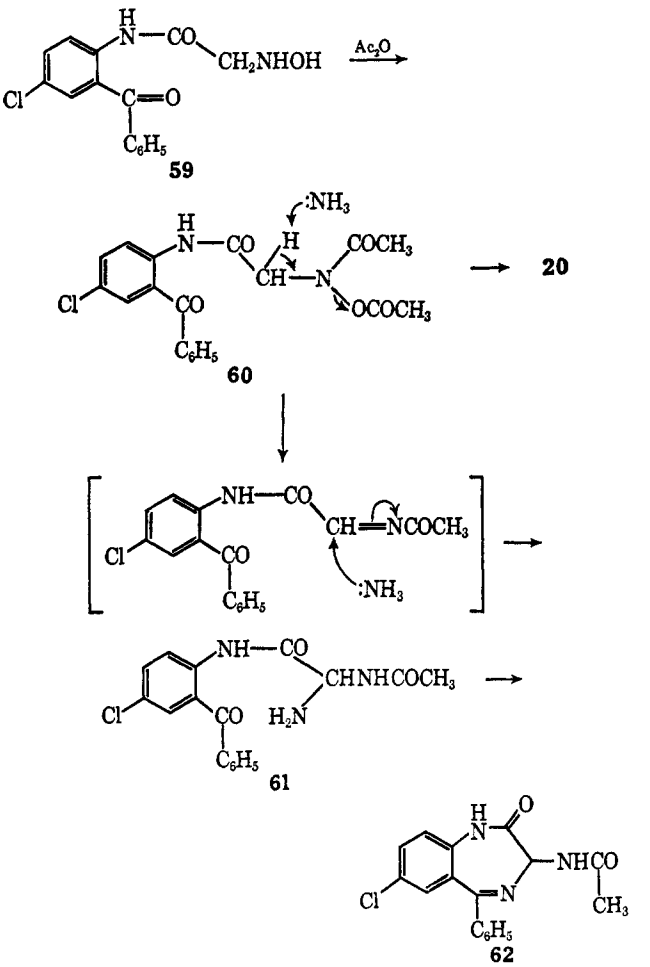
53

Imines of type **51** have also been obtained[96] by treatment of the corresponding aminobenzophenones with ammonia under pressure; further reaction with bromoacetyl bromide gave benzodiazepinones directly.

The chloroacetamidobenzophenone *syn*-oxime **54**, when treated with sodium hydroxide, gave[97] the 3-hydroxybenzodiazepinone **57** *via* the intermediate benzoxadiazocinone **56**; the proposed mechanism is shown. The synthesis of **57** by another rearrangement is discussed in section B.2.d. Another route leading to two types of benzodiazepines uses the hydroxylamine **59** (made by a method analogous to the synthesis of **47**), as starting material. It was diacetylated to **60** which, on heating in ethanolic hydrogen chloride,[98,99]



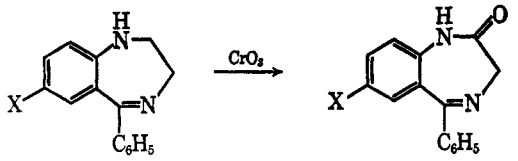
gave the benzodiazepin-2-one 4-oxide **20**. On the other hand, treatment of **60** with ethanolic ammonia gave **61**;



(89) A. L. Nelson and A. I. Rachlin, Belgian Patent 648,149; *Chem. Abstr.*, **63**, 14889 (1965).
(90) O. Keller, N. Steiger, and L. H. Sternbach, U. S. Patent 3,121,103; *Chem. Abstr.*, **61**, 5671 (1964).
(91) W. Metlesics and L. H. Sternbach, Belgian Patent 629,352; *Chem. Abstr.*, **60**, 13261 (1964).
(92) R. Littell and D. S. Allen, *J. Med. Chem.*, **8**, 892 (1965).
(93) R. Littell and D. S. Allen, *ibid.*, **8**, 722 (1965).
(94) Hoffman-La Roche, South African Patent 66/6909 (1967).
(95) Clin-Byla, Netherlands Patent, 6,507,637; *Chem. Abstr.*, **64**, 15902 (1966).
(96) Hoffmann-La Roche, South African Patent 66/6999 (1967).
(97) A. Stempel, I. Douvan, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **32**, 2417 (1967).
(98) S. C. Bell, U. S. Patent 3,313,805; *Chem. Abstr.*, **64**, 17621 (1966).
(99) S. C. Bell, U. S. Patent 3,257,382; *Chem. Abstr.*, **65**, 12221 (1966).

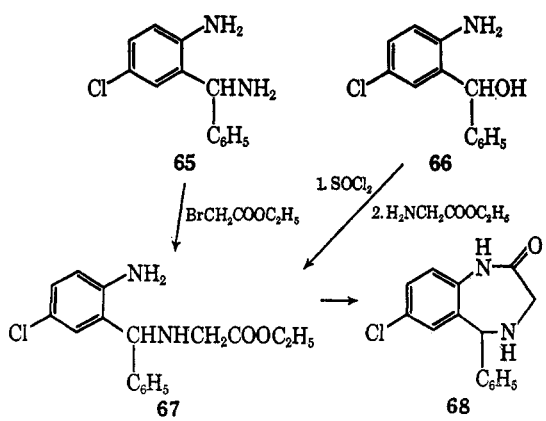
the proposed mechanism[100-102] is shown. Cyclization of **61** afforded the 3-acetamidobenzodiazepinone **62**. Compound **20** could also be obtained[98] directly from **59** by heating in acid media.

Benzodiazepines **63** (section F) (X = Cl, NO_2, or CF_3) have been oxidized with chromium trioxide and sulfuric acid in acetic acid or acetone solution to give[103] benzodiazepin-2-ones of ty pe **64**.



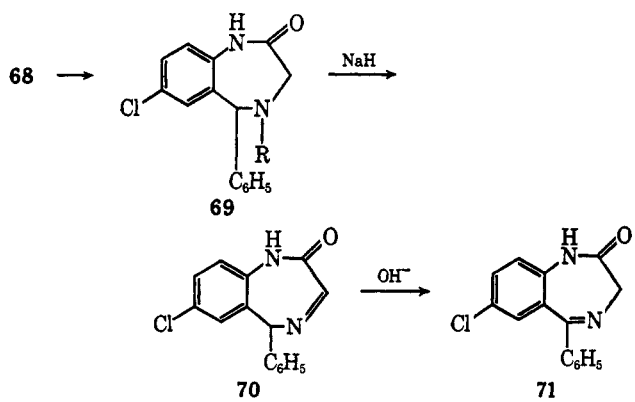
63 **64**

Syntheses of the tetrahydrobenzodiazepin-2-one **68** from the 2-aminobenzhydrylamine **65**, or from the 2-aminobenzhydrol **66**, *via* the ester **67**, have been reported.[103]



65 **66** **67** **68**

Compounds of type **68** could be oxidized (section B.2.b) to dihydro derivatives of type **71**. Another method described[101,104] for conversion of **68** into **71**



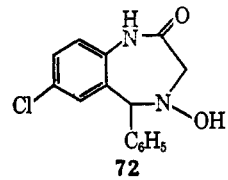
69 **70** **71**

involved tosylation or mesylation to **69** (R = tosyl or mesyl), followed by base elimination of the appropriate sulfinate anion. The product obtained was either the 1,3-dihydro- or 1,5-dihydrobenzodiazepinone, **71** and **70**, respectively, depending on reaction conditions. Compound **70** could be converted into **71** by further treatment with base.

2. *Reactions*

a. Reduction

Deoxygenation of the N-oxide **20** has been effected by catalytic hydrogenation over Raney nickel,[64] or by treatment with phosphorus trichloride,[64,70] to give compound **71**. Further reduction of **71** (hydrogen over platinum) gave[64] the tetrahydrobenzodiazepinone **68**. Catalytic reduction of **20** over platinum[64] afforded the hydroxylamine **72**, whereas reduction of **20** over palladium in ethanolic hydrochloric acid resulted[70] in deoxygenation and dechlorination to give **64** (X = H). Reduction of **71** with lithium aluminum hydride is discussed in



72

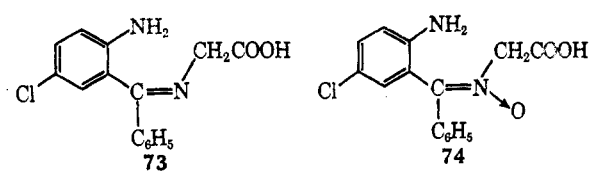
section F.1. An indirect method for reduction of the carbonyl function in **71** is discussed in section F.1. Catalytic dechlorination of a 3-chloro substituent, with hydrogen over palladium, has been described.[105]

b. Oxidation

Compound **71** was converted into the N-oxide **20** by peracetic acid oxidation.[64,70] Tetrahydrobenzodiazepinones **68** have been oxidized[103] to the corresponding dihydro compounds **71**, using chromium trioxide, selenium dioxide, or silver oxide as oxidizing agents.

c. Hydrolysis and aminolysis

Alkaline hydrolysis of **71** and **20** resulted in scission of the amide likages, giving the imines **73** and **74**, respectively.[64,70] Treatment[64,70] of these imines with acid reconverted **74** into the lactam **20**, whereas **73**, which

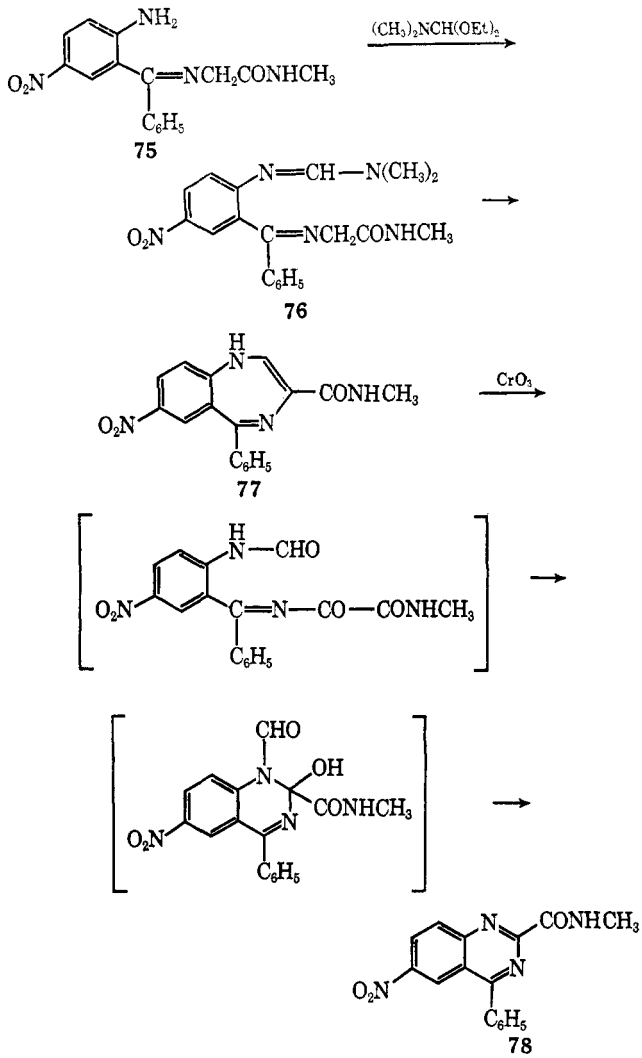


73 **74**

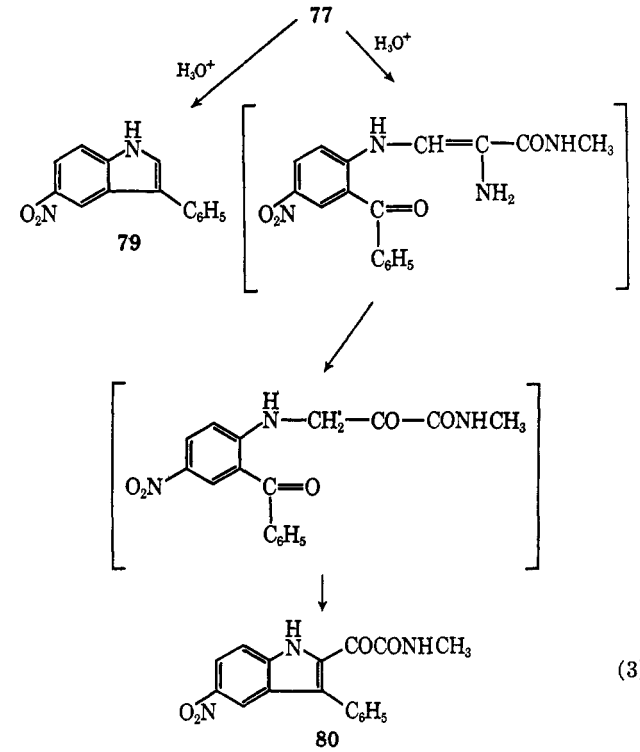
was isolated as the sodium salt, was hydrolyzed by acid to 2-amino-5-chlorobenzophenone and glycine.[70]

(100) S. C. Bell, R. J. McCaully, and S. J. Childress, *Tetrahedron Letters*, **33**, 2889 (1965).
(101) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Med. Chem.*, **11**, 172 (1968).
(102) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Heterocyclic Chem.*, **4**, 647 (1967).
(103) R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1308 (1965).
(104) R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Heterocyclic Chem.*, **4**, 355 (1967).
(105) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

When the nitrobenzodiazepinone **64** (X = NO_2) was treated with methylamine, aminolysis occurred,[106] with formation of the amide **75**. The latter was converted into N-methyl-7-nitro-5-phenyl-1*H*-1,4-benzodiazepine-3-carboxamide (**77**) by reaction with dimethylformamide acetal, followed by cyclization of the resulting dimethylaminomethylenimino derivative **76**. Oxidation of **77** with chromic acid gave the quinazolinecarboxamide **78**, as shown. Treatment of **77** with dilute



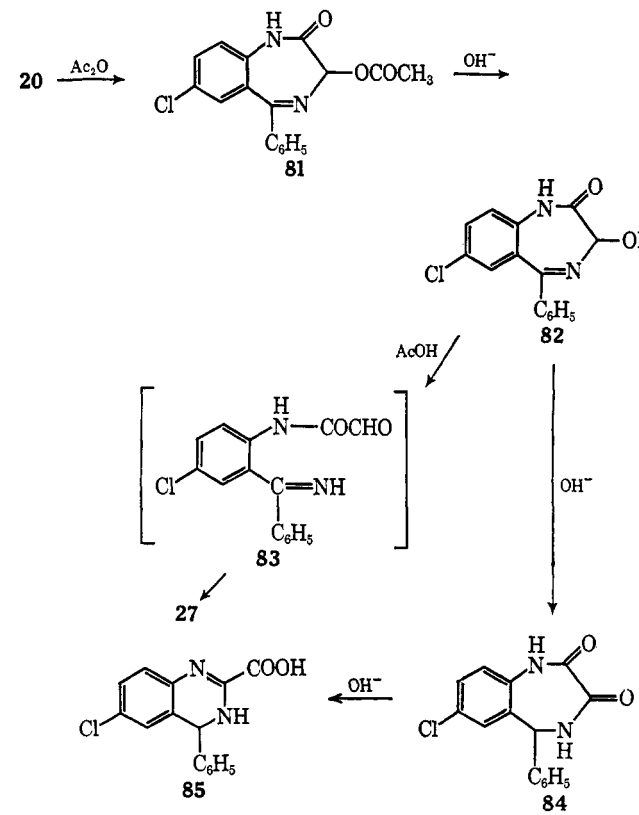
mineral acid resulted[106] in ring contraction to the indoles **79** and **80**; the mechanism of eq 3 was proposed for formation of **80**.



(3)

d. Acylation

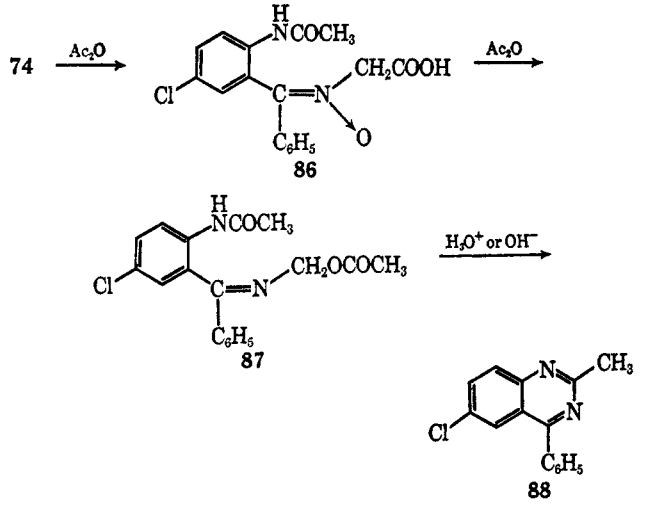
Treatment of **20** with acetic anhydride resulted in a Polonovsky-type rearrangement (*cf.* section A.2.d) to give [105] the 3-acetoxy compound **81**. A similar rearrangement occurred with benzoyl chloride. Alkaline hydrolysis of **81** afforded initially the 3-hydroxy compound **82**; further treatment with alkali resulted[105] in conversion into the 2,3-dione **84** and the dihydroquinazolinecarboxylic acid **85**.



Hot acetic acid caused **82** to rearrange to the quinazoline aldehyde **27**, by ring opening to **83** and subse-

(106) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

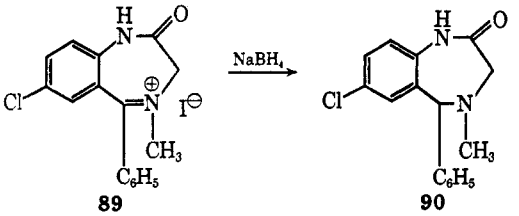
quent recyclization.[107] Treatment of **82** with primary amines afforded aldimines of **27**. Treatment of **74** with acetic anhydride gave [108] the acetanilide **86**, which was further acetylated, with concomitant decarboxylation, to the diacetyl derivative **87**. The last compound was readily cyclized, with acid or alkali, to the quinazoline **88**. This compound was also obtained[108] by acetylation of **81** to an N_1-acetyl derivative, followed by alkaline hydrolysis and cyclization.



Some other rearrangements of benzodiazepin-2-ones under acylating conditions are discussed in section B.2.k.

e. Alkylation

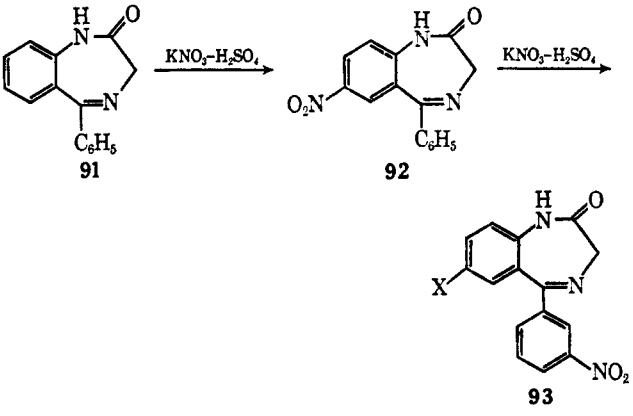
Treatment of benzodiazepin-2-ones (*e.g.*, **71**) with sodium methoxide, followed by an alkyl halide or sulfate, gave the N_1-alkyl derivatives.[64,70,74] Nitrones (*e.g.*, **20**) were alkylated in the same manner.[64] Methylation of **71** with methyl iodide in acetone afforded[70] the benzodiazepinium iodide **89**, which was reduced with sodium borohydride to the 4-methyltetrahydrobenzodiazepin-2-one **90**. The same compound was obtained by alkylation of **68** with methyl iodide in the absence of base.[109] By taking advantage of the difference in



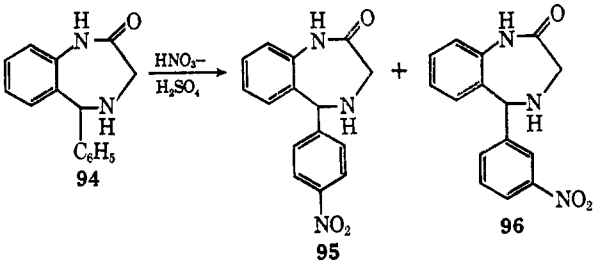
basicity between N_1 and N_2 in compounds of type **68**, it was possible[109] to methylate in positions 1 or 4, or both. Methylation of **20** with diazomethane[39] gave the O-methyl derivative **10** (section A.1). A 3-ethoxybenzodiazepinone was made [71,105] by treatment of a 3-chloro analog (section B.2.i) with ethanol. The 1-methylbenzodiazepin-2-one **109** was methylated[110] in the 3 position by treatment with sodium hydride and methyl iodide.

f. Nitration

Potassium nitrate–sulfuric acid[47] converted **91** into the 7-nitro derivative **92**. Further nitration of **92** gave[111] the dinitro compound **93** (X = NO_2). Nitration



of **93** (X = Cl) yielded a 3′,9-dinitro derivative,[112] whereas nitration of the tetrahydrobenzodiazepinone **94** afforded a mixture from which the 5-nitrophenyl derivatives **95** and **96** were isolated.



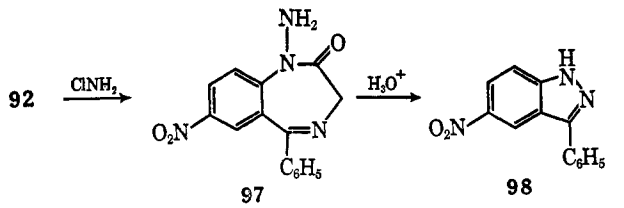
g. Thiation

Treatment of **71** with phosphorus pentasulfide in pyridine gave [61,67] the corresponding thione **12**. Methylation of **12** under basic conditions afforded the S-methyl compound **14** (section A.1). A 3-thiobenzodiazepin-2-one was obtained[113] from the corresponding 3-chloro compound (section B.2.i) and thiourea.

h. Amination

Treatment of **92** with sodium hydride and chloramine afforded[114] the 1-amino derivative **97**. Acid hydrolysis of **97** gave 5-nitro-3-phenylindazole (**98**).

(107) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **29**, 506 (1964).
(108) S. C. Bell and P. H. L. Wei, *ibid.*, **30**, 3576 (1965).
(109) R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).
(110) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Am. Chem. Soc.*, **88**, 3173 (1966).
(111) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.* 4977 (1963).
(112) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **30**, 521 (1965).
(113) American Home Products, British Patent 1,035,918; *Chem. Abstr.*, **65**, 15408 (1966).
(114) W. Metlesics, R. F. Tavares, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1311 (1965).

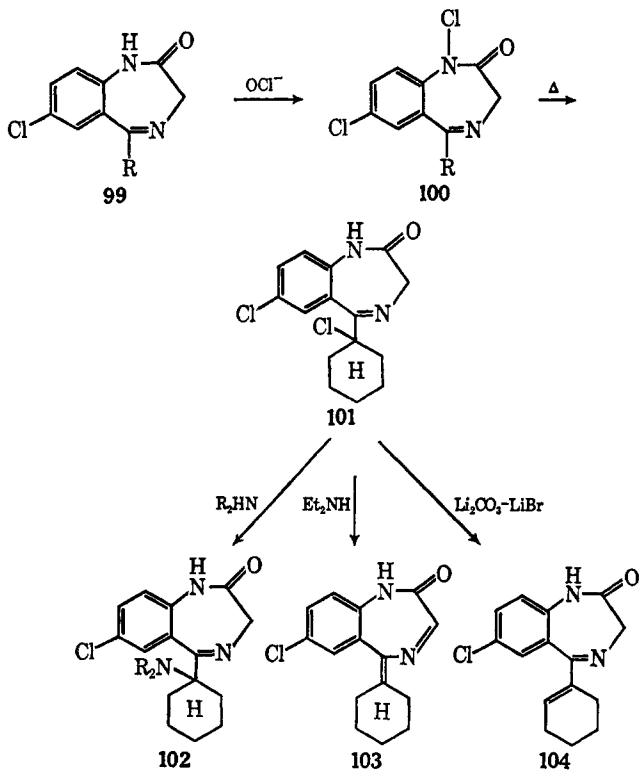


Amination of benzodiazepin-2-ones in position 2 has been discussed in section A.1.

3-Aminobenzodiazepin-2-ones have been made[71,115] by treatment of the corresponding 3-chloro compounds (section B.2.i) with ammonia or amines.[116] A 3-acetamido compound was obtained by a primary synthesis.[100] 7-Aminobenzodiazepin-2-ones have been made by reduction of nitro compounds, usually with hydrogen over Raney nickel.[47] 7-Dialkylamino compounds have obtained,[91] in one step, by reductive alkylation of 7-nitro analogs.

i. Halogenation

Dihydrobenzodiazepin-2-ones of general formula **99** (R = aryl, alkyl, or cycloalkyl) underwent N_1 chlorination to give[86,117,118] compounds **100**, when treated with sodium hypochlorite or *t*-butyl hypochlorite. Compounds **100** were oxidizing agents able to oxidize



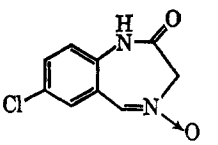
iodide to iodine. The 1-chloro derivative **100** could readily be rearranged[86,117] to give, in cases where the R grouping has at least one hydrogen atom α to the 5 position of the heterocyclic ring, compounds of type **101**. Compound **100** (R = CH_3) could be repeatedly subjected to this rearrangement to give **99** (R = CH_2Cl, $CHCl_2$, or CCl_3). The benzodiazepinone **100** (R = C_6H_5), in which there is no available α-hydrogen in the R grouping, could be rearranged[119] to the 3-chloro derivative of **99** (R = C_6H_5). Dehydrohalogenation of **101**, with a mixture of lithium carbonate and bromide, afforded[86,117] the cyclohexenyl derivative **104**, whereas use of diethylamine gave an isomeric compound, to which structure **103** was assigned.[117] On treatment with a number of other secondary amines, **101** was converted into amino derivatives of type **102**. In a similar manner, reaction of **101** with potassium cyanide gave **99** (R = 1-cyanocyclohexyl).

The benzodiazepinone **71** has been chlorinated in the **3** position by treatment[120] with N-chlorosuccinimide in the presence of a catalytic amount of azodiisobutyronitrile. The same compound was obtained[105] by treatment of the 3-hydroxybenzodiazepinone **82** with thionyl chloride. Synthesis of the 3-chlorobenzodiazepin-2-one 4-oxide **41**, by ring enlargement, has been described in section B.1.

7-Chlorobenzodiazepinones have been prepared[47] from the 7-amino analogs by means of the Sandmeyer reaction.

j. Grignard reactions

Treatment of the benzodiazepinone 4-oxide **105** with phenylmagnesium bromide gave[44] the 4-hydroxy-5-phenyl compound **72**.



k. Skeletal rearrangements

Treatment of the benzodiazepinone **71** with acetic anhydride and sodium acetate resulted[121] in ring contraction to the oxazoloquinoline **106**, by the proposed mechanism (Scheme II). The 1-methyl analog of **71** likewise underwent rearrangement to the 1-methyl derivative of **107**, which obviously could not cyclize to an oxazole.

When **71** was treated with acetic anhydride in pyridine, a different ring contraction resulted[122] to give the isoindole **108** by the mechanism proposed in Scheme III.

(115) S. C. Bell, U. S. Patent, 3,198,789; *Chem. Abstr.*, **63**, 18129 (1965).

(116) 3-Amino compounds could be converted into 3-hydroxy analogs by treatment with nitrous acid.[100]

(117) Clin-Byla, Netherlands Patent 6,600,095; *Chem. Abstr.*, **65**, 15404 (1966).

(118) J. Schmitt, P. Comoy, M. Suquet, J. Boitard, J. LeMeur, J.-J. Basselier, M. Brunaud, and J. Salle, *Chim. Ther.*, **2**, 171 (1967).

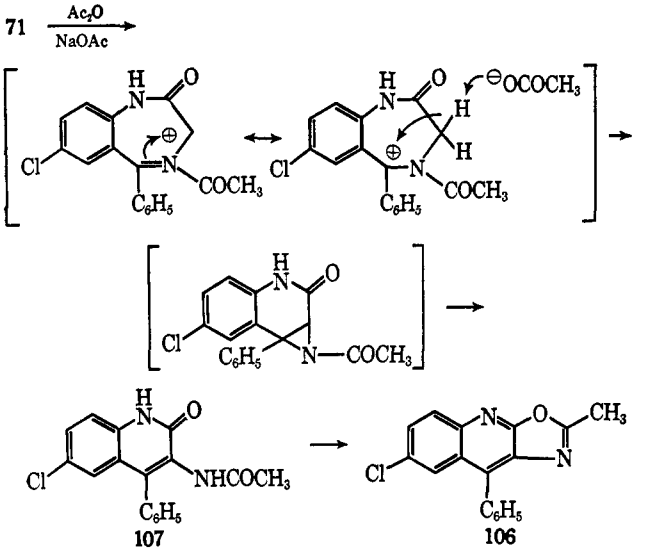
(119) Hoffmann-La Roche, South African Patent 66/6908 (1967).

(120) Hoffmann-La Roche, South African Patent 66/7088 (1967).

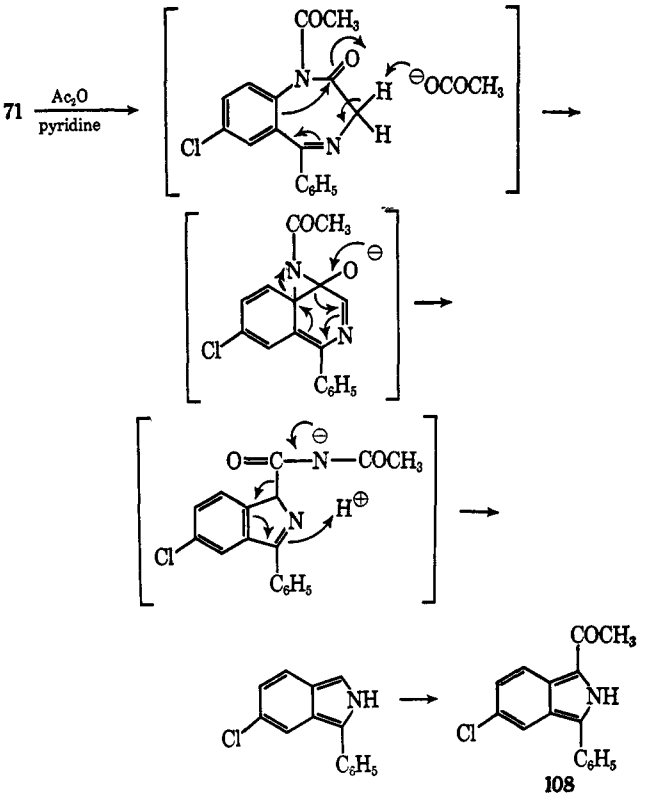
(121) R. I. Fryer, and L. H. Sternbach, *J. Org. Chem.*, **30**, 524 (1965).

(122) R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc., C*, 366 (1967).

SCHEME II

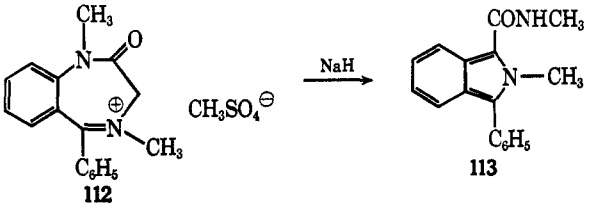


SCHEME III

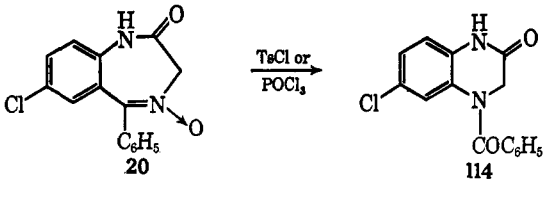


1-Alkyl-substituted benzodiazepin-2-ones underwent a similar ring contraction to isoindolecarboxamides, when treated[110] with sodium hydride in N,N-dimethylformamide; *e.g.*, **109** afforded mixtures of the interconvertible tautomers **110** and **111**, both of which were isolated by variations in the reaction conditions. Two mechanisms were proposed, as shown in Scheme IV.

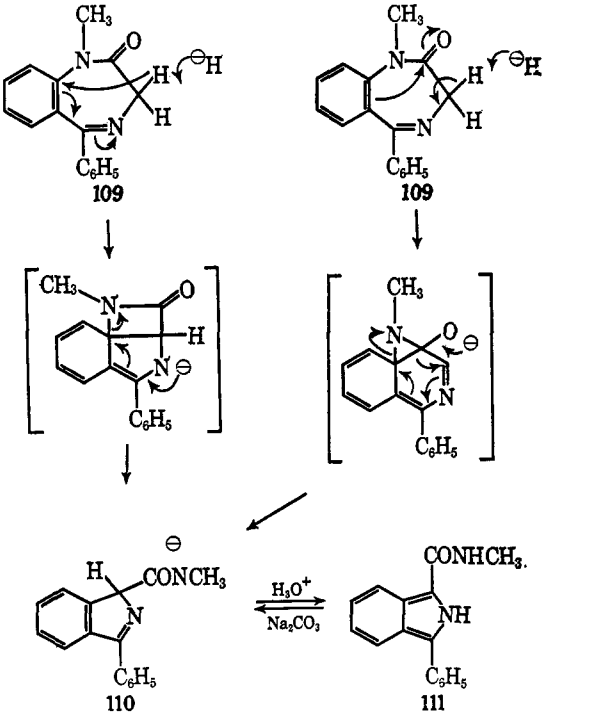
The benzodiazepinium methyl sulfate **112** likewise ring-contracted under the same conditions to give the corresponding dimethylisoindolecarboxamide **113**.



Treatment of the N-oxide **20** with *p*-toluenesulfonyl chloride, or with phosphoryl chloride, resulted in a Beckmann rearrangement[107] to give 4-benzoyl-6-chloro-3,4-dihydroquinoxalin-2(1*H*)-one (**114**).



SCHEME IV



C. 1,4-BENZODIAZEPIN-3-ONES

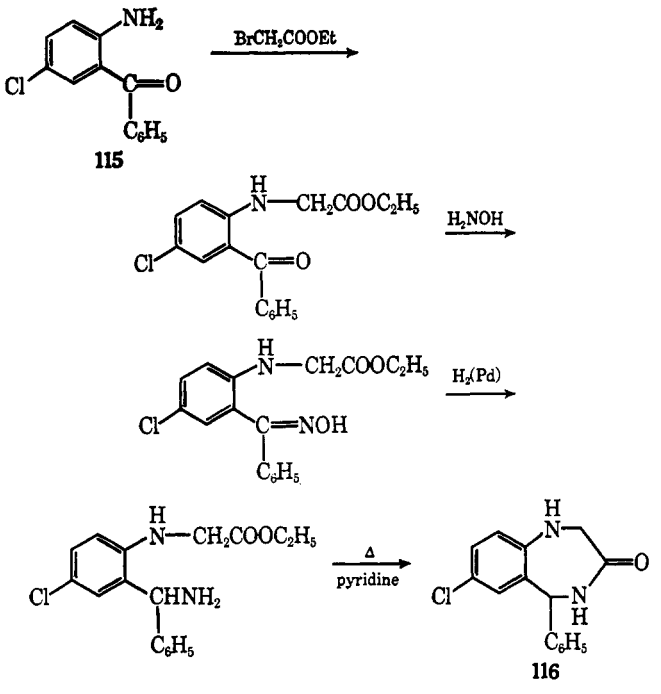
1. Synthesis

7-Chloro-1,2,4,5-tetrahydro-5-phenyl-3*H*-1,4-benzodiazepin-3-one (**116**) was synthesized from 2-amino-5-chlorobenzophenone (**115**), as shown in Scheme V.[123]

A 2-aminobenzodiazepin-3-one derivative **31** was discussed in section A.2.d.

(123) G. A. Archer, and L. H. Sternbach, U. S. Patent 3,317,518; *Chem. Abstr.*, **65**, 16988 (1966).

SCHEME V



115 116

2. Reactions

a. Reduction

Reduction of **31** with lithium aluminum hydride gave[65] the corresponding 3-hydroxy derivative. Catalytic dechlorination of **116**, with hydrogen over palladium and potassium acetate, afforded the 7-deschloro derivative.[123] Lithium aluminum hydride reduction of **116** converted it[123] into 7-chloro-2,3,4,5-tetrahydro-5-phenyl-1*H*-1,4-benzodiazepine (**169**) (section F.1).

b. Ring contractions

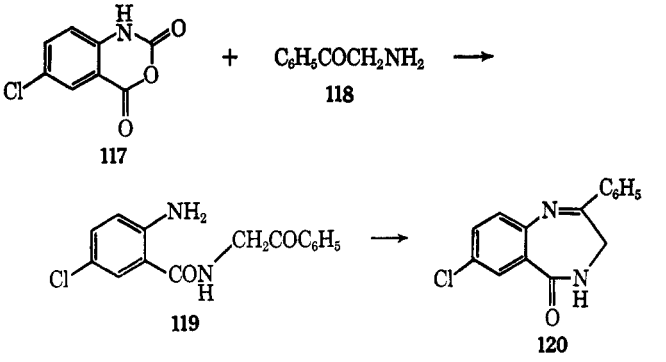
The acid- and base-catalyzed ring contractions of compound **31** to quinazoline derivatives[65] were discussed in section A.2.d.

D. 1,4-BENZODIAZEPIN-5-ONES

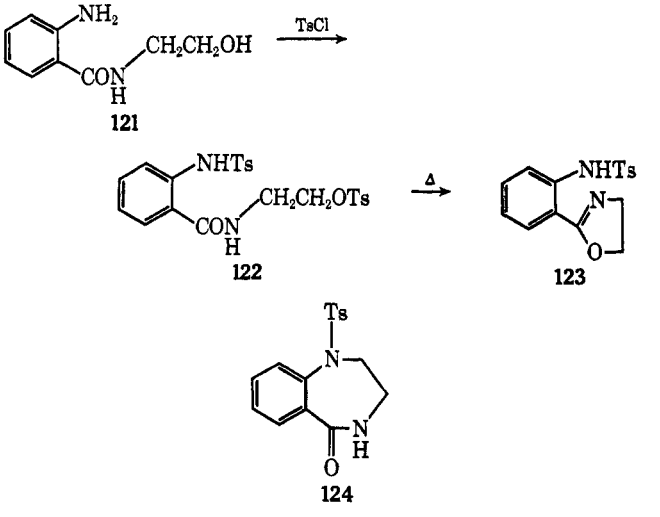
1. Synthesis

Cyclization of the amino ketone **119** gave[124,125] 7-chloro-3,4-dihydro-2-phenyl-5*H*-1,4-benzodiazepin-5-one (**120**). Compound **119** was prepared from 5-chloroisatoic anhydride (**117**) and ω-aminoacetophenone (**118**).

On the other hand, cyclization of the amino alcohol **121**, *via* the ditosylate 122, gave[124-126] 2-[*o*-(*p*-toluenesulfonamido)phenyl]-2-oxazoline (**123**) and not the desired 1,2,3,4-tetrahydro-1-*p*-tolylsulfonyl-5*H*-1,4-benzodiazepin-5-one (**124**), as had been claimed originally.[124] An alternative cyclization of **121**, by treatment with thionyl chloride followed by sodium carbonate, also afforded an oxazoline instead of a benzodiazepin-5-one.

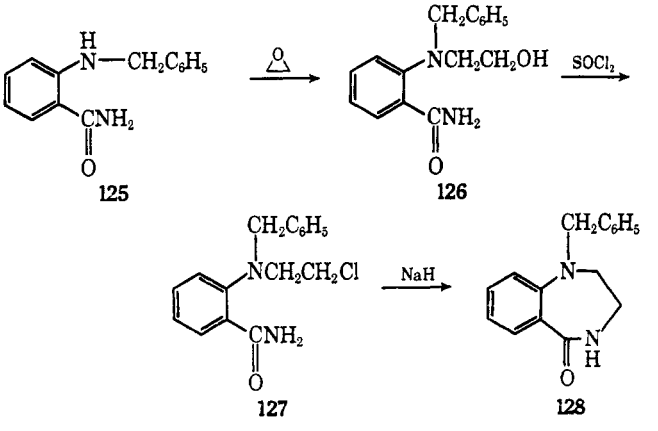


117 118 119 120



121 122 123 124

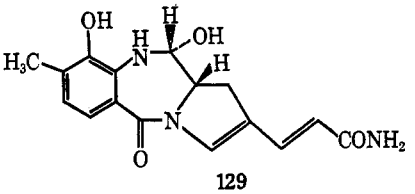
The 1-benzylbenzodiazepin-5-one **128** was prepared[127] by cyclization of the aminoalkyl halide **127**, which was made as shown. It was not possible to debenzylate **128** to the corresponding NH compound.



125 126 127 128

The cytotoxic antibiotic anthramycin (**129**) and its simpler analog (**130**) are benzodiazepin-5-ones;[128,129]

(124) A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **29**, 1998 (1964).
(125) A. A. Santilli and T. S. Osdene, *ibid.*, **30**, 2100 (1965).
(126) G. F. Field, W. J. Zally, and L. H. Sternbach, *ibid.*, **30**, 2098 (1965).
(127) A. A. Santilli and T. S. Osdene, *ibid.*, **31**, 4268 (1966).
(128) W. Leimgruber, V. Stefanovic, F. Schenker, A. Karr, and J. Berger, *J. Am. Chem. Soc.*, **87**, 5791 (1965).
(129) W. Leimgruber, A. D. Batcho, and F. Schenker, *ibid.*, **87**, 5793 (1965).



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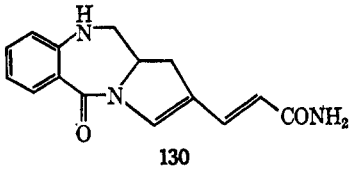
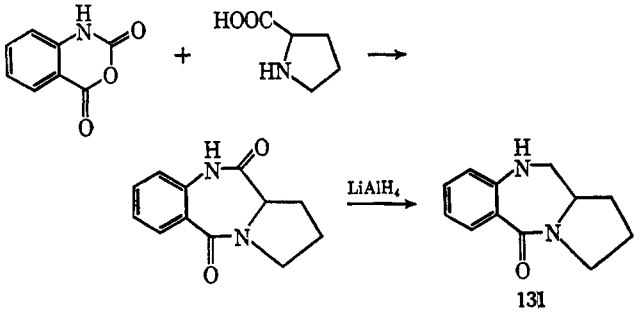


130

their structures and stereochemistry[129a] have been determined, and a number of interesting interconversions were described.[128,129] As a model for comparison with **129** and **130**, the simpler benzodiazepin-5-one **131** was synthesized[129] as shown.

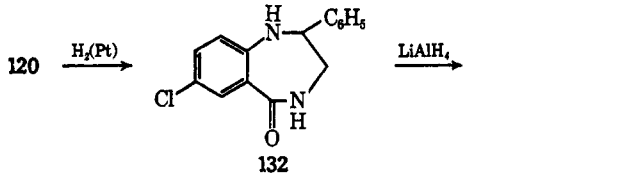


131

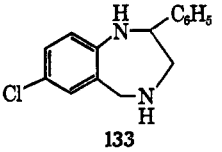
2. *Reactions*

a. Reduction

Catalytic hydrogenation of **120** over platinum gave[125] the dihydro derivative **132**, which was also obtained[124] by treatment of **120** with a limited quantity of lithium aluminum hydride. Further treatment with this reagent afforded[124] 7-chloro-2,3,4,5-tetrahydro-2-phenyl-1*H*-1,4-benzodiazepine (**133**).



132



133

b. Thiation

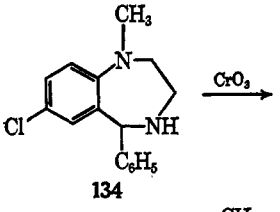
Treatment of **128** with phosphorus pentasulfide in pyridine afforded[127] the corresponding 5-thione.

(129a) W. Leimgruber, A. D. Batcho, and F. Schenker, "Fourth International Symposium on the Chemistry of Natural Products," IUPAC, Stockholm, 1966, p 106.

E. 1,4-BENZODIAZEPINEDIONES

1. *Synthesis*

Formation of a benzodiazepine-2,3-dione (**84**) was described in section B.2.d. The corresponding 1-methyl analog **135** was likewise obtained[105] by rearrangement (section B.2.d) and was also formed[103] by oxidation of compounds **134** or **136**.



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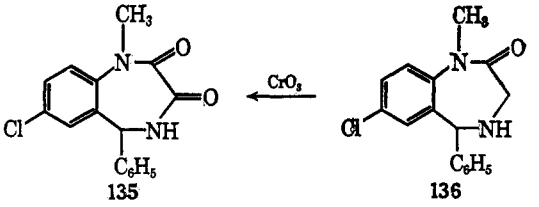
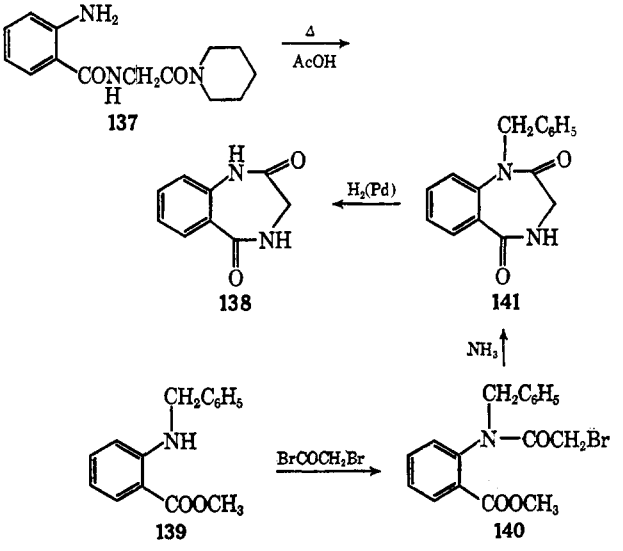


135 136

Cyclization of *o*-aminohippuric acid piperidide (**137**) gave[130] 3*H*-1,4-benzodiazepine-2,5(1*H*,4*H*)-dione (**138**), which was also obtained from N-benzylanthranilic acid methyl ester (**139**), as shown. It should be noted that cyclization of haloacetylanthranilic acids of type **140** with ammonia has been reported[131,132] to give either benzodiazepinediones of type **141** or quinazolinones of type **145**, depending on reaction conditions; *e.g.*,



137 138 141 139 140

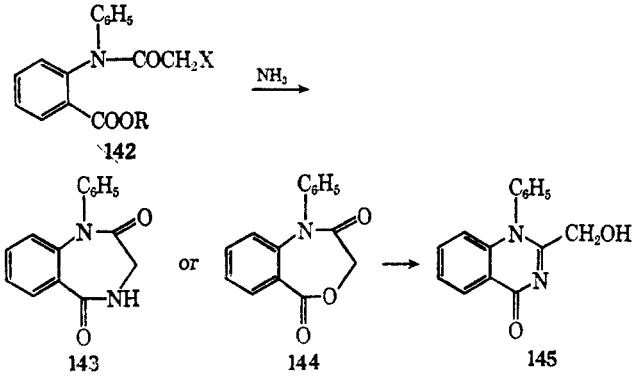
cyclization of **142** (R = CH_3; X = Br) afforded **143**, whereas **142** (R = H; X = Cl) gave[132] 2-hydroxymethyl-1-phenyl-4(1*H*)-quinazolinone (**145**), *via* the

(130) M. Uskoković, J. Iacobelli, and W. Wenner, *J. Org. Chem.*, **27**, 3606 (1962).

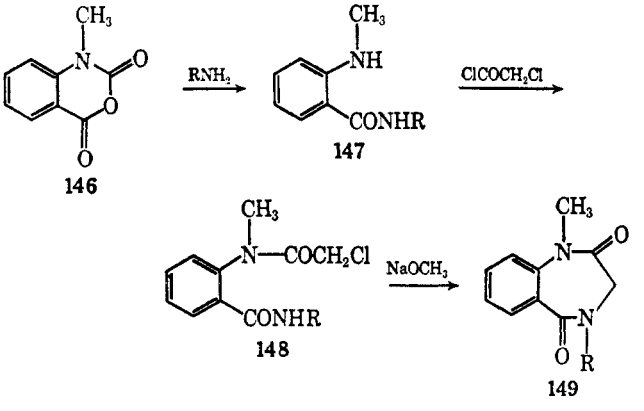
(131) M. Uskoković, J. Iacobelli, V. Toome, and W. Wenner, *ibid.*, **29**, 582 (1964).

(132) J. Iacobelli, M. Uskoković, and W. Wenner, *J. Heterocylic Chem.*, **2**, 323 (1965).

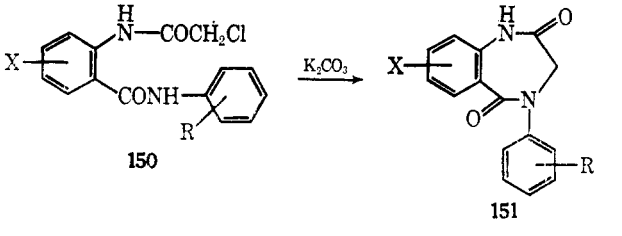
intermediate 1-phenyl-4,1-benzoxazepine-2,5-(1*H*,3*H*)-dione (**144**).



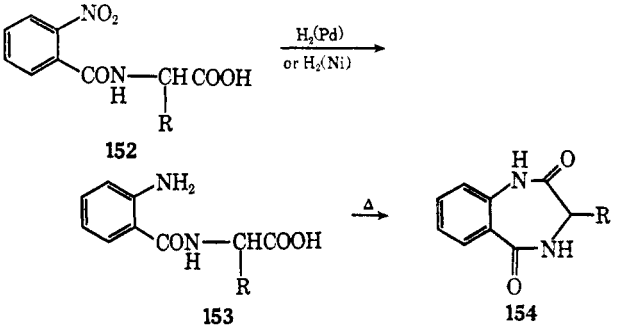
An alternative approach[133] to compounds **149** involved cyclization of chloroacetylanthranilamides **148**, prepared from isatoic anhydrides **146**, as shown.

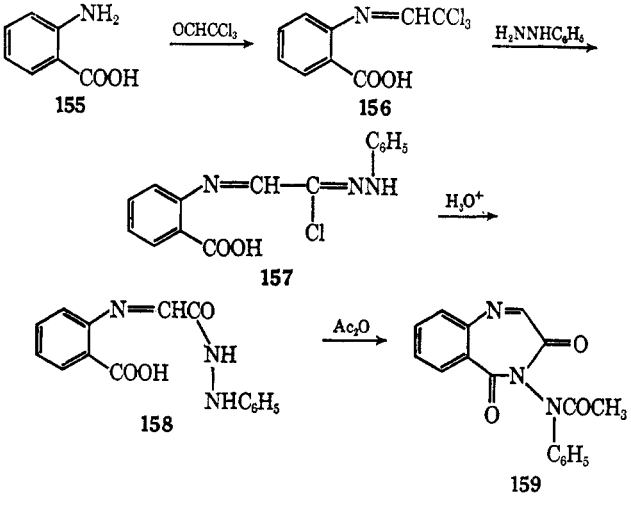


Cyclization of compounds **150** has been reported[134] to give benzodiazepinediones **151**, having NH in position 1.

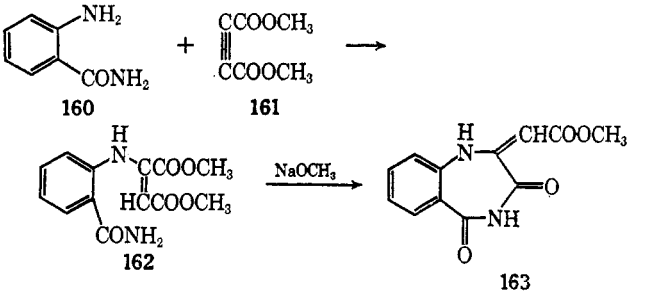


Another approch to 3-substituted benzodiazepinediones **154** involved[135,136] condensation of *o*-nitrobenzoic acid with various amino acids (R = alkyl) to give *o*-nitrobenzamides **152**, which were catalytically reduced, and the resulting aminobenzamides **153** were cyclized to **154**. A similar reductive cyclization was used[136a] to synthesize the 4-phenyl derivative of **154** (R = H), which was also obtained[136a] by thermal cyclization of the ethyl ester of *o*-amino-N-phenylhippuric acid. 4-(N-Phenylacetamido)-3*H*-1,4-benzodiazepine-3,5(4*H*)-dione (**159**) was made[137] by thermal cyclization of the acetyl derivative of the phenylhydrazide **158**, which was prepared from anthranilic acid (**155**), as shown.





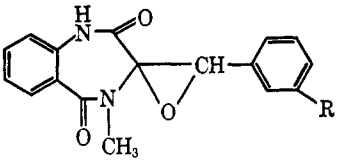
The benzodiazepinedione **163** was obtained[138] by base-catalyzed cyclization of the Michael adduct **162**, made from anthranilamide (**160**) and dimethyl acetylenedicarboxylate (**161**).



The mould metabolites cyclopenin[139,140] and cyclopenol[140] were isolated from strains of the organism

(133) C. M. Lee, *J. Heterocyclic Chem.*, **1**, 235 (1964).
(134) Sumimoto, Japanese Patent 21,617; *Chem. Abstr.*, **66**, 65541 (1967).
(135) E. Hoffmann and B. Jagnicinski, *J. Heterocyclic Chem.*, **3**, 348 (1966).
(136) P. M. Carabeteas and L. S. Harris, *J. Med. Chem.*, **9**, 6 (1966).
(136a) J. Krapcho and C. F. Turk, *ibid.*, **9**, 191 (1966).
(137) S. Gärtner, *Ann.*, **332**, 226 (1904).
(138) N. D. Heindel and T. F. Lemke, *J. Heterocyclic Chem.*, **3**, 389 (1966).
(139) A. Bracken, A. Pocker, and H. Raistrick, *Biochem. J.*, **57**, 587 (1954).
(140) J. H. Birkinshaw, M. Luckner, Y. S. Mohammed, K. Mothes, and C. E. Stickings, *ibid.*, **89**, 196 (1963).

Penicillium cyclopium Westling, and have been ascribed[141] the benzodiazepine-2,5-dione structures **164** and **165**, on the basis of physical data and degradative results. Formula **164** for cyclopenin has recently been



164, R = H
165, R = OH

confirmed[141a] by synthesis.

2. Reactions

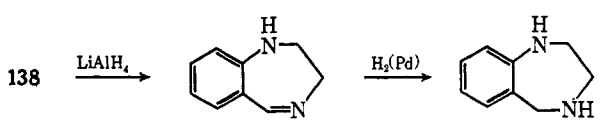
a. Hydrolysis and aminolysis

The benzodiazepine-2,5-dione **138** was stable to aqueous alkali or glacial acetic acid; hot 70% sulfuric acid caused hydrolysis[130] to anthranilic acid (**155**). The benzodiazepine-3,5-dione **159** was, however, readily hydrolyzed with hot sodium hydroxide solution to give[137] the phenylhydrazide **158**.

Treatment of the benzodiazepine-2,5-dione **138** with methylamine in hot methanol resulted[130] in ring opening in the 1,2 position by a transamidation reaction to give *o*-aminohippurylmethylamide (**137**; methyl instead of piperidyl).

b. Reduction

Lithium aluminum hydride reduced the benzodiazepine-2,5-dione **138** to a mixture of 2,3-dihydro-1*H*-1,4-benzodiazepine (**166**) and the corresponding tetrahydro derivative **167**, which could also be obtained[130] by catalytic hydrogenation of **166** over palladium. The reduction of diones, having substituents in the 1 or 4 positions, to the fully reduced benzodiazepines has also been reported.[133,136,142]



166 **167**

Hydrogenolysis of the 1-benzylbenzodiazepine-2,5-dione **141** over palladium afforded[130] the 1*H* compound **138**; however, an attempted hydrogenolysis of the 4-benzyl analog **149** (R = $C_6H_5CH_2$) was unsuccessful.[133]

c. Alkylation

Treatment of the benzodiazepine-2,5-dione **138** with sodium methoxide and methyl iodide yielded[142] a mixture of the 1-methyl (**149**, R = H) and 1,4-dimethyl (**149**, R = CH_3) derivatives. Compounds having a basic side chain in position 1 have been prepared[136a] by alkylation of **151** (R = X = H) with sodamide and the appropriate dialkylaminoalkyl halide.

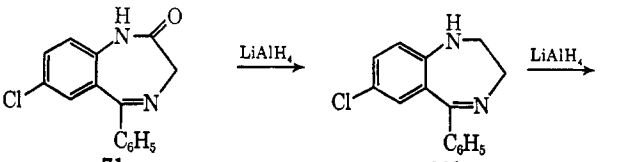
F. 1,4-BENZODIAZEPINES

1. Synthesis

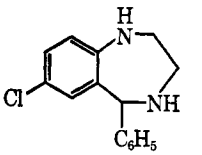
Benzodiazepines without functional groups in the 2 position have mostly been made by reduction of suitable benzodiazepinones (*e.g.*, **71** → **168** → **169**), although a number of direct syntheses have also been described.

An indirect reductive method involved conversion[61] of benzodiazepin-2-ones into the corresponding 2-thiones, followed by Raney nickel desulfurization; in this manner the benzodiazepine-2-thione **12** was converted into the 2,3-dihydrobenzodiazepine **168**.

Reduction of the benzodiazepin-2-one **71** with lithium aluminum hydride gave[143,144] 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (**168**) or the tetrahydro derivative **169**, depending on reaction conditions. The latter compound was also obtained[143] by reduction of the tetrahydrobenzodiazepin-2-one **68**, or of the benzodiazepin-3-one derivative **116**.

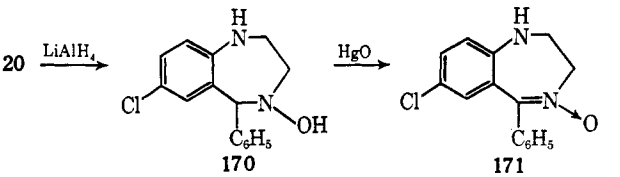


71 **168**



169

In a similar manner, reduction of the 4-oxide **20**, with the same reagent, afforded[144] the 4-hydroxy derivative **170**, which could be oxidized with mercuric oxide to give **171**. The lithium aluminum hydride reduction



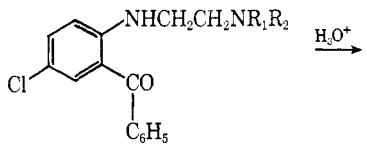
170 **171**

of benzodiazepin-3-ones, -5-ones, and -2,5-diones has been discussed in sections C–E.

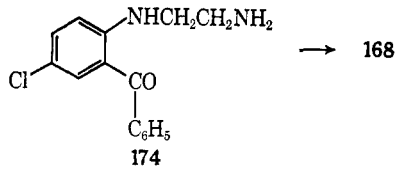
Compound **168** has also been obtained[143] by alkylation of 2-amino-5-chlorobenzophenone with β-bromo-

(141) Y. S. Mohammed and M. Luckner, *Tetrahedron Letters*, **28**, 1953 (1963).
(141a) H. Smith, P. Wegfahrt, and Rapoport, *J. Am. Chem. Soc.*, **90**, 1668 (1968).
(142) M. Uskokovic, and W. Wenner, U. S. Patent 3,261,828; *Chem. Abstr.*, **65**, 10601 (1966).
(143) L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).
(144) T. S. Sulkowski and S. J. Childress, *ibid.*, **28**, 2150 (1963).

ethylbenzamide to give **172**, or with β-bromoethylphthalimide to form **173**, followed by hydrolysis of the protecting group. The resulting aminoethylaminobenzophenone **174** cyclized spontaneously to **168**. The latter compound was also made[143] by treatment of 2-amino-5-chlorobenzophenone with ethylenimine and aluminum chloride.

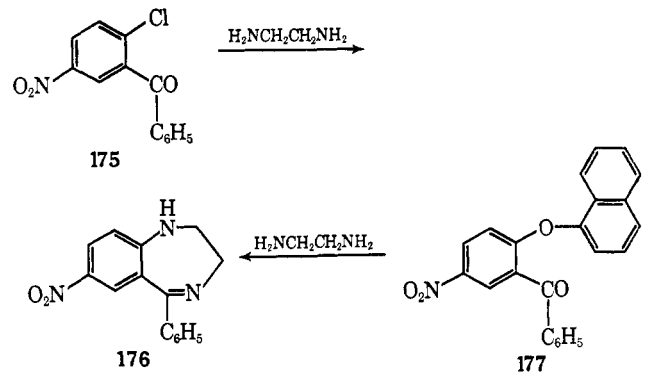


172, $R_1 = COC_6H_5$; $R_2 = H$
173, R_1R_2 = phthalimido



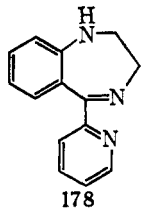
174

Condensation of 2-chloro-5-nitrobenzophenone (**175**) or of the α-naphthyl ether **177** with ethylenediamine afforded[145,146] the 7-nitrobenzodiazepine **176**. Activation of the halogen atom to nucleophilic displacement was needed for good yields, since 2,5-dichlorobenzophenone with ethylenediamine gave[145] **168** in only 10% yield, whereas the yields reported[145] for the reaction using **175** or the 2-chloro-5-trifluoromethyl analog, having electron-withdrawing groups *para* to the halogen atom,



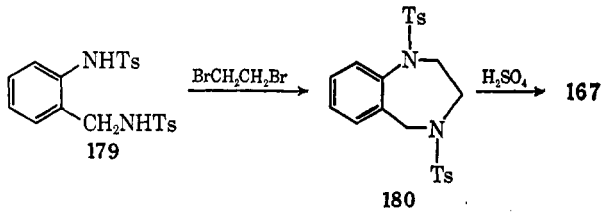
175 176 177

were 90 and 61%, respectively. This method of synthesis has been used[147] for the preparation of 5-(2-, 3-, and 4-pyridyl) analogs of **176**; a variation involved use of 2-(2-fluorobenzoyl)pyridine[147] or 3-(2-fluorobenzoyl)-indole,[148] which did not require further activation of the halogen, to give compounds **178** and **218** (section F.2.j).



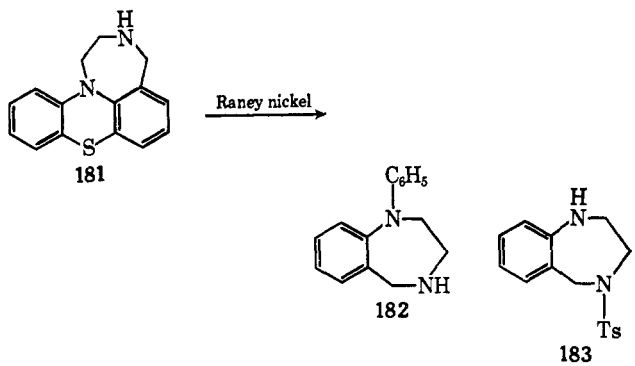
178

2,3,4,5-Tetrahydro-1*H*-1,4-benzodiazepine (**167**) has been made[149,150] by alkylation of *o*-aminobenzylamine ditoluenesulfonamide (**179**) with ethylene dibromide, followed by acid hydrolysis of the tosyl groups of the product, **180**.



179 180

The 1-phenylbenzodiazepine **182** was obtained[150] by reductive desulfurization of the diazepinophenothiazine **181**, using Raney nickel; compound **182** was also prepared by conversion of **167** into the 4-tosyl derivative **183** and phenylation in the 1 position, followed by acid hydrolysis.

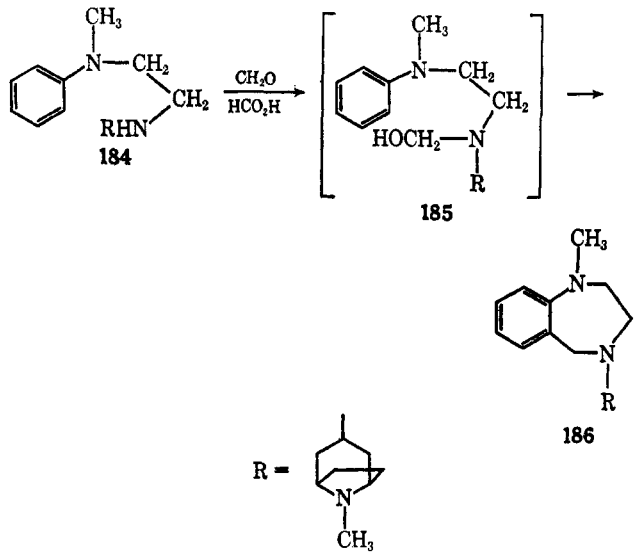


181 182 183

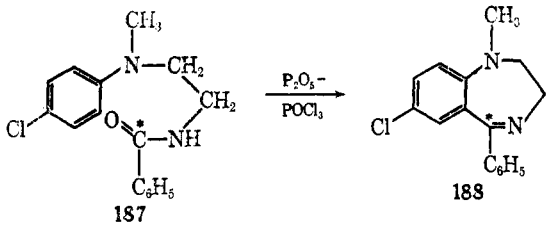
Attempted methylation of the tropanylethylenediamine derivative **184**, by the Eschweiler–Clark method (formaldehyde and formic acid), gave[151] 2,3,4,5-tetrahydro-1-methyl-4-(3-tropanyl)-1*H*-1,4-benzodiazepine (**186**) by an intramolecular cyclization of the postulated methylol intermediate **185**.

Another synthesis, by a Bischler–Napieralski cyclization, has recently been described[152] for the preparation of the 5-^{14}C-labeled 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (**188**). The benzamide **187** was made from ^{14}COOH benzoic acid, *via* the acid

(145) L. H. Sternbach, G. A. Archer, and E. Reeder, *J. Org. Chem.*, **28**, 3013 (1963).
(146) J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961).
(147) G. A. Archer, A. Stempel, S. S. Ho, and L. H. Sternbach, *J. Chem. Soc., C*, 1031 (1966).
(148) E. E. Garcia, J. G. Riley, and R. I. Fryer, Abstracts, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967.
(149) S. Shiotani and K. Mitsuhashi, *J. Pharm. Soc. Japan*, **84**, 656 (1964); *Chem. Abstr.*, **61**, 10685 (1964).
(150) T. Ichii, *J. Pharm. Soc. Japan*, **82**, 999 (1962); *Chem. Abstr.*, **58**, 5666 (1963).
(151) S. Archer, T. R. Lewis, M. J. Unser, J. O. Hoppe, and H. Lape, *J. Am. Chem. Soc.*, **79**, 5783 (1957).
(152) H. H. Kaegi, Abstracts of the International Conference on the Use of Radioactive Isotopes in Pharmacology, Geneva, Switzerland, 1967.



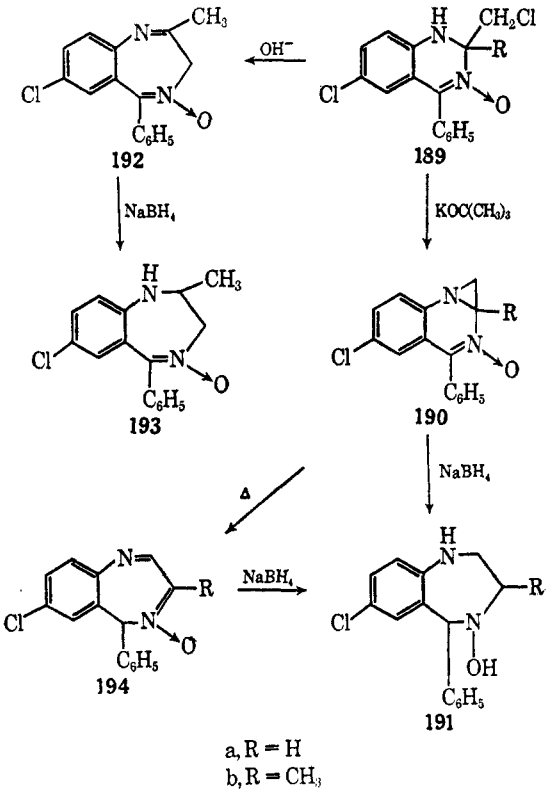
chloride, and was then cyclized with phosphorus pentoxide in phosphoryl chloride to give a 60% yield of **188**.



Treatment of the dihydroquinazoline 3-oxide **189a** with potassium *t*-butoxide gave[153,154] the aziridino derivative **190a**. Borohydride reduction converted **190a** into the 4-hydroxytetrahydrobenzodiazepine **191a**. A ready isomerization of **190a** occurred on heating to give 7-chloro-5-phenyl-5*H*-1,4-benzodiazepine 4-oxide (**194a**), which was reduced to **191a** using sodium borohydride.

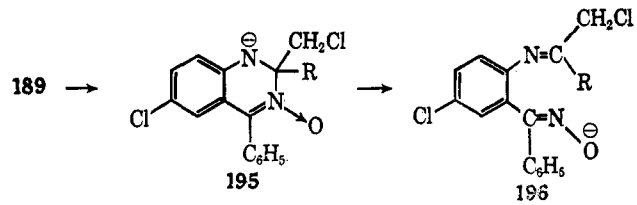
The reaction of the 2-methyldihydroquinazoline oxide **189b** with potassium *t*-butoxide likewise afforded[153,154] the 5*H*-benzodiazepine **194b** *via* the presumed aziridino intermediate **190b**, which was insufficiently stable for isolation. A minor by-product from **189b** was 7-chloro-2-methyl-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (**192**), which was also obtained, as a major product, by treatment of **189b** with sodium hydroxide.

It was considered[153,154] that the mechanism of this ring enlargement involved proton abstraction from **189** to form the anion **195**, which could then undergo either cyclization to the aziridine **190** or ring opening to the oxime **196**. The mechanism was thus analogous to the scheme proposed[71] for the transformation of 2-chloromethylquinazoline 3-oxides into benzodiazepine 4-oxides, with the difference that, in the latter case, the



a, R = H
b, R = CH_3

intermediate of type **195** (R = OH) was formed by *addition* of base (section B.1), whereas, in the present case, it was the result of the proton *abstraction*. The course of the reaction, to give an aziridine **190** or a 3*H*-benzodiazepine **192**, was attributed[154] to the relative stabilities of the respective anions **195**; an elec-



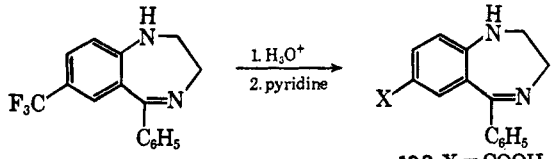
tron-releasing substituent (*e.g.*, R = CH_3) would destabilize **195** to form **192** *via* **196**. In the absence of such a group (*e.g.*, R = H), **195** was transformed into **190**, and finally to **194**.

2. *Reactions*

a. Hydrolysis

Acid hydrolysis of the 2,3-dihydro-1*H*-1,4-benzodiazepine **168** resulted[143] in cleavage of the imine group to give the hydrochloride of **174**, which recyclized spontaneously when treated with base. The 5-nitro analog of **174** was also made by acid hydrolysis[145] of **176** and was easily isolated as the free base. The 7-trifluoromethyl-2,3-dihydro-1*H*-1,4-benzodiazepine **197** gave the corresponding 7-carboxylic acid **198**, together with the decarboxylation product **199**, when treated vigorously with hydrochloric acid, followed by recyclization of the amino ketone intermediate.[145]

(153) G. F. Field, W. J. Zally, and L. H. Sternbach, *Tetrahedron Letters*, **23**, 2609 (1966).
(154) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Am. Chem. Soc.*, **89**, 332 (1967).



197 198, X = COOH 199, X = H

Acid hydrolysis of the 3*H*-1,4-benzodiazepine 4-oxide **192** gave[154] 2-amino-5-chlorobenzophenone. Rearrangements of a 5-indolyl- and of a 3-acetoxy-1,4-benzodiazepine on acid and base hydrolysis, respectively, are discussed in sections F.2.j and F.2.c.

b. Reduction

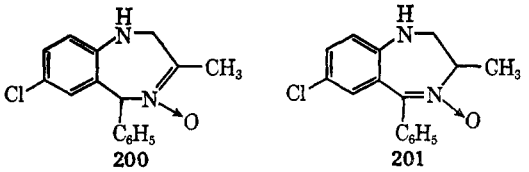
2,3-Dihydro-1*H*-1,4-benzodiazepines have been reduced to the 2,3,4,5-tetrahydro-1*H* derivatives, using lithium aluminum hydride[143] or hydrogen over palladium[130] or platinum.[18] Reduction of 5*H*-benzodiazepines of type **194** to the 4-hydroxytetrahydro derivatives **191** was achieved[154] with sodium borohydride, lithium aluminum hydride, or tetramethylammonium borohydride; likewise **171** was reduced[155] to the 4-hydroxy derivative **170**. Selective reduction of the 1,2 double bond in the 3*H*-benzodiazepine **192**, using sodium borohydride, gave[154] the corresponding 2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide (**193**). Reduction of **192** with hydrogen over Raney nickel resulted[154] in deoxygenation, together with hydrogenation of the 1,2 bond. Deoxygenation of 4-oxides has also been effected[154,155] with phosphorus trichloride.

7-Nitro-1,4-benzodiazepines were reduced to the corresponding 7-amino compounds, without reduction of the imine grouping, by hydrogenation over Raney nickel.[145,147]

c. Oxidation

Chromium trioxide oxidation of 2,3-dihydro-1*H*-1,4-benzodiazepines (*e.g.*, **168**) gave[103] the corresponding 1,3-dihydro-2*H*-2-ones (*e.g.*, **71**). The 2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine **134** could be oxidized in stages to give[103] the 1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one **136** or the benzodiazepinedione **135**.

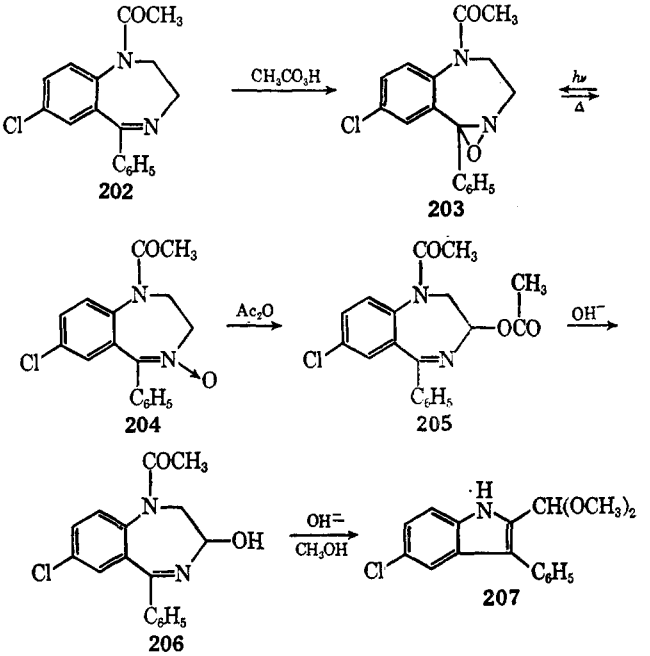
Treatment of the 2,3-dihydro-1*H*-1,4-benzodiazepine 4-oxide **193** with manganese dioxide resulted[154] in oxidation in the 1,2 position to **192**. Mercuric oxide was used[154] to convert the tetrahydro-4-hydroxybenzodiazepine **191b** (mixture of two stereoisomers) into a mixture of isomeric nitrones **200** and **201**.



200 201

(155) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, 28, 2459 (1963).

Oxidation of the 1-acetylbenzodiazepine **202** with peracetic acid afforded[155] the oxaziridine **203**, which was thermally isomerized into the nitrone **204**; this rearrangement was reversed by exposure to light.



202 203 204 205 206 207

Treatment of the nitrone **204** with acetic anhydride resulted[156] in a Polonovsky rearrangement to the diacetyl derivative **205**. Mild alkaline hydrolysis of **205** gave the 3-hydroxybenzodiazepine **206**; more vigorous treatment with methanolic sodium hydroxide yielded the indolecarboxaldehyde dimethyl acetal **207**.

d. Acylation

Benzodiazepines have been acylated in the **1** position by treatment with acid anhydrides[136,143,144] or acid chlorides.[136] The rearrangement of a benzodiazepine 4-oxide, on treatment with acetic anhydride, is discussed in section F.2.c. Reaction of **167** with *p*-toluenesulfonyl chloride in pyridine afforded[150] the 4-tosyl derivative **183**.

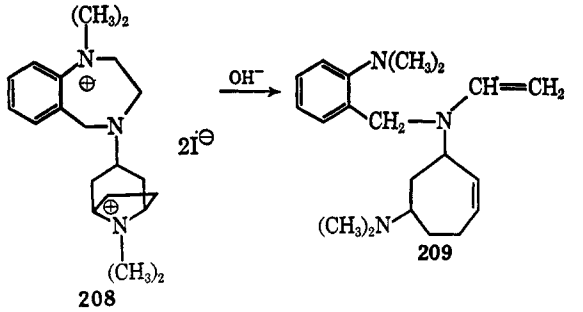
e. Alkylation

Methylation of the 2,3-dihydro-1*H*-1,4-benzodiazepine **168**, by treatment with sodium hydride and methyl iodide, gave[143] the corresponding 1-methyl derivative **188** in 25% yield. The 7-nitrobenzodiazepine **176** was methylated much more easily[145] to give the 1-methyl analog in 76% yield. The nitrone[156] **171** and also 5-(2-, 3-, and 4-pyridyl)benzodiazepines[147] were likewise methylated in the 1 position. Compound **176** was alkylated in the 1 position with other reagents to give compounds having the groups $-CH_2CON(CH_3)_2$,[82] $-CH_2CONHCH_3$,[82] and $-CH_2CH_2N(C_2H_5)_2$.[157]

(156) W. Metlesics, G. Silverman, and L. H. Sternbach, *ibid.*, 29, 1621 (1964).

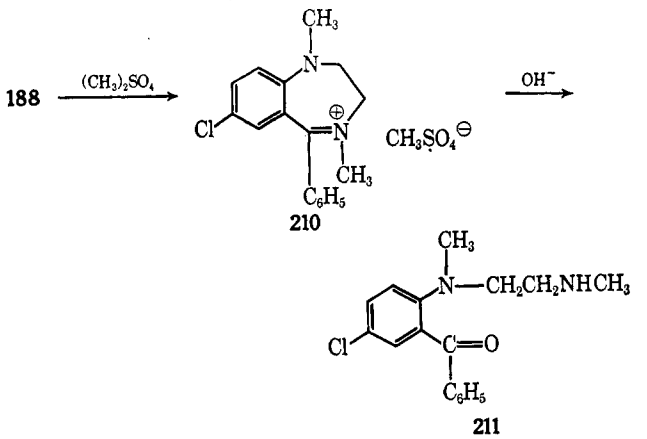
(157) G. A. Archer, R. I. Fryer, E. Reeder, and L. H. Sternbach, U. S. Patent 3,299,053; *Chem. Abstr.*, 64, 3578 (1966).

Treatment of the 4-(3-tropanyl)benzodiazepine **186** with methyl iodide afforded[151] the bismethiodide **208**, which underwent a Hoffmann degradation on exposure to IRA-400 anion-exchange resin (hydroxide form) to give the vinylamine **209**.



208 **209**

Methylation of the benzodiazepine **188** with dimethyl sulfate in refluxing benzene gave[158] 7-chloro-2,3-dihydro-1,4-dimethyl-5-phenyl-1*H*-1,4-benzodiazepinium methyl sulfate (**210**), which was cleaved to the amino ketone **211** by treatment with base.

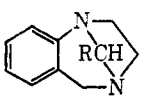


210 **211**

The benzodiazepine-7-carboxylic acid **198** was converted[145] into the corresponding methyl ester by treatment with diazomethane.

f. Condensation with aldehydes

Condensation of the tetrahydrobenzodiazepine **167** with formaldehyde or benzaldehyde gave[149] methano derivatives **212** and **213**, respectively. The latter compound was easily hydrolyzed to **167**, by treatment with cold 0.1 *N* hydrochloric acid; **212** was stable under these conditions.



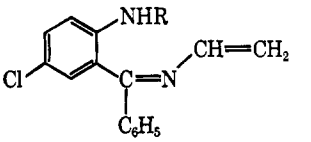
212, R = H
213, R = C_6H_5

g. Sandmeyer reactions

7-Amino-2,3-dihydro-1*H*-1,4-benzodiazepines have been converted into 7-chloro, bromo, and cyano derivatives by treatment of the diazonium salts with cuprous chloride, bromide, or cyanide.[82,145,147,157]

h. Ring opening of 1-sulfonamides

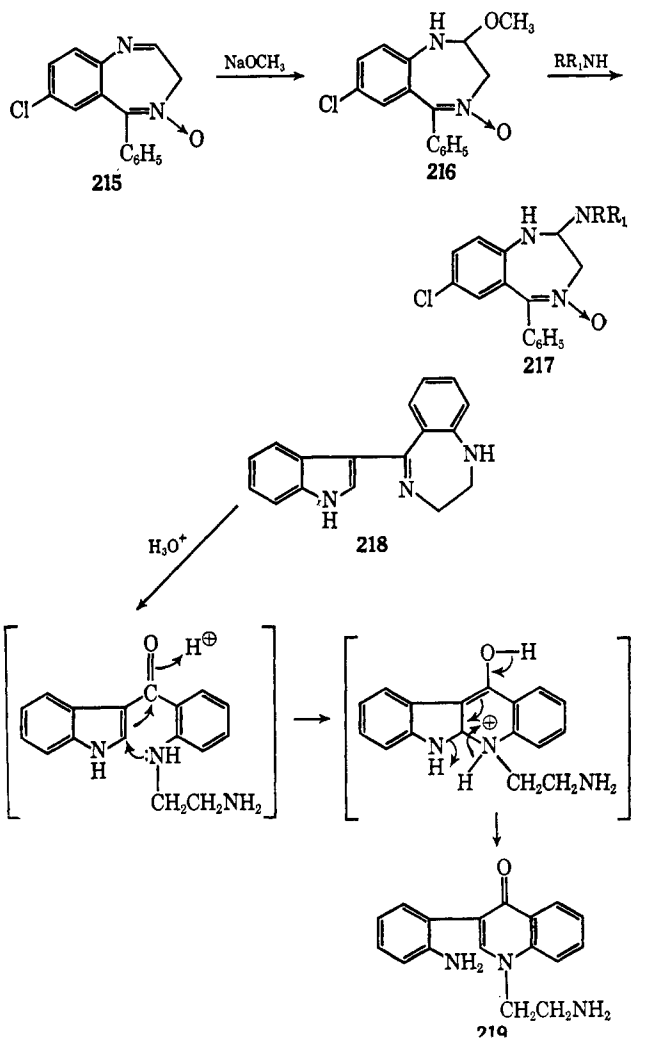
Treatment of the 1-methylsulfonyl or *p*-tolylsulfonyl derivatives of the benzodiazepine **168** with sodium hydride in N,N-dimethylformamide resulted[104] in cleavage to the respective vinylimines **214**.



214, R = Ms or Ts

i. Addition of nucleophiles

Treatment of **215** with sodium methoxide in methanol resulted[159] in addition of methanol in the 1,2 position to give the dihydrobenzodiazepine 4-oxide **216**. The methoxy group in this compound was labile and could be replaced by primary or secondary amines to give compounds of type **217**.



215 **216** **217** **218** **219**

(158) Hoffmann-La Roche, South African Patent 66/5349 (1967).

(159) Hoffmann-La Roche, Netherlands Patent 6,614,923; *Chem. Abstr.*, **67**, 90855 (1967).

j. Skeletal rearrangements

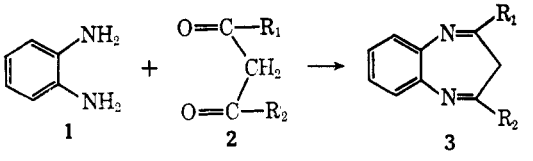
Acid hydrolysis of the 5-(3-indolyl)benzodiazepine **218** led to the 4-quinolone derivative **219**, for which the following mechanism was proposed.[148]

V. 1,5-BENZODIAZEPINES, -ONES, AND -DIONES

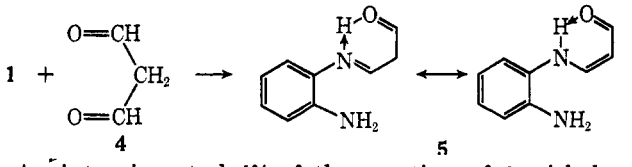
A. 1,5-BENZODIAZEPINES

1. Synthesis

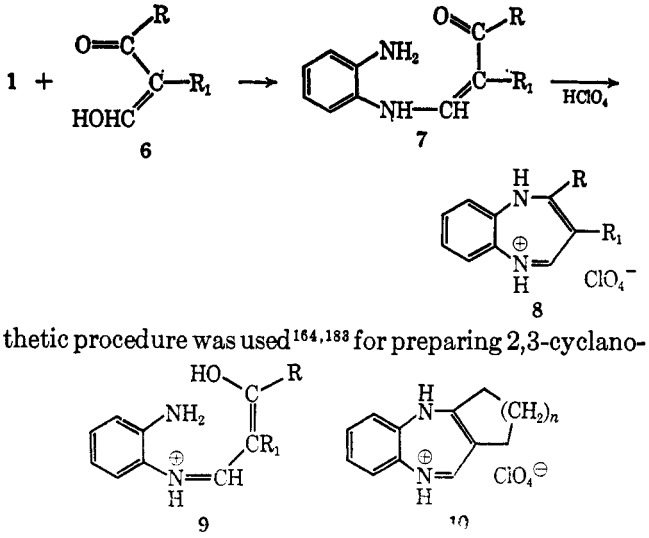
Condensation of *o*-phenylenediamine (**1**) with β-dicarbonyl compounds **2** has been the most widely used method for the synthesis of 3*H*-benzodiazepines **3**. The reaction has been shown to be pH dependent[160,161] for the case of acetylacetone (**2**, $R_1 = R_2 = CH_3$),

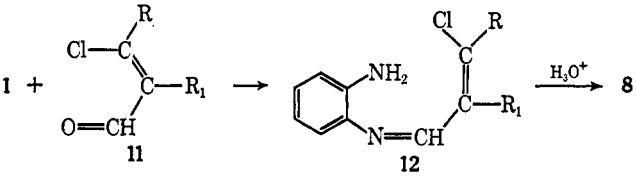


which afforded 2,4-dimethyl-3*H*-1,5-benzodiazepine (**3**, $R_1 = R_2 = CH_3$) in optimum yield at pH 4–6. The majority of syntheses of **3** have used acid catalysis, *e.g.*, acetic acid or dry hydrogen chloride in ethanol. This method has been used for the preparation of **3** having R_1 and R_2, or both, as alkyl,[161–167] methoxymethyl,[161] bromomethyl,[168] benzyl,[164] phenyl, or substituted phenyl,[163,167,169] $C_6H_5COCH_2CO$,[169] COOH,[170] and selenophen-2-yl.[171] Benzodiazepines **3**, having substituents in the 3 position, have also been obtained in analogous manner; 2,3,4-trimethyl-[172–175] 3-phenyl-,[176,177] 3-(2-benzimidazolyl)-2,4-dimethyl-,[178] 3-nitro-,[179,180] 3-bromo-,[177] and 3-hydroxyimino-2,4-dimethylbenzodiazepines[167,181] have been described. Attempted condensation of **1** with malondialdehyde **4** resulted in the anil **5**, for which a chelated structure was proposed;[177] the desired 1,5-benzodiazepine **3** ($R_1 = R_2 = H$) was later obtained[161] by reaction of **1** with 1-ethoxy-1,3,3-trimethoxypropane.



An intensive study[164] of the reaction of **1** with hydroxymethylene ketones **6** in alcoholic perchloric acid has shown that benzodiazepine perchlorates **8** were obtained only when R was alkyl or benzyl; when R was aryl, enamines of type **7** resulted,[182] probably due to their stabilization as immonium ions **9**. The same synthetic procedure was used[164,183] for preparing 2,3-cyclanobenzodiazepine perchlorates **10** (n = 1–3) from cyclic hydroxymethylene ketones. An analogous synthesis of compounds **8** and **10**, using readily available β-chlorovinylaldehydes **11**, instead of hydroxymethylene ketones **6**, has been described by the same authors.[184,185] Both methods gave the same benzodiazepinium salts **8** and **10**; however, the β-chlorovinylaldehyde reagents were more versatile and could be used to prepare compounds **8** having R = phenyl or substituted phenyl, whereas the former procedure using **6** failed. That the imine **12** was an intermediate was shown[185] by reaction

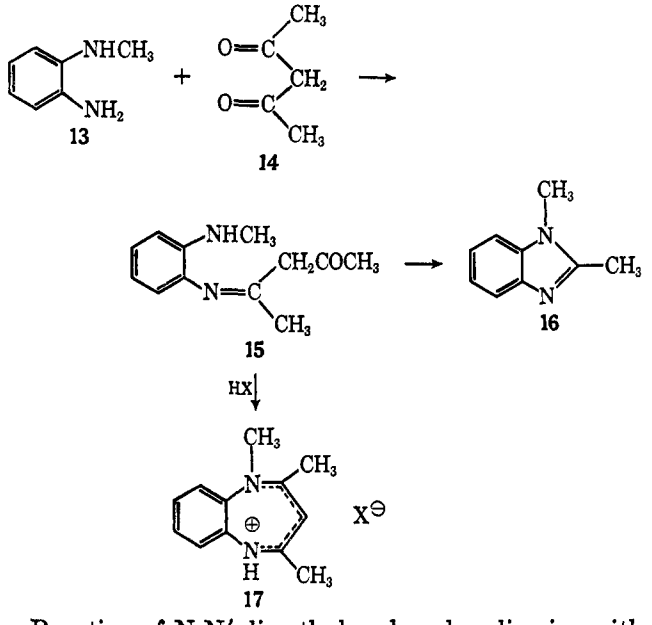




(160) C. A. C. Haley and P. Maitland, *J. Chem. Soc.*, 3155 (1951).
(161) D. Lloyd, R. H. McDougall, and D. R. Marshall, *J. Chem. Soc.*, 3785 (1965).
(162) B. Emmert and H. Gsottschneider, *Ber.*, **66**, 1871 (1933).
(163) J. Thiele and G. Steimmig, *ibid.*, **40**, 955 (1907).
(164) M. Weissenfels, R. Kache, and W. Kräuter, *J. Prakt. Chem.*, **35**, 166 (1967).
(165) W. J. Barry, I. L. Finar, and E. F. Mooney, *Spectrochim. Acta*, **21**, 1095 (1965).
(166) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1147 (1940).
(167) J. A. Barltrop, C. G. Richards, D. M. Russell, and G. Ryback, *J. Chem. Soc.*, 1132 (1959).
(168) A. Becker, *Helv. Chim. Acta*, **32**, 1584 (1949).
(169) I. L. Finar, *J. Chem. Soc.*, 4094 (1958).
(170) J. Schmitt, *Ann.*, **569**, 17 (1950).
(171) Yu. K. Yur'ev, N. N. Magdesieva, and V. V. Titov, *Soviet J. Org. Chem.*, **1**, 159 (1965); *Chem. Abstr.*, **62**, 14666 (1965).
(172) S. B. Val'sman, *Trans. Inst. Chem. Kharkov Univ.*, **4** (13), 157 (1938).
(173) S. B. Val'sman, *Chem. Abstr.*, **34**, 5847 (1940).
(174) J. O. Halford and R. M. Fitch, *J. Am. Chem. Soc.*, **85**, 3354 (1963).
(175) Repeated attempts to synthesize the 2,3,3,4-tetramethylbenzodiazepine were unsuccessful.[1,172,173]
(176) H. Rupe and A. Huber, *Helv. Chim. Acta*, **10**, 846 (1927).
(177) W. Ruske and E. Hüfner, *J. Prakt. Chem.*, **18**, 156 (1962).
(178) T. N. Ghosh, *J. Indian Chem. Soc.*, **15**, 89 (1938).
(179) F. E. King and P. C. Spensley, *J. Chem. Soc.*, 2144 (1952).
(180) R. M. Acheson, *ibid.*, 4731 (1956).
(181) J. A. Barltrop and C. G. Richards, *Chem. Ind.* (London), 466 (1957).
(182) Phenyl ketones such as benzoylacetone[167] or dibenzoylmethane[163,167,169] have been successfully condensed with **1** to give benzodiazepines **3**.
(183) M. Weissenfels, U. Thrust, and M. Mühlstädt, *J. Prakt. Chem.*, **20**, 117 (1963).
(184) M. Weissenfels, *Z. Chem* **4**, 458 (1964).
(185) M. Weissenfels, H. Schurig, and G. Hühsam, *Ber*, **100**, 584 (1967).

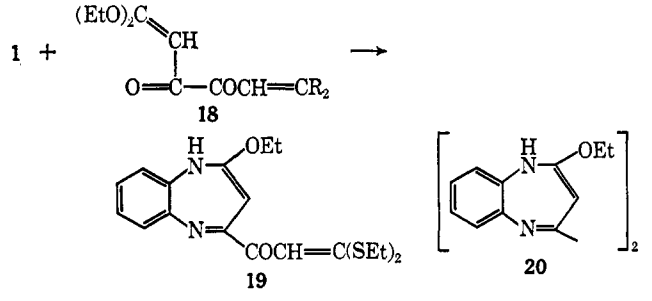
of **1** and **11** in neutral solution to give **12**, which on treatment with acid afforded the benzodiazepinium salt **8**. All attempts to convert the salts **8** or **10** into the parent bases were unsuccessful,[185] owing to the instability of the latter compared with that of 2,4-disubstituted benzodiazepines. Treatment of **1** with β-chlorovinylmethyl ketone likewise gave[186] the 2-methylbenzodiazepinium hydrochloride corresponding to **8** (R = CH_3; R_1 = H); N-methyl-*o*-phenylenediamine (**13**) with the same reagent afforded only N-methylbenzimidazolium chloride.

Condensation of N-methyl-*o*-phenylenediamine (**13**) with acetylacetone (**14**) gave[173,186] 4-(*o*-methylaminophenylimino)pentan-2-one (**15**) or 1,2-dimethylbenzimidazole (**16**), depending on reaction conditions, accompanied by only small amounts of the 1-methylbenzodiazepine (**17**), which was isolated as a dinitrobenzoate salt. Compound **15** could be converted into **17** by acid-catalyzed dehydration.

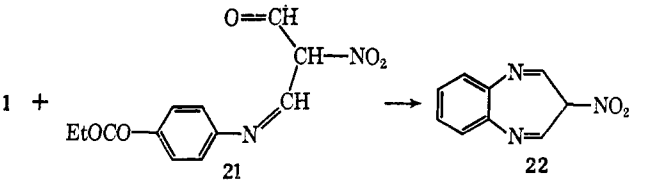


Reaction of N,N′-dimethyl-*o*-phenylenediamine with acetylacetone gave only a 1,2,3-trimethylbenzimidazolium salt; the expected 1,2,4,5-tetramethylbenzodiazepine could not be detected.[186]

Treatment of **1** with the diketothioacetal **18** (R = SEt) afforded[187] the 2-ethoxybenzodiazepine **19**; the corresponding diacetal **18** (R = OEt) yielded the dimeric benzodiazepine **20**, in the same reaction.

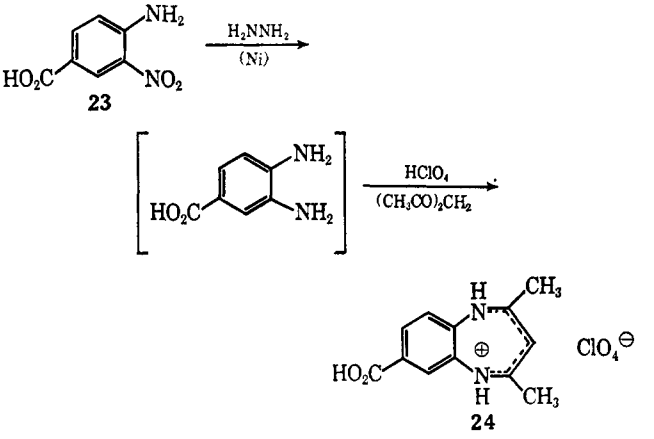


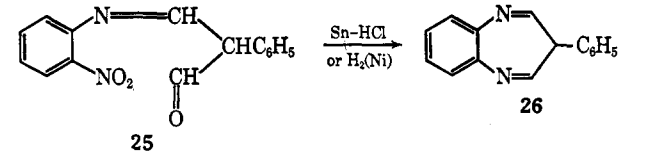
Reaction of the Schiff base **21**, from ethyl *p*-aminobenzoate and nitromalondialdehyde, with *o*-phenylenediamine (**1**) resulted in extrusion of *p*-aminobenzoate with formation[179,180] of the 3-nitrobenzodiazepine **22**, which was also obtained by using 3-nitromalondialdehyde.



Compounds **3**, having substituents in the benzene ring, were made from the appropriate *o*-phenylenediamines; *e.g.*, 7-chloro, 7-nitro, 7-carboxy, 7-methoxy, and 7,7-ethylenedioxy derivatives of **3** (R_1 = R_2 = CH_3) were described,[161] as also 2,4-dimethyl-7-hydroxy-3*H*-1,5-benzodiazepine-8-carboxylic acid.[188]

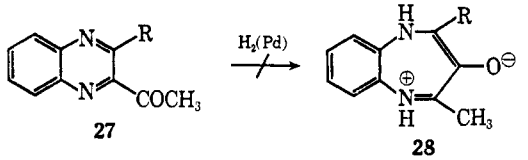
Benzodiazepines have been prepared by reduction of *o*-nitroamines to *o*-phenylenediamines, followed by reaction *in situ* with a β-dicarbonyl compound; *e.g.*, reduction of 4-amino-3-nitrobenzoic acid (**23**) with hydrazine and Raney nickel in ethanol, followed by addition of acetylacetone, gave[161] the 7-carboxy-2,4-dimethylbenzodiazepinium salt (**24**), isolated as a perchlorate. This technique avoided unnecessary exposure of easily oxidized phenylenediamines to air. In an alternative procedure, the condensation product **25**, from hydroxymethylenephenylacetaldehyde and *o*-nitroaniline, was reduced with tin and hydrochloric acid, iron in acetic acid, or with hydrogen and Raney nickel to give[176] the 3-phenylbenzodiazepine **26** directly.





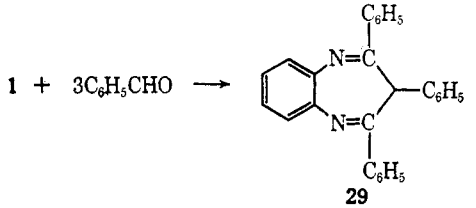
(186) W. Ruske, and G. Grimm, *J. Prakt. Chem.*, **18**, 163 (1962).
(187) H. D. Stachel, *Ber.*, **95**, 2172 (1962).
(188) J. Perello, J. Bartulin, and H. Urrutia, *Bol. Soc. Chilena Quim.*, **10**, 18 (1960); *Chem. Abstr.*, **56**, 5907 (1962).

The synthesis of a 3-hydroxy-1*H*-benzodiazepine (**111**) is described in section B.1. The claimed synthesis[189] of compounds **28**, by the reduction of 2-acetylquinoxalines **27**, was later refuted by the same authors,[190] who showed that the products were dihydroquinoxalines.



27 **28**

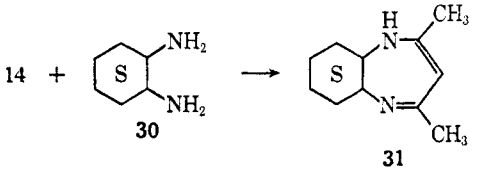
Treatment of *o*-phenylenediamine (**1**) with benzaldehyde gave a low yield of 2,3,4-triphenyl-3*H*-1,5-benzodiazepine (**29**), in addition to benzimidazoles.[191-193] This method has been extended to reactions of 4-chloro-



29

o-phenylenediamine[194] and 4-methyl-*o*-phenylenediamine[195,196] with benzaldehyde,[194,196] *m*-nitrobenzaldehyde,[192,193,195] and *p*-methoxybenzaldehyde.[195]

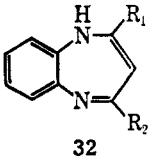
The 5a,6,7,8,9,9a-hexahydro-1*H*-benzodiazepine **31** was obtained by reaction of 1,2-diaminocyclohexane (**30**) with acetylacetone (**14**) and assigned[161] the 1*H* structure. Analogous cyclopentanodihydrodiazepines[197] and naph-



30 **31**

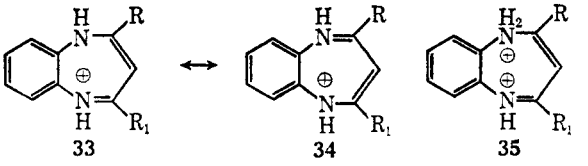
thodiazepines[161,198] have been described.

The structures of 1,5-benzodiazepine bases have been shown to be best represented in the 3*H* form **3**, in preference to the 1*H* isomers **32**. This assignment is firmly supported by ir,[167,169] uv,[167,174] and nmr[165,190,199,200]



32

spectral data. The generally colorless benzodiazepines **3** form intensely blue or violet monoacid salts, for which resonance canonical formulas **33** ↔ **34**, among others, can be written,[161] which explain their color. These compounds have also been depicted[177] as in **17** and **24**. The equivalence of the methyl groups in **33** and **34** (R = R_1 = CH_3) has been shown[165,199] by nmr spectral studies.

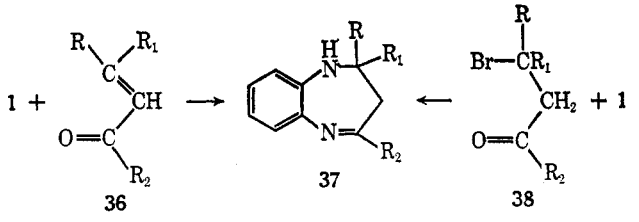


33 **34** **35**

The diacid salts **35** are colorless, owing to the disruption in conjugation by introduction of the $-{}^{+}NH_2-$ grouping; cations of type **35** exist only in strongly acidic media.[161]

The unstable yellow tautomer **32** (R = R_1 = CH_3) has been obtained[166] by basification of an aqueous solution of the corresponding hydrochloride **33**: compound **32** was transformed into the stable isomer **3** (R_1 = R_2 = CH_3), on standing for a short period.

Dihydrobenzodiazepines **37** have been prepared by the reaction of *o*-phenylenediamine (**1**) with α,β-unsaturated carbonyl compounds **36** (R = alkyl; R_1 and R_2 = alkyl or hydrogen)[198,201-203] or with the corresponding β-bromocarbonyl compounds[198,202] **38**.



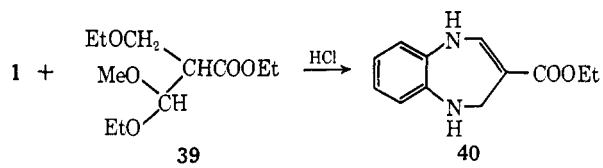
36 **37** **38**

Benzodiazepines were not obtained when R was phenyl. Compound **37** (R = R_1 = R_2 = CH_3)[201] had been obtained previously[204] but assigned an incorrect dihydroquinoxaline structure. N-Methyl-*o*-phenylenediamine (**13**) condensed with mesityl oxide **36** (R = R_1 = R_2 = CH_3) to give[186] only the dimethylbenzimidazole **16**, whereas reaction of N-phenyl-*o*-phenylenediamine with methyl β-bromoisobutyl ketone (**38**, R = R_1 = R_2 = CH_3) afforded[202] a mixture of 2,3-

(189) J. A. Barltrop and C. G. Richards, *Chem. Ind.* (London), 1011 (1957).
(190) J. A. Barltrop, C. G. Richards, and D. M. Russell, *J. Chem. Soc.*, 1423 (1959).
(191) S. Weil and H. Marcinkowska, *Roczniki Chem.*, **14**, 1312 (1934); *Chem. Abstr.*, **29**, 6233 (1935).
(192) N. V. Subba Rao and C. V. Ratnam, *Current Sci.* (India), **24**, 299 (1955); *Chem. Abstr.*, **50**, 12992 (1956).
(193) N. V. Subba Rao and C. V. Ratnam, *Proc. Indian Acad. Sci.*, **43A**, 173 (1956); *Chem. Abstr.*, **51**, 1149 (1957).
(194) N. V. Subba Rao and C. V. Ratnam, *ibid.*, **47A**, 77 (1958); *Chem. Abstr.*, **52**, 18381 (1958).
(195) N. V. Subba Rao and C. V. Ratnam, *ibid.*, **45A**, 253 (1957); *Chem. Abstr.*, **52**, 1145 (1958).
(196) N. V. Subba Rao and C. V. Ratnam, *ibid.*, **44A**, 331 (1956); *Chem. Abstr.*, **51**, 8731 (1957).
(197) D. Lloyd and D. R. Marshall, *J. Chem. Soc.*, 2597 (1956).
(198) W. Ried and E. Torinus, *Ber.*, **92**, 2902 (1959).
(199) H. A. Staab and F. Vögtle, *ibid.*, **98**, 2701 (1965).
(200) A. Mannschreck, G. Rissmann, F. Vögtle, and D. Wild, *ibid.*, **100**, 335 (1967).
(201) W. Ried and P. Stahlhofen, *ibid.*, **90**, 815 (1957).
(202) L. K. Mushkalo, *Nauk Zap. Kiivs'k Derzh. Univ.*, **16**, No. 15 (1957); *Nauk Zap. L'vivs'k. Derzh. Univ. Khim. Zb.*, No. 8, 133 (1957); *Chem. Abstr.*, **53**, 18057 (1959).
(203) J. Sprague, *U. S. Govt. Res. Rept.*, **31**, 301 (1959); *Chem. Abstr.*, **54**, 12156 (1960).
(204) J. B. Ekeley and R. J. Wells, *Ber.*, **38**, 2259 (1905).

dihydro-2,2,4-trimethyl-1-phenyl-1*H*-1,5-benzodiazepine and the alternative condensation product, 2,3-dihydro-2,2,4-trimethyl-5-phenyl-1*H*-1,5-benzodiazepinium bromide.

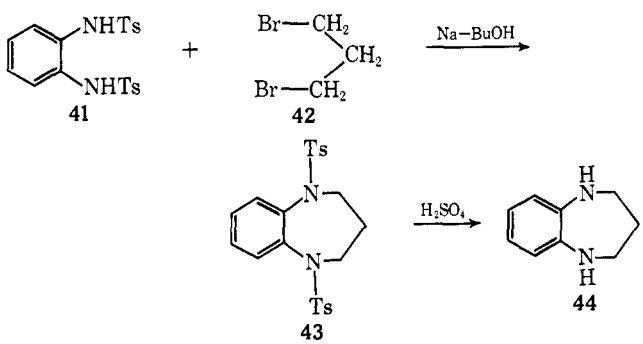
Condensation of **1** with 2-methoxyethoxymethyl-3-ethoxypropionate **39** has been reported[205] to give the 3-ethoxycarbonylbenzodiazepine **40**, which was ascribed the 4,5-dihydro-1*H* structure. The corresponding 3-cyano analog was likewise prepared.



39 40

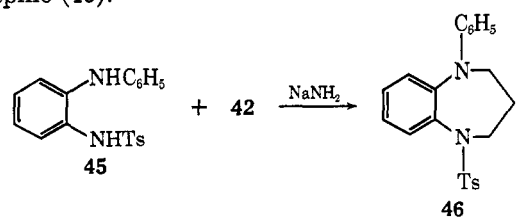
The synthesis of tetrahydrobenzodiazepines by reduction of benzodiazepinones or of other benzodiazepines is discussed in sections A.2.a, B.2.a, and C.2.c.

Reaction of N,N′-di-*p*-tolylsulfonyl-*o*-phenylenediamine (**41**) with 1,3-dibromopropane (**42**) afforded[206–209] the 1,5-ditosylbenzodiazepine **43**, which could be hydrolyzed[207,208] to 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**44**) by treatment with hot 70% sulfuric acid. Milder hydrolysis with cold 90% sulfuric acid afforded[207] the 1-tosyl derivative of **44**. The preparation of **44** *via* the dibenzenesulfonyl derivative has also been described.[210]



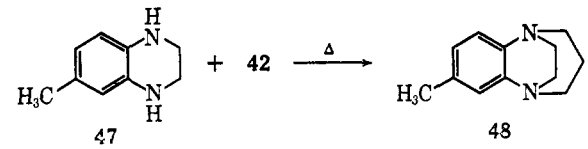
41 42 43 44

Alkylation of N-phenyl-N′-tosyl-*o*-phenylenediamine (**45**) with 1,3-dibromopropane (**42**) has been used[209] for the synthesis of 1-phenyl-5-tosyltetrahydrobenzodiazepine (**46**).



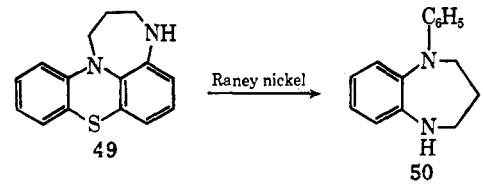
45 46

The reaction of the tetrahydroquinoxaline **47** with **42** gave a product to which the 1,5-ethanotetrahydrobenzodiazepine structure **48** was ascribed.[211]



47 48

Desulfurization of the diazepinophenothiazine **49** with Raney nickel gave[209] 1-phenyltetrahydrobenzodiazepine (**50**).

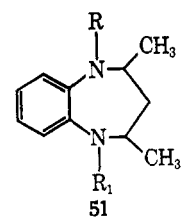


49 50

2. *Reactions*

a. Reduction

Reduction of the 2,4-dimethylbenzodiazepine **3** ($R_1 = R_2 = CH_3$) with hydrogen over a palladium catalyst gave[190] *cis* and *trans* isomers of the tetrahydrodimethylbenzodiazepine **51** (R = R_1 = H), which were separated by chromatography on alumina. The configurations were assigned on the basis of nmr spectral



51

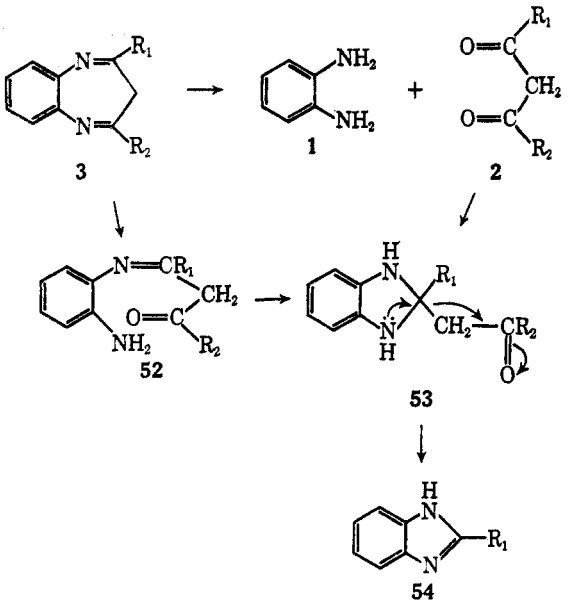
data. Compound **3** ($R_1 = R_2 = CH_3$) was likewise reduced with hydrogen over a platinum catalyst[208] but was unaffected by lithium aluminum hydride.[161]

Catalytic hydrogenation of the trimethylbenzodiazepine **37** (R = $R_1 = R_2 = CH_3$) over Raney nickel afforded[201] the corresponding tetrahydro derivative.

b. Hydrolysis

Benzodiazepines **3**, and their mesomeric monocations **33** ⟷ **34**, are fairly readily hydrolyzed in aqueous solution, resulting[161,163,167] in a ring contraction to the corresponding 2-substituted benzimidazoles **54**. The mechanism[167] of this reaction could involve either hydrolysis of **3** to *o*-phenylenediamine (**1**) and the diketone **2**, or fission of only one C=N bond to give the ketone **52**, followed in either case by cyclization to the benzimidazoline **53**, and aromatization to give **54**. The conversion of benzodiazepinium salts into benzimidazolium

(205) A. Takamizawa and K. Hirai, Japanese Patent 18,950; *Chem. Abstr.*, **66**, 37969 (1967).
(206) J. Davoll, *J. Chem. Soc.*, 308 (1960).
(207) H. Stetter, *Ber.*, **86**, 197 (1953).
(208) O. E. Fancher and G. Nichols, U. S. Patent 2,899,359; *Chem. Abstr.*, **54**, 598 (1960).
(209) T. Ichii, *J. Pharm. Soc. Japan*, **82**, 992 (1962); *Chem. Abstr.*, **58**, 5666 (1963).
(210) O. Hinsberg and A. Strupler, *Ann.*, **287**, 220 (1895).
(211) T. S. Moore and I. Doubleday, *J. Chem. Soc.*, 1170 (1921).

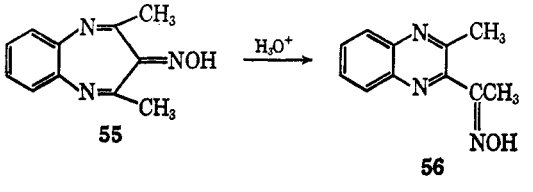


salts has also been observed[161] on pyrolysis of the former, which suggests that recorded melting points in this series may not be particularly meaningful.

Hydrolysis of **3** (R_1 = CH_3; R_2 = C_6H_5) gave[163] both expected products, namely **54** (R_1 = CH_3 or C_6H_5), whereas 2-methyl-4-(selenophen-2-yl)-3*H*-1,5-benzodiazepine afforded[171] only 2-methylbenzimidazole.

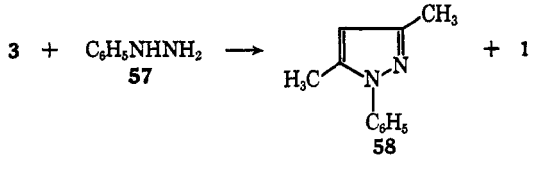
Benzodiazepines **3**, having an electron-withdrawing group (*e.g.*, nitro or carboxyl) in the 7 position, were very easily hydrolyzed in alkaline media to give[161] the corresponding 4-substituted *o*-phenylenediamines.

A different type of ring contraction resulted when the 3-hydroxyiminobenzodiazepine **55** was treated with acid, which led[181] to 2-acetyl-3-methylquinoxaline oxime (**56**). Further hydrolysis afforded the 2-acetylquinoxaline **63** (see section A.2.d).

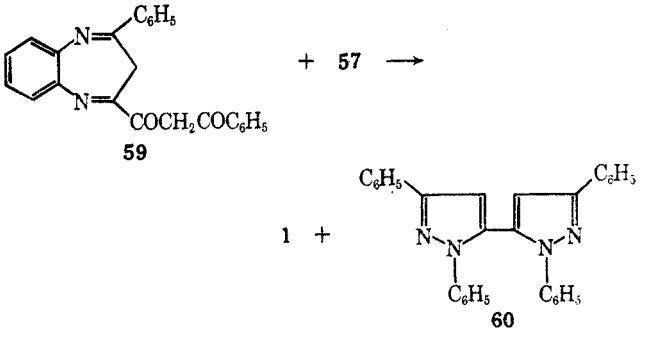


c. Reaction with phenylhydrazine

Treatment of the benzodiazepine **3** (R_1 = R_2 = CH_3) with phenylhydrazine (**57**) gave[163,167,169] 3,5-dimethyl-1-phenylpyrazole (**58**), together with *o*-phenylenediamine (**1**). The diketobenzodiazepine **59** yielded[169] the di-

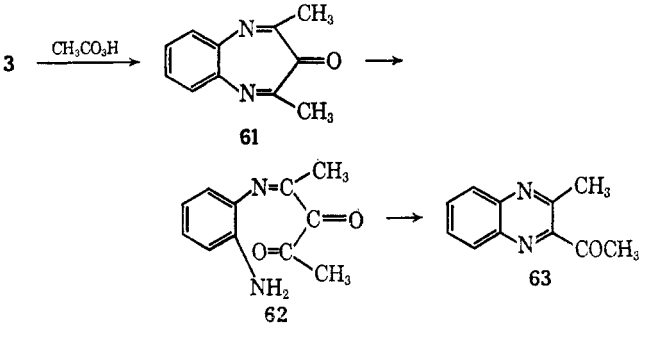


pyrazolyl compound **60** in a similar manner.



d. Oxidation

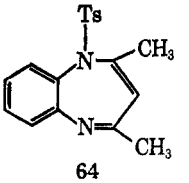
An attempt to prepare the diazatropone **61**, by oxidation of **3** (R_1 = R_2 = CH_3) with peracetic acid, resulted[167] in formation of 2-acetyl-3-methylquinoxaline (**63**), probably by initial production of **61**, followed by ring contraction *via* the diketone **62**.



e. Acylation and sulfonylation

Benzoylation of the tetrahydrobenzodiazepine **51** (R = R_1 = H) with benzoyl chloride in aqueous sodium hydroxide afforded[190] the 1-benzoyl derivative, whereas further benzoylation in pyridine gave the 1,5-dibenzoyl compound **51** (R = R_1 = C_6H_5CO–).

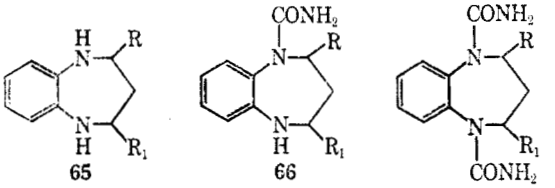
Reaction of the tetrahydrobenzodiazepine **44** with benzenesulfonyl chloride in benzene yielded[210] the 1,5-dibenzenesulfonyl derivative; treatment of the same compound with *p*-toluenesulfonyl chloride in pyridine afforded[209] the 1-tosyl derivative. The 3*H*-benzodiazepine **3** (R_1 = R_2 = CH_3) reacted with tosyl chloride to give[212] a compound, to which the 1*H*-1-tosyl structure **64** was ascribed.



Treatment of tetrahydrobenzodiazepines **65** with nitrourea afforded[213,214] the 1-carbamoyl or 1,5-di-

(212) W. Paterson and G. R. Proctor, *J. Chem. Soc.*, 485 (1965).
(213) O. E. Fancher, G. Nichols, and D. A. Stauffer, U. S. Patent 3,021,325; *Chem. Abstr.*, **57**, 4687 (1962).
(214) Miles, British Patent 858,558; *Chem. Abstr.*, **55**, 17072 (1961).

carbamoyl derivatives **66** and **67**, respectively, depending on reaction conditions.



65 **66** **67**

f. Alkylation

2,3,4,5-Tetrahydro-1-phenyl-5-*p*-tolylsulfonyl-1*H*-1,5-benzodiazepine (**46**) has been prepared[209] by treatment of the tosyl derivative of **44** with iodobenzene in the presence of potassium carbonate and copper powder.

Treatment of the 3*H*-benzodiazepine **3** ($R_1 = R_2 = CH_3$) with sodamide and methyl iodide in liquid ammonia resulted[167] in formation of the 3-methyl derivative.

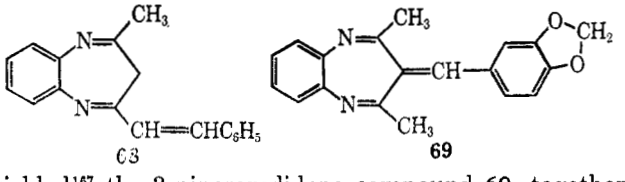
g. Nitrosation

Tetrahydrobenzodiazepines **65** and dihydrobenzodiazepines **37** gave[201,210] dinitroso derivatives when treated with sodium nitrite in acid.

Treatment of the 3*H*-benzodiazepine **3** ($R_1 = R_2 = CH_3$) with sodium nitrite in acetic acid gave[167] the 1-nitroso derivative, together with 2-methylbenzimidazole (**54**, $R_1 = CH_3$) and 2-acetyl-3-methylquinoxaline (**63**), presumably by formation and rearrangement of the oxime **55**.

h. Condensation with aldehydes and esters

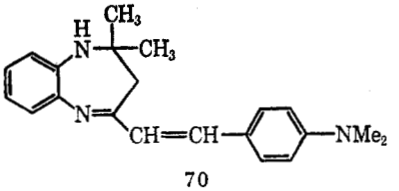
The 2,4-dimethylbenzodiazepine **3** ($R_1 = R_2 = CH_3$) condensed with benzaldehyde in alkaline media, to give[167] a mixture of 2-methyl-4-styrylbenzodiazepine (**68**) and the corresponding 2,4-distyryl derivative. Treatment of **3** ($R_1 = R_2 = CH_3$) with piperonaldehyde



63 **69**

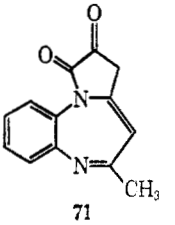
yielded[167] the 3-piperonylidene compound **69**, together with smaller amounts of the 2-methyl-3,4-dipiperonylidene derivative.

The dihydrobenzodiazepine **37** ($R = R_1 = R_2 = CH_3$), having only one reactive methyl substituent, formed[202] the mono-*p*-dimethylaminostyryl derivative **70**, when heated with *p*-dimethylaminobenzaldehyde in pyridine or acetic anhydride.



70

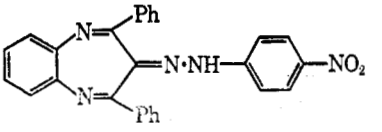
Condensation of the 2,4-dimethylbenzodiazepine **3** ($R_1 = R_2 = CH_3$) with diethyl oxalate afforded[215] the tricyclic diazaazulene derivative **71**.



71

i. Coupling with diazonium ions

Treatment of the 2,4-diphenylbenzodiazepine **3** ($R_1 = R_2 = C_6H_5$) with *p*-nitrobenzenediazonium chloride gave a compound, to which the *p*-nitrophenylhydrazone structure **72** was ascribed.[167]



72

j. Nitration

Attempted nitration of the 2,4-dimethylbenzodiazepine **3** ($R_1 = R_2 = CH_3$) with copper nitrate or urea nitrate gave[161] only tars.

k. Bromination

Treatment of the 2,4-dimethylbenzodiazepinium bromide or perchlorate **33** ($R = R_1 = CH_3$) with 6 equiv of bromine gave[161] the dark blue crystalline 6,7,8,9-tetrabromo-1,5-benzodiazepinium bromide. The free base **3** ($R_1 = R_2 = CH_3$), on reaction with bromine in nitromethane, afforded[177] the hydrobromide of the 3-bromo derivative.

B. 1,5-BENZODIAZEPINONES

1. Synthesis

Condensation of *o*-phenylenedimine (**1**) with β-keto esters **73**, under neutral or basic conditions, gave[206,216,217] 1,3-dihydro-2*H*-1,5-benzodiazepin-2-ones **74**. Heating **1** with ethyl acetoacetate (**73**, $R = CH_3$) in xylene afforded[206,216] mixtures of **74** ($R = CH_3$) and the benzimidazol-2-one **75** ($R = CH_3$), whereas condensation in the presence of an acid catalyst gave[206,216,218] ethyl β-(*o*-aminoanilino)crotonate (**76**). That compound **76** was not an intermediate in the for-

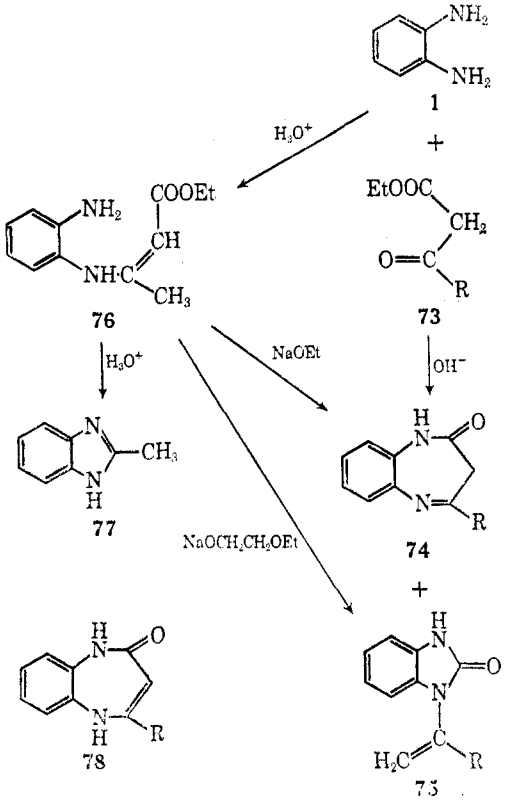
(215) S. Veibel and S. F. Hromadko, *Ber.*, **93**, 2752 (1960).

(216) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1298 (1960).

(217) N-Methyl-*o*-phenylenediamine (**13**) reacted differently with ethyl benzoylacetate, to give[206] 1-methyl-2-phenacylbenzimidazole; with ethyl acetoacetate it afforded a compound of type **76**, which could not be cyclized.[186]

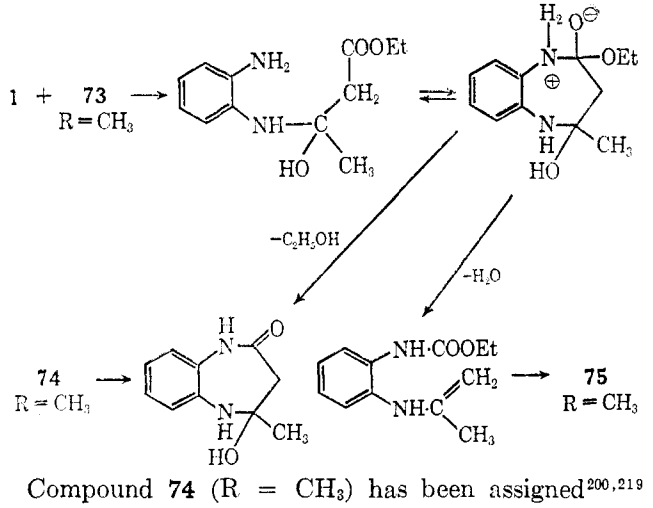
(218) W. A. Sexton, *J. Chem. Soc.*, 303 (1942).

mation of **74** and **75** was shown[206,216] by its failure to cyclize under the reaction conditions and its conversion into 2-methylbenzimidazole (**77**) under acid catalysis.

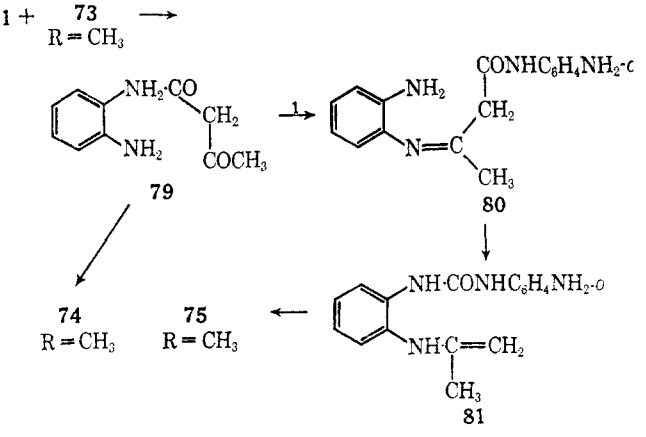


Compound **74** (R = CH_3) was, however, obtained[206] by cyclization of **76** with sodium ethoxide in boiling ethanol; further treatment with sodium 2-ethoxyethoxide in boiling 2-ethoxyethanol resulted in ring contraction to **75** (R = CH_3), which was also obtained[206] by treatment of **76** with the same reagent.

The following mechanism[216] adequately explained the formation of the observed products from condensation of **1** with ethyl acetoacetate.



Compound **74** (R = CH_3) has been assigned[200,219] the imine structure, having a 4,5 double bond, largely on the basis of the nmr spectra, which showed the presence of a CH_3, a CH_2, and one NH group. Earlier authors[206,216,220,221] have preferred the isomeric 3,4-double-bond enamine structure **78**, largely because **74** (R = CH_3) failed to form a methiodide salt. Nmr spectra of some tetrahydrobenzodiazepin-2-ones have also been reported.[222] An alternative proposed mechanism[206] involved initial condensation of **1** with **73** (R = CH_3) to give *o*-aminoacetoacetanilide (**79**), from which **74** (R = CH_3) could be readily formed. The suggested route to **75** (R = CH_3) involved aminolysis of **79** by excess *o*-phenylenediamine, followed by condensation to the anil **80** and further conversion into **75** (R = CH_3), as shown.



This method has been used for the synthesis of benzodiazepin-2-ones **74**, in which R = trifluoromethyl,[223] 3-pyridyl,[221] 2-furyl,[224] and phenyl;[220,221,224,225] analogs of **74** having naphthyl,[198,221,226] pyridyl,[221,227] or pyrimidinyl[228,229] instead of phenyl in ring A, have also been described.

Reaction of **1** with diketene **82** has been used[230] to prepare the benzodiazepinone **83**.

Reduction of *o*-nitroacetoacetanilide **84** with iron and hydrochloric acid afforded[218] a compound described as a benzimidazole, to which structure **83** was later assigned.[206]

(219) E. Müller, R. Haller, and K. W. Merz, *Ann.*, **697**, 193 (1966).

(220) A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta*, **43**, 1046 (1960).

(221) R. Barchet and K. W. Merz, *Tetrahedron Letters*, **33**, 2239 (1964).

(222) G. S. Sidhu, G. Thyagarajan, and V. T. Bhalerao, *J. Chem. Soc., C*, 969 (1966).

(223) F. B. Wigton and M. M. Joullié, *J. Am. Chem. Soc.*, **81**, 5212 (1959).

(224) W. Ried and P. Stahlhofen, *Ber.*, **90**, 828 (1957).

(225) α-Phenylacetoacetic ester reacted differently with **1** to give[220] 1-β-methylstyrylbenzimidazol-2-one instead of a benzodiazepinone.

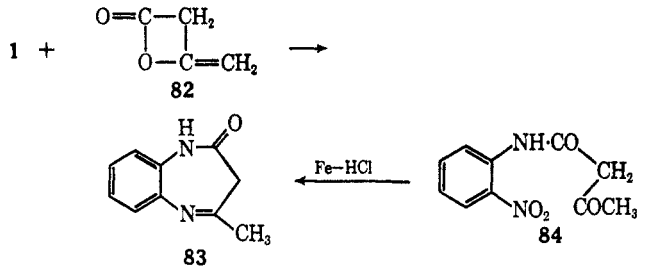
(226) W. Ried and W. Höhne, *Ber.*, **87**, 1801 (1954).

(227) M. Israel, L. C. Jones, and E. J. Modest, *J. Heterocyclic Chem.*, **4**, 659 (1967).

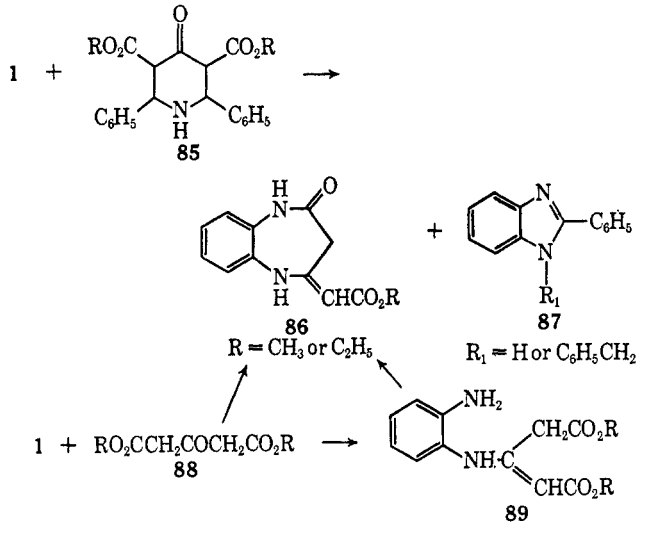
(228) W. H. Nyberg, C. W. Noell, and C. C. Cheng, *ibid.*, **2**, 110 (1965).

(229) M. Israel, S. K. Tinter, D. H. Trites, and E. J. Modest, Abstracts of the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967.

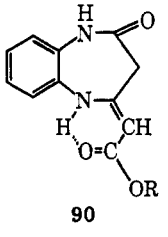
(230) W. Ried and P. Stahlhofen, *Ber.*, **90**, 825 (1957).



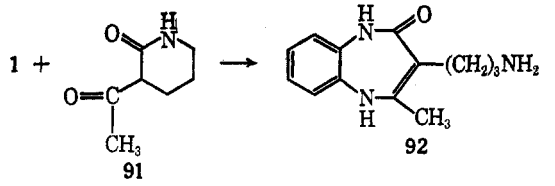
Treatment of 1 with the piperidonedicarboxylic acid esters **85** resulted[219,231] in ring opening of the latter, with formation of the 4-alkoxycarbonylmethylene-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **86** together with 2-phenylbenzimidazoles **87**.



Compounds of type **86** were also obtained[219] by condensation of acetonedicarboxylic acid esters **88** with **1** either directly, or *via* the intermediates **89**. Hydrolysis and decarboxylation of compounds **86** gave the 4-methylbenzodiazepin-2-one **83**. Compounds **86** were assigned[219] the enamine structure, with an exocyclic double bond, largely by interpretation of ir and nmr spectra, which indicated that they existed largely in hydrogen-bonded form **90**.



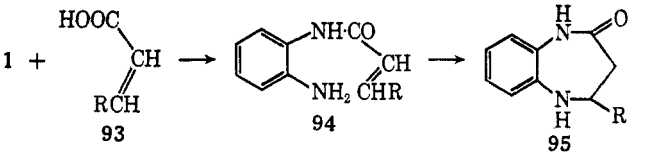
The α-acetylpiperidinone **91** has been reported[232] to react with *o*-phenylenediamine to give the benzodiazepin-2-one **92**, which was assigned the endocyclic enamine structure.



In addition to the syntheses discussed below, 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-ones **95** have been prepared (section B.2.a.) by reduction of the corresponding 1,3-dihydro derivatives already described.

Catalytic hydrogenation of *o*-nitroacetoacetanilides (*e.g.*, **84**) over Raney nickel gave[233] the corresponding tetrahydrobenzodiazepinones **95**.

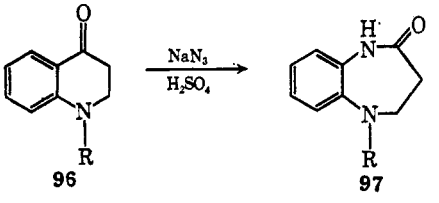
Condensation of *o*-phenylenediamine (**1**) with α,β-unsaturated acids **93** gave compounds **95**. In this manner, compounds **95** having R = hydrogen,[234] methyl,[206,213,235] phenyl,[236,237] and phenyl substituted by hydroxy, methoxy, nitro, amino, or acetyl groups,[236]



have been prepared from the appropriate acids **93** and **1**, as well as from *o*-phenylenediamines having methyl[226] or chloro[213,236] substituents. The reaction of naphthalenediamines with α,β-unsaturated acids gave analogous products.[198,226]

The mechanism of the condensation reaction has been shown[236] to proceed *via* the intermediate anilide **94**; cyclization of **94** (R = C_6H_5) gave the same benzodiazepinone **95** (R = C_6H_5) as was obtained from *o*-phenylenediamine and cinnamic acid. In a variation of the above procedure, β-bromocarboxylic acids were used[198] instead of α,β-unsaturated acids.

Dihydroquinol-4-ones (**96**, R = CH_3 or C_6H_5), on treatment with sodium azide and sulfuric acid (Schmidt reaction), underwent ring enlargement to give compounds assigned[238] structures **97** (R = CH_3 or C_6H_5), without rigorous proof.



(231) K. W. Merz, R. Haller, and E. Müller, *Naturwissenschaften*, **50**, 663 (1963).

(232) H. Wamhoff, Abstracts, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967.

(233) J. Hornyna, Czech Patent 113,422; *Chem. Abstr.*, **63**, 18129 (1965).

(234) G. B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.*, **71**, 1985 (1949).

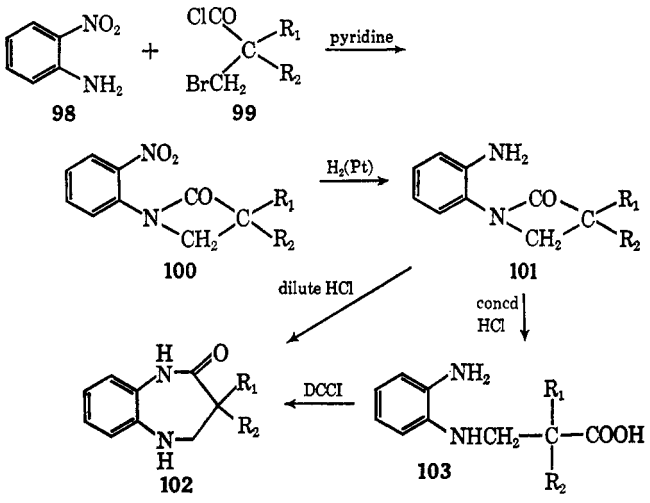
(235) W. Ried and G. Urlass, *Ber.*, **86**, 1101 (1953).

(236) S. H. Dandegaonker and G. B. Desai, *Indian J. Chem.*, **1**, 298 (1963).

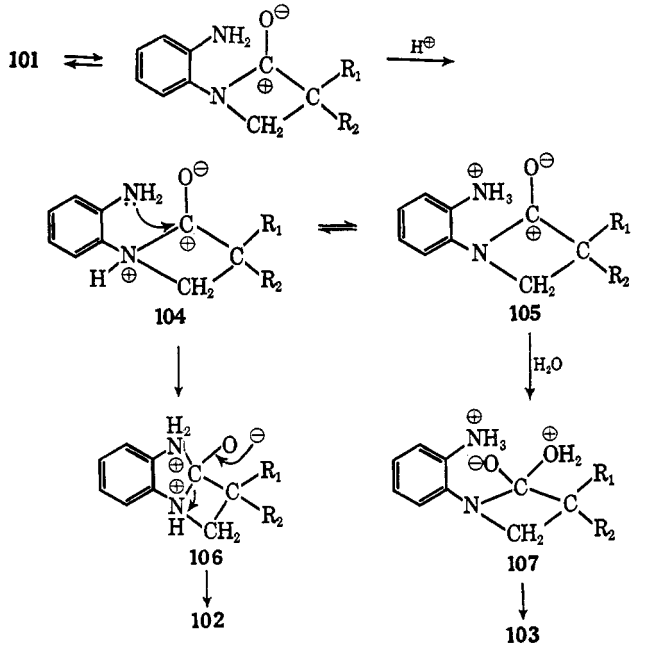
(237) It has also been reported[235] that cinnamic acid reacted differently with *o*-phenylenediamine to give *exclusively* 2-styrylbenzimidazole instead of a benzodiazepinone.

(238) P. I. Ittyerah, and F. G. Mann, *J. Chem. Soc.*, 467 (1958).

3,3-Disubstituted benzodiazepin-2-ones (**102**) have been prepared[239] by ring enlargement of 3,3-disubstituted azetidin-2-ones (**101**), which were synthesized from *o*-nitroaniline (**98**) and β-halo acid halides **99**, as shown. The ring enlargement of **101** occurred on treatment with dilute acids; use of concentrated

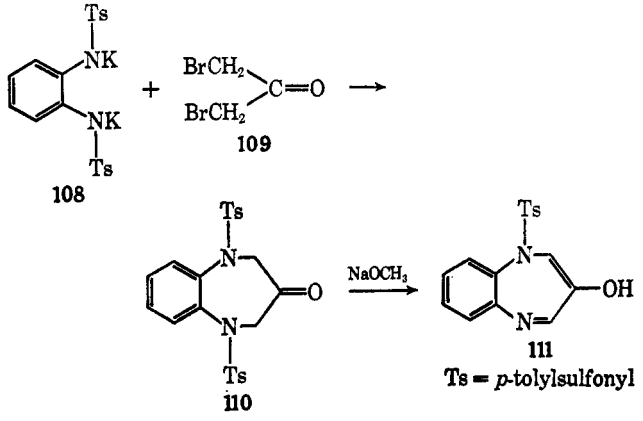


hydrochloric acid resulted in hydrolysis to the amino acid **103**; the latter compound was a by-product in the formation of **102** but was not an intermediate, since it did not cyclize under the conditions used for the ring enlargement. Compound **103** could, however, be converted into **102** by treatment with dicyclohexylcarbodiimide (DCCI). Treatment of **103** with thionyl chloride, followed by heating of the resulting acid chloride in pyridine, resulted in the alternative cyclization to the azetidinone **101**. The benzodiazepinone **102** was also obtained, in low yield, by reaction of the acid chloride **99** with *o*-phenylenediamine (**1**). The ring-enlargement reaction was used[239] for the synthesis of compounds **102** (R_1 and R_2 = alkyl or phenyl) and was also successful for preparation of the corresponding 1-phenyl derivative, using *o*-aminodiphenylamine as starting material.



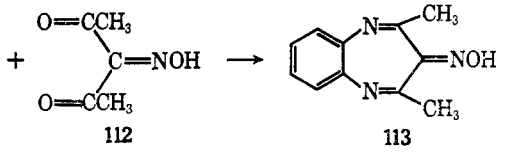
The proposed mechanism[239] for the conversion of **101** into **102** involved an intramolecular transamidation of the former by nucleophilic attack of the primary amino group on the polarized carbonyl of the azetidinone, in the protonated form **104**. In stronger acid media, the protonated form **105** could undergo nucleophilic attack by water, leading to the amino acid **103**.

The benzodiazepin-3-one derivative **110** was prepared[212] by alkylation of the dipotassium salt of ditosyl-*o*-phenylenediamine (**108**) with 1,3-dibromoacetone (**109**). Treatment of **110** with sodium methoxide or



potassium *t*-butoxide gave a red compound, to which structure **111** was assigned.[212]

Condensation of *o*-phenylenediamine (**1**) with oximinoacetylacetone (**112**) gave[181] the benzodiazepin-3-one oxime **113**, from which the free ketone could not be obtained by acid hydrolysis.



2. *Reactions*

a. Reduction

Hydrogenation of dihydrobenzodiazepin-2-ones **74** over a palladium or Raney nickel catalyst afforded[206,216,224,230] the corresponding tetrahydro derivative **95**. Reduction of **95** (R = H) with lithium aluminum hydride gave[206] 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**44**). Compound **95** (R = CH_3) was analogously reduced[208] to the tetrahydro derivative.

b. Oxidation

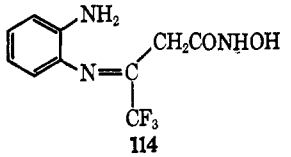
The tetrahydrobenzodiazepin-2-one **102** (R_1 = Et; R_2 = C_6H_5) was oxidized with ferric chloride to give[239] the corresponding 1,3-dihydrobenzodiazepin-2-one.

(239) B. J. R. Nicolaus, E. Bellasio, G. Pagani, L. Mariani, and E. Testa, *Helv. Chim. Acta*, 48, 1867 (1965).

c. Hydrolysis and aminolysis

Acid hydrolysis of the dihydrobenzodiazepinone **83** gave[206] acetone and a low yield of 2-methylbenzimidazole. The 3,3-disubstituted benzodiazepinones **102** were hydrolyzed[239] to the amino acids **103** by long treatment with hot concentrated hydrochloric acid; aqueous sodium hydroxide did not affect compounds of type **102**. Benzodiazepinones **86**, having an alkoxycarbonylmethylene side chain underwent hydrolysis and decarboxylation when heated with acids or bases to give[219] the 4-methylbenzodiazepinone **83**; further treatment led to *o*-phenylenediamine and acetone as products.

The lactam ring of the dihydrobenzodiazepinone **74** (R = CF_3) was cleaved by hydroxylamine to give[223] the open hydroxamic acid **114**. Treatment of the latter with dilute sulfuric acid reconverted it into the benzodiazepinone.



114

d. Ring contractions

Treatment of the dihydrobenzodiazepinone **74** (R = CH_3) with sodium 2-ethoxyethoxide gave[206] the benzimidazolone **75** (R = CH_3). Similar treatment of the esters **86** resulted[219] in transesterification, with formation of **86** (R = $CH_2CH_2OC_2H_5$). The 4-phenylbenzodiazepinone **74** (R = C_6H_5) rearranged to benzimidazolone when heated above its melting point,[221] presumably *via* a compound of type **75**.

e. Alkylation

Treatment of tetrahydrobenzodiazepinones **102** with alkyl halides gave[239] the 5-alkyl derivatives. Dihydrobenzodiazepinones **74** have been alkylated in the 1 position by treatment[240,241] with sodamide and dialkylaminoalkyl halides; tetrahydrobenzodiazepinones **95** have been alkylated in like manner.[242]

f. Acylation

Tetrahydrobenzodiazepinones **102** have been acetylated with acetyl chloride in pyridine to give[239] the 5-acetyl derivatives. Dihydrobenzodiazepinone **83** was acetylated in the 1 position by treatment[230] with acetic anhydride. The carbamoyl group ($CONH_2$) has been introduced into the 5 position of tetrahydrobenzodiazepinones **95** or **102** by treatment with sodium cyanate[239] or nitrourea.[213,214]

(240) J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).
(241) L. H. Werner, U. S. Patent 2,957,867; *Chem. Abstr.*, **55**, 7451 (1961).
(242) J. Krapcho and C. Turk, U. S. Patent 3,321,468; *Chem. Abstr.*, **68**, 21970 (1968).

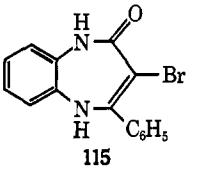
g. Nitrosation

Treatment of tetrahydrobenzodiazepinones **95** or **102** with sodium nitrite, or isoamyl nitrite, in acetic acid afforded[224,226,230,235,239] the corresponding 5-nitroso derivatives, which could be reduced, with zinc and acetic acid, to the 5-amino compounds.[239]

Catalytic hydrogenation of the nitroso compounds resulted[226,235] in cleavage to the benzodiazepinone starting materials.

h. Halogenation

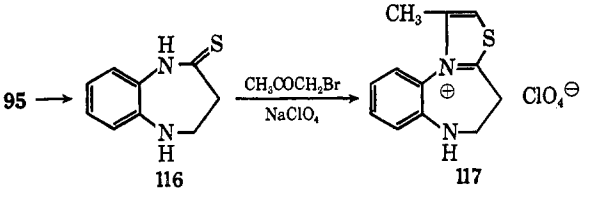
Bromination of the dihydrobenzodiazepinone **78** (R = C_6H_5)[243] gave a bromo derivative assigned[221] structure **115**.



115

i. Thiation

Treatment of tetrahydrobenzodiazepinone **95** (R = H) with phosphorus pentasulfide gave[244] the corresponding 2-thione **116**, which was further converted into **117** by reaction with bromoacetone and sodium perchlorate.



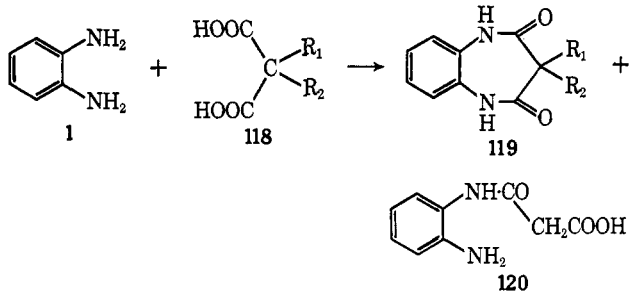
116 **117**

C. 1,5-BENZODIAZEPINEDIONES

1. Synthesis

Condensation of *o*-phenylenediamine (**1**) with malonic acid (**118**, $R_1 = R_2 = H$) gave[245-250] 3*H*-1,5-benzodiazepine-2,4(1*H*,5*H*)-dione (**119**, $R_1 = R_2 = H$), together with the malonanilide **120**, which could be readily cyclized[247] to **119**. Malonic acid esters have also been used[245,246,249,251,252] instead of **118**, and an interesting variation involved the addition of **1** to carbon suboxide

(243) The structure should probably be written **74** (R = C_6H_5); see section B.1.
(244) A. I. Kiprianov and V. P. Khilya, *Zh. Org. Khim.*, **3**, 1091 (1967); *Index Chemicus*, **26**, 83935 (1967).
(245) R. Meyer, *Ann.*, **327**, 1 (1903).
(246) R. Meyer and H. Lüders, *ibid.*, **415**, 29 (1918).
(247) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).
(248) R. L. Shriner and P. G. Boermans, *J. Am. Chem. Soc.*, **66**, 1810 (1944).
(249) J. Büchi, H. Dietrich, and E. Eichenberger, *Helv. Chim. Acta*, **39**, 957 (1956).
(250) G. Glotz, *Bull. Soc. Chim. France*, [5] **3**, 511 (1936).
(251) R. Meyer, *Ann.*, **347**, 17 (1906).
(252) A. S. F. Ash, A. M. Creighton, and W. R. Wragg, U. S. Patent 3,133,056; *Chem. Abstr.*, **61**, 8327 (1964).



(O=C=C=C=O) to give[253] **119** (R_1 = R_2 = H). Using these methods, benzodiazepinediones **119** have been prepared from the appropriate malonic acid derivatives, having R_1 = H, R_2 = alkyl,[246,249,252] phenyl,[252] or acetamido,[252] or R_1 and R_2 = alkyl.[249,252] Substituted *o*-phenylenediamines gave the expected benzodiazepinediones; *e.g.*, 3,4-diaminotoluene yielded[251] a 7-methyl derivative of **119**.

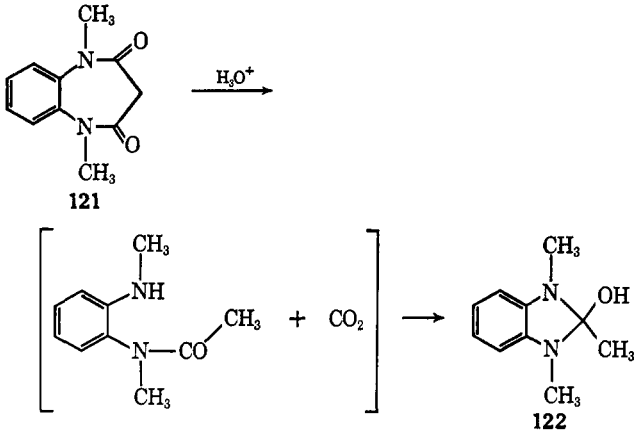
2. Reactions

a. Alkylation

Benzodiazepinediones **119** have been alkylated by treatment[248,249] with sodium ethoxide or hydroxide, followed by an alkyl halide; in this manner N-monoalkyl or N,N′-dialkyl derivatives were obtained.

b. Hydrolysis

Compound **119** (R_1 = H; R_2 = CH_3) was soluble in aqueous sodium hydroxide, and was reprecipitated unchanged by dilute acids;[246] concentrated hydrochloric acid hydrolyzed it, with formation of *o*-phenylenediamine. Hydrolysis of benzodiazepine-2,4-dione **121** with dilute sulfuric acid afforded[248] 2-hydroxy-1,2,3-trimethylbenzimidazoline (**122**), as shown.



c. Reduction

Treatment of the benzodiazepinedione **119** (R_1 = R_2 = H) with lithium aluminum hydride in tetrahydrofuran gave[209] the corresponding 2,3,4,5-tetrahydro-1*H*-benzodiazepine (**44**).

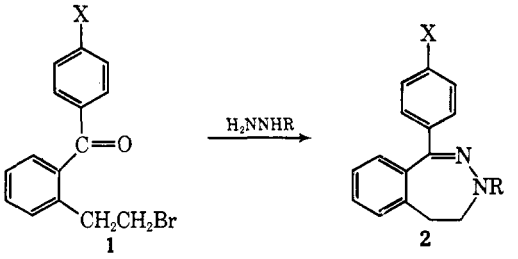
(253) J. Van Alphen, *Rec. Trav. Chim.*, **43**, 823 (1924).

VI. 2,3-BENZODIAZEPINES

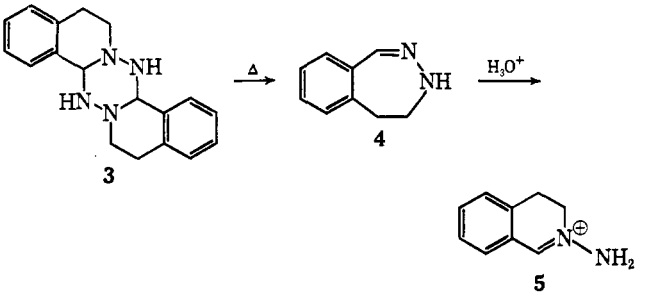
A. SYNTHESIS

1. 2,3-Benzodiazepines

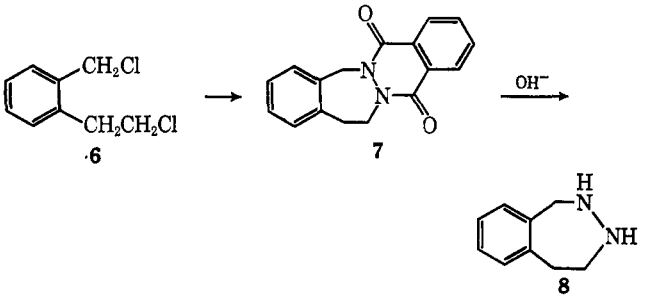
The reaction of 2-(2-bromoethyl)benzophenone (**1**, X = H) with hydrazine gave[254] 4,5-dihydro-1-phenyl-3*H*-2,3-benzodiazepine (**2**, X = R = H). 2-Hydroxyethyl analogs **2** (R = $HOCH_2CH_2$) were likewise prepared from benzophenones **1** (X = H and OCH_3).



Pyrolysis of the diisoquinolinotetrazine **3** alone, or better, in isoquinoline as solvent, afforded[255] 4,5-dihydro-3*H*-2,3-benzodiazepine (**4**). Treatment of **4** with cold



dilute sulfuric acid gave the cation **5** which, on basification, yielded **3**. Reduction[255] of **4**, with hydrogen over palladium, gave 2,3,4,5-tetrahydro-1*H*-2,3-benzodiazepine (**8**), which was also prepared from the dichloride **6** and phthalhydrazide, *via* the intermediate **7**.



2. 2,3-Benzodiazepinones

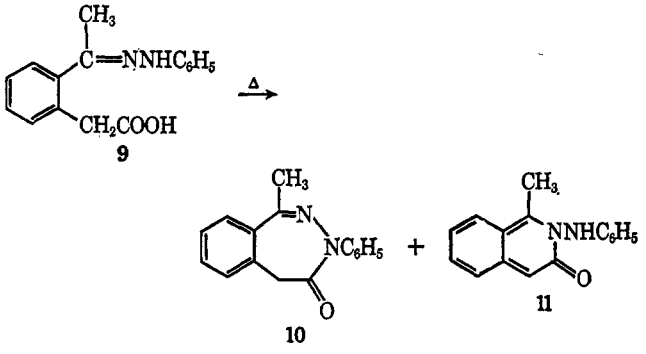
Intramolecular condensation of *o*-acetylphenylacetic acid phenylhydrazone (**9**) gave[256] mixtures containing 3,5-dihydro-1-methyl-3-phenyl-4*H*-2,3-benzodiazepin-

(254) C. van der Stelt, P. S. Hofman, and W. Th. Nauta, *ibid.*, **84**, 633 (1965).

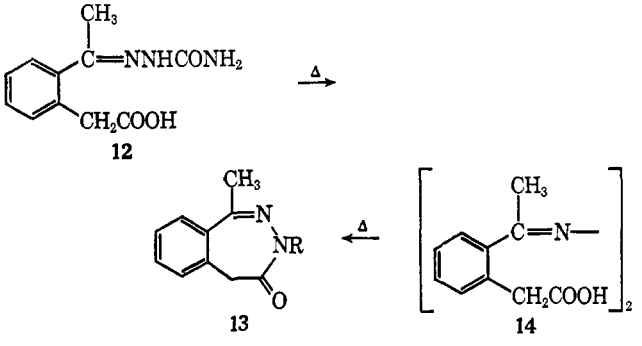
(255) E. Schmitz and R. Ohme, *Ber.*, **95**, 2012 (1962).

(256) J. O. Halford, R. W. Raiford, and B. Weissmann, *J. Org. Chem.*, **26**, 1898 (1961).

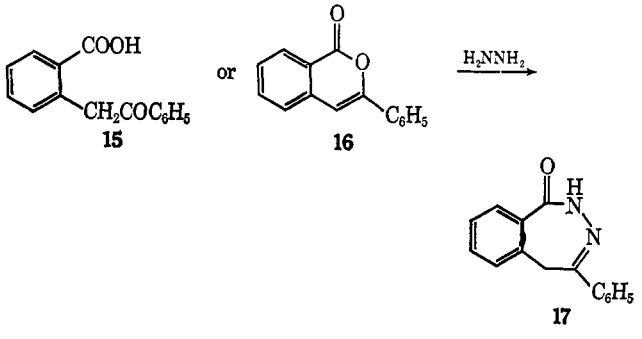
4-one (**10**) and 1-methyl-2-phenylamino-3(2*H*)-isoquinolone (**11**). Compound **10** was the major product of pyrolytic dehydration of **9** at 190°, whereas **11** was the main product of cyclization in sulfuric–acetic acid mixtures. The analog **13** was obtained likewise, by



pyrolysis of *o*-acetylphenylacetic acid semicarbazone (**12**) or the corresponding azine **14**.

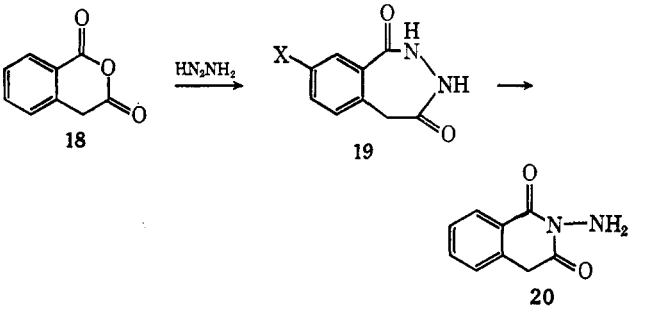


The reaction of β-desoxybenzoin-*o*-carboxylic acid (**15**) or of 3-phenylisocoumarin (**16**) with hydrazine gave[257] 2,5-dihydro-4-phenyl-1*H*-2,3-benzodiazepin-1-one (**17**). The 4-(*m*-tolyl)[258] and 4-(*p*-hydroxyphenyl)[259]



analogs of **17** were obtained in like manner from the appropriate isocoumarins. Treatment of 3-methylisocoumarin with phenylhydrazine yielded[260] 2,5-dihydro-4-methyl-2-phenyl-1*H*-2,3-benzodiazepin-1-one.

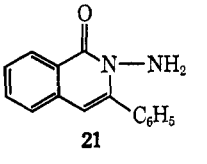
Treatment of homophthalic anhydride (**18**) with hydrazine in boiling ethanol yielded[261] 2,3-benzodiazepine-5*H*-1,4(2*H*,3*H*)-dione (**19**, X = H); when the reaction was carried out in acetic acid, the initially formed **19** rearranged to N-aminohomophthalimide (**20**). The 8-nitro derivative **19** (X = NO_2) was synthesized from 4-nitrohomophthalic anhydride.



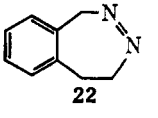
B. REACTIONS

1. *Hydrolysis*

Sodium hydroxide in boiling ethylene glycol cleaved[256] the benzodiazepin-4-one **10** to the phenylhydrazone **9**. Treatment of **10** with 1 *M* sulfuric acid in glacial acetic acid resulted[256] in isomerization to the isoquinolone **11**. In an analogous manner, treatment of the benzodiazepin-1-one **17** with dilute mineral acids (or phosphoryl chloride) converted it[257] into the isomeric 2-amino-3-phenyl-1(2*H*)-isoquinolone (**21**).



Conversion[255] of the benzodiazepine **4** into **3**, by treatment with dilute sulfuric acid, has been described above; the intermediate cation **5** was obtained as a crystalline picrate, by treatment of **4** with ethanolic picric acid. Acid treatment of 4,5-dihydro-1*H*-2,3-benzodiazepine (**22**) (see section B.2) resulted[255] in rearrangement to the 3*H* isomer **4**.



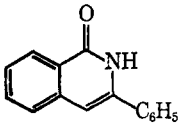
2. *Oxidation*

The cyclic hydrazine derivative **8** was readily oxidized with alkaline hydrogen peroxide to give[255] compound **22**. Benzodiazepine-1,4-diones of type **19** exhibited a weak chemiluminescence[261] when oxidized with alkaline peroxide.

3. *Reduction*

Zinc and hydrochloric acid, or fuming hydriodic acid, reduced[257] the benzodiazepin-1-one **17** to the isoquinolone **23**, possibly *via* formation and reduction of

(257) H. Wölbling, *Ber.*, **38**, 3845 (1905).
(258) A. Lieck, *ibid.*, **38**, 3853 (1905).
(259) M. Buu-Hoï, *Compt. Rend.*, **209**, 321 (1939).
(260) J. Gottlieb, *Ber.*, **32**, 958 (1899).
(261) W. F. Whitmore and R. C. Cooney, *J. Am. Chem. Soc.*, 1237 (1944).

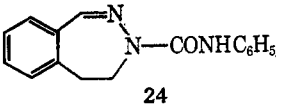


23

the aminoisoquiolone **21**. Catalytic hydrogenation of **4** to **8** has been described above. Reduction of the 8-nitrobenzodiazepine **19** (X = NO_2) with hydrogen over Raney nickel in aqueous ammonia afforded[261] the 8-amino derivative.

4. *Acylation*

Treatment of 8-amino-2,3-benzodiazepine-5*H*-1,4-(2*H*,3*H*)-dione (**19**, X = NH_2) with acetic anhydride gave[261] the corresponding acetamino derivative **19** (X = CH_3CONH). The benzodiazepine **4** with phenyl isocyanate afforded[255] the urea **24**.



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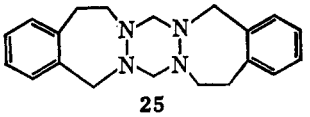
5. *Alkylation*

Treatment of the benzodiazepin-1-one **17** with sodium hydroxide and methyl iodide yielded[257] the 2-methyl derivative; the 2-ethyl analog was prepared in an analogous manner.

6. *Condensation with Aldehydes*

The benzodiazepine **8** was condensed with formaldehyde to give[255] the dimeric tetrazine derivative **25**.



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7. *Nitrosation*

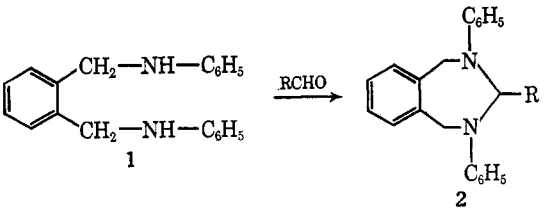
Treatment of the benzodiazepin-1-one **17** with nitrogen trioxide in acetic acid gave[257] a mononitroso compound, probably the 2-nitroso derivative.

VII. 2,4-BENZODIAZEPINES

A. SYNTHESIS

1. *2,4-Benzodiazepines*

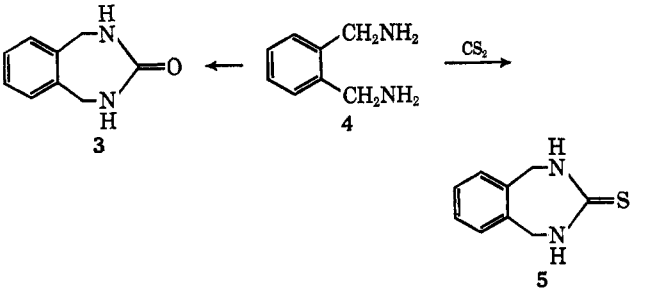
2,3,4,5-Tetrahydro-2,4-diphenyl-1*H*-2,4-benzodiazepine (**2**) (R = H) was prepared[262] by condensation of N,N′-diphenyl-*o*-xylene-α,α'-diamine (**1**) with formaldehyde. Compounds of type **2**, having other aromatic substituents in the 2 and 4 positions, were likewise made[262,263] from the appropriate diamines. Benzaldehyde was found to react in the same way as formaldehyde, to give **2** (R = C_6H_5). An alternative general route to **2** (R = alkyl or aryl) involved condensation[29] of α,α'-diamino-*o*-xylene (**4**) with the appropriate alkyl or aryl imidate.



1 2

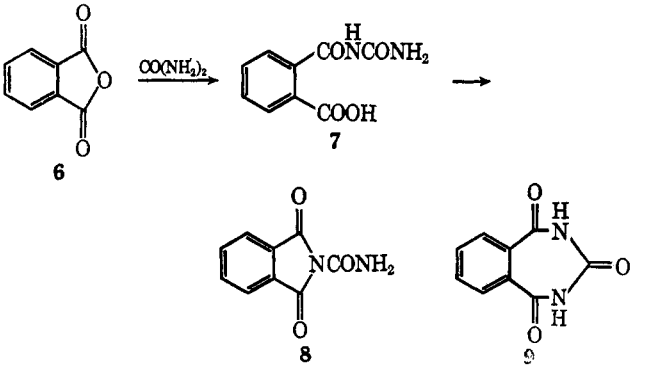
2. *2,4-Benzodiazepinones*

Cyclization of **4** with N,N′-carbonyldiimidazole gave[29] 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepin-3-one (**3**). The corresponding 3-thione **5** was prepared[264] by treatment of **4** with carbon disulfide.



3 4 5

Several reports in the literature[265-267] claimed the synthesis of 1*H*-2,4-benzodiazepine-1,3,5-(2*H*,4*H*)-trione (**9**) by the reaction of phthalic anhydride (**6**) (or phthaloyl chloride) with urea, to form the ureide **7**, followed by cyclization of the latter with phosphoryl chloride. A study of the chemical reactions of the product showed,[268] however, that it was the carboxamidophthalimide **8**, which deduction was confirmed by

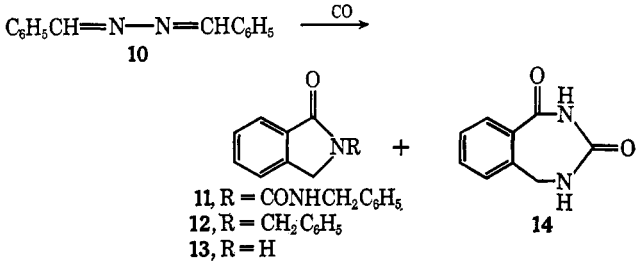


6 7 8 9

(262) M. Scholtz and K. Jaross, *Ber.*, **34**, 1504 (1901).
(263) M. Scholtz, and R. Wolfrum, *ibid.*, **43**, 2304 (1910).
(264) E. F. Elslager, D. F. Worth, N. F. Haley, and S. C. Perricone, Abstracts, First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967.
(265) A. Piutti, *Ann.*, **214**, 17 (1882).
(266) T. W. Evans and W. M. Dehn, *J. Am. Chem. Soc.*, **51**, 3651 (1929).
(267) C. S. Smith and C. J. Cavallito, *ibid.*, **61**, 2218 (1939).
(268) V. Hahn, P. Hammes, and Z. Gerić, *Experientia*, **10**, 11 (1954).

X-ray[269] and dipole moment[270] studies. Other compounds, made by a similar method from substituted phthalic anhydrides, are probably also of type **8**, and not benzodiazepinetriones as claimed.[271]

Treatment of benzaldehyde azine (**10**) with carbon monoxide at 235–245° under pressure, in the presence of dicobalt octacarbonyl catalyst, gave the three phthalimidine derivatives **11–13**, together with a 12% yield of a compound to which the structure 5*H*-2,4-benzodiazepine-1,3(2*H*,4*H*)-dione (**14**) was assigned[272] on the basis of elemental analysis and infrared and nmr spectra.



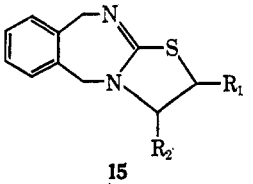
B. REACTIONS

1. Hydrolysis

The 1,3-dione **14** was hydrolyzed by hot sulfuric acid or sodium hydroxide to carbon dioxide and ammonia, respectively.[272]

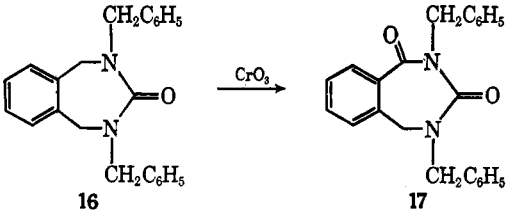
2. Alkylation

Treatment of the 3-thione **5** with various alkyl halides yielded[264] thiazolo-2,4-benzodiazepines of type **15**.



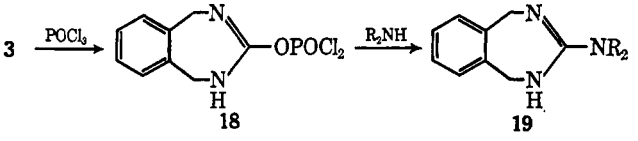
3. Oxidation

Chromic acid oxidation of the tetrahydrobenzodiazepin-3-one **3** gave[273] 1-oxo-2-isoindolinecarboxamide (**13**, R = $CONH_2$), instead of the desired dihydrobenzodiazepinedione **14**. Oxidation of the dibenzyl analog **16**, however, yielded the dione **17**.



4. Phosphorylation and Amination

Treatment of the tetrahydrobenzodiazepin-3-one **3** with phosphoryl chloride gave[29] the 3-phosphoryl derivative **18**, which was converted into the 3-amino-4,5-dihydro-1*H*-2,4-benzodiazepines **19** (R = H or CH_3) by reaction with ammonia or dimethylamine, respectively.



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(269) D. Grdenić and A. Bezjak, *Arkiv Kemi*, **25**, 101 (1953); *Chem. Abstr.*, **48**, 11146 (1954).
(270) M. Kesler, *Arkiv Kemi*, **27**, 67 (1955); *Chem. Abstr.*, **49**, 15313 (1955).
(271) M. B. Chaudhari and K. S. Nargund, *J. Univ. Bombay*, **A19** (Pt 3), 60 (1950); *Chem. Abstr.*, **47**, 2143 (1953).
(272) A. Rosenthal and S. Millward, *Can. J. Chem.*, **42**, 956 (1964).
(273) A. M. Felix, and R. I. Fryer, *J. Heterocyclic Chem.*, **5**, 291 (1968).