Journal of Heterocyclic Chemistry

Volume 9, Number 4 August 1972

Rearrangements of 1,4-Benzodiazepine Derivatives

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Received March 27, 1972

The skeletal rearrangement of 1,4-benzodiazepines to other heterocyclic systems are reviewed together with a discussion of possible mechanisms. Simple rearrangements involving migrations without skeletal changes are included for the sake of completeness.

Introduction.

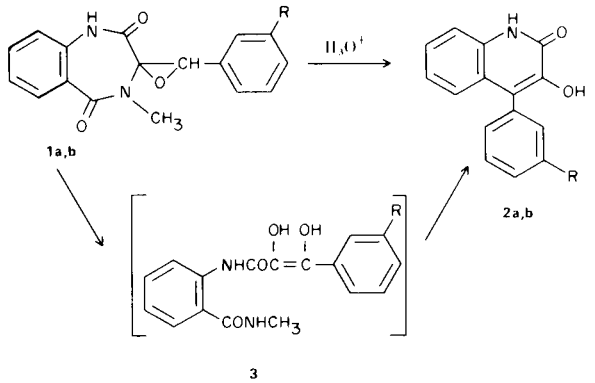
The capacity of polyfunctional molecules to undergo major structural rearrangements either through space, through existing bonds or by interactions between functional groups is well known in alkaloid chemistry. The number of rearrangement pathways possible seems to increase exponentially with the number of functional groups present in some systems. This review is a compilation of rearrangements of the 1,4-benzodiazepine system and surveys the literature through the beginning of 1972. No attempt will be made to include the chemistry on structure proofs of the compounds described. The chemistry and pharmacological properties of the 1,4-benzodiazepine system have been adequately reviewed elsewhere (1-6).

The benzodiazepine ring system already contains two functional groups and additional ones can be incorporated at any or in any combination of the positions on the heterocyclic ring. Most of the rearrangements observed in this system are impelled by a common driving force *i.e.* ring contraction leading to aromatization. Functional group changes without skeletal changes could lead to 4n but not 4n + 2πe systems. Thus, in substituted benzodiazepines a variety of functional group interactions are possible and the thermodynamic setting is highly conducive to skeletal changes. A variety of ring systems have been obtained, and in some instances these rearrangements prove to be useful synthetic tools for the preparations of some of these products.

The rearrangement of the 1,4-benzodiazepine ring system can, in general, be separated into two groups - (a) those involving intermediates in which the ring is opened (*cf.* Dimroth) and (b) those involving intermediates in which the 7-membered ring is bridged.

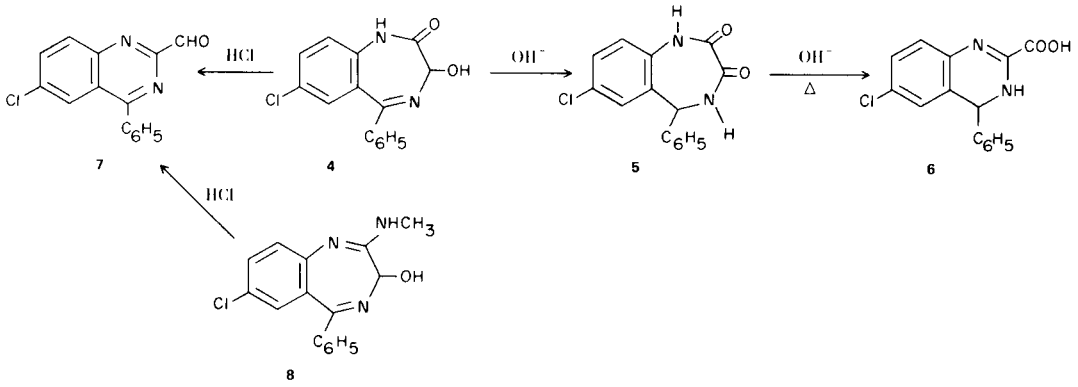
Rearrangements Involving Ring Open Intermediates.

The first rearrangement of this type was reported in 1954 (7). It was found that cyclopenin, compound **1a** (a natural product of, at that time, unknown structure) rearranged on treatment with acid to Viridicatin (**2a**). Later, other workers (8) found that the related cyclopenol (**1b**) was converted to Viridicatol (**2b**) under the same conditions. The structure of cyclopenin and cyclopenol was finally established in 1963 (9), and **3** was proposed as an intermediate in the rearrangement, formed by hydrolysis of the epoxide and the 3,4 bond.

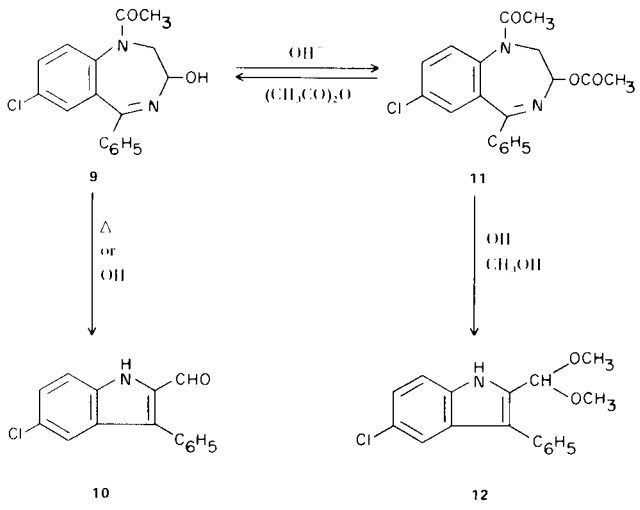


a: R H
b: R OH

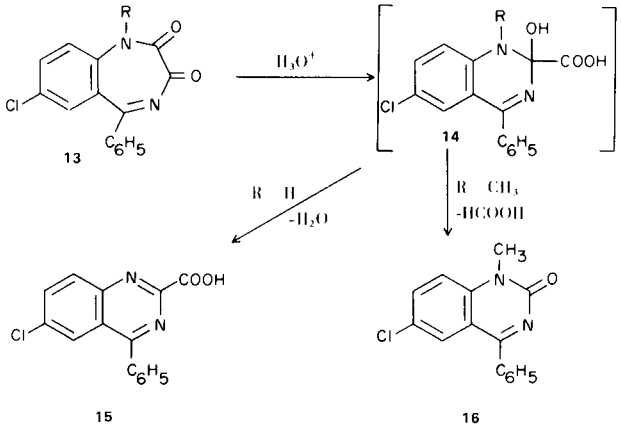
Three related rearrangements which also involve cleavage of the 3,4 bond are shown below. The starting materials vary only in their substitution at the 2-position and the 3,4 bond can, in all cases, be formally considered as a condensation product of an aldehyde with an imine.



Compound **4** was reported to undergo a hydride shift in base to give the dicarbonyl derivative **5** (10). Under more vigorous conditions, compound **5** underwent a ring contraction to give the dihydroquinazoline carboxylic acid, compound **6**. It has also been shown that **4** can be converted directly to the quinazoline carboxaldehyde **7** by treatment with mineral acid (11). The conversion of **4** to **7** with glacial acetic acid was also reported (12). Treatment of **4** with hydrazine or with methylamine resulted in the formation of the corresponding hydrazone or methyleneimine derivative of compound **7** (12). These reactions can be considered as undergoing a ring opening between positions 3 and 4 followed by recyclization between positions 2 and 4. Compound **4** was also reported to be formed from **8** under similar conditions (11). The related 3-hydroxybenzodiazepine **9** underwent similar ring opening, but in this instance, the active methylene group of the intermediate iminoaldehyde recyclized with the carbonyl group at the 5 position followed by loss of ammonia to give the indole carboxaldehyde **10** (13). When the corresponding 3-acetoxy derivative (11) was rearranged in methanol, compound **12**, the dimethyl acetal of **10** was formed.

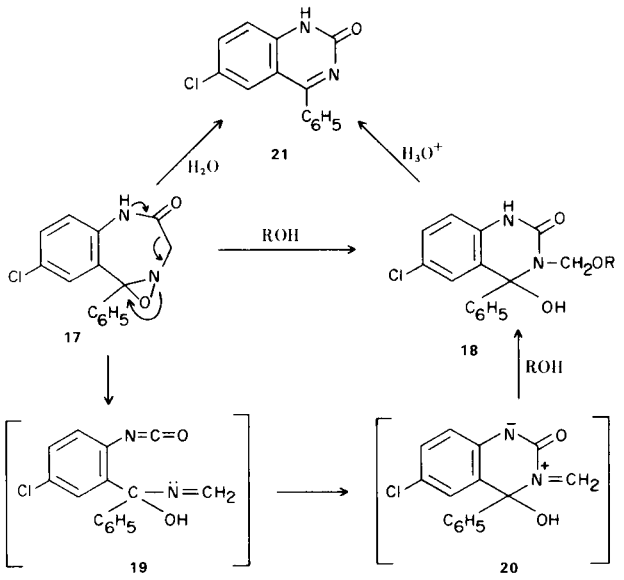


An analogous rearrangement of the benzodiazepindione **13**, a compound at one oxidative state higher than compounds **4** and **5**, was also reported (14). In this instance, the dihydroquinazoline **14** was proposed as the intermediate formed after cyclization of the initial hydrolysis product. When **13** was unsubstituted at the 1-position, elimination of water from **14** gave the quinazoline carboxylic acid **15**. However, when **13** was substituted with an alkyl group at position 1, the intermediate **14** could eliminate only the elements of formic acid to give the quinazolone **16**.



The well known interconversion of nitrones and oxaziridines has also been demonstrated in the 1,4-benzodiazepine-4-oxide series (15). These oxazirinobenzodiazepines have been reported to undergo a facile alcoholitic ring contraction to give dihydroquinazoline derivatives (16). Thus, compound **17** on treatment with an alcohol gave **18** in which one molecule of the alcohol has been added. Again, an open intermediate (**19**) was postulated which could then recyclize by intramolecular attack of the imino nitrogen on the isocynate function to give **20**. This intermediate could then add one mole of the alcohol in an irreversible step to give the observed product. It is stated that the mechanism is supported

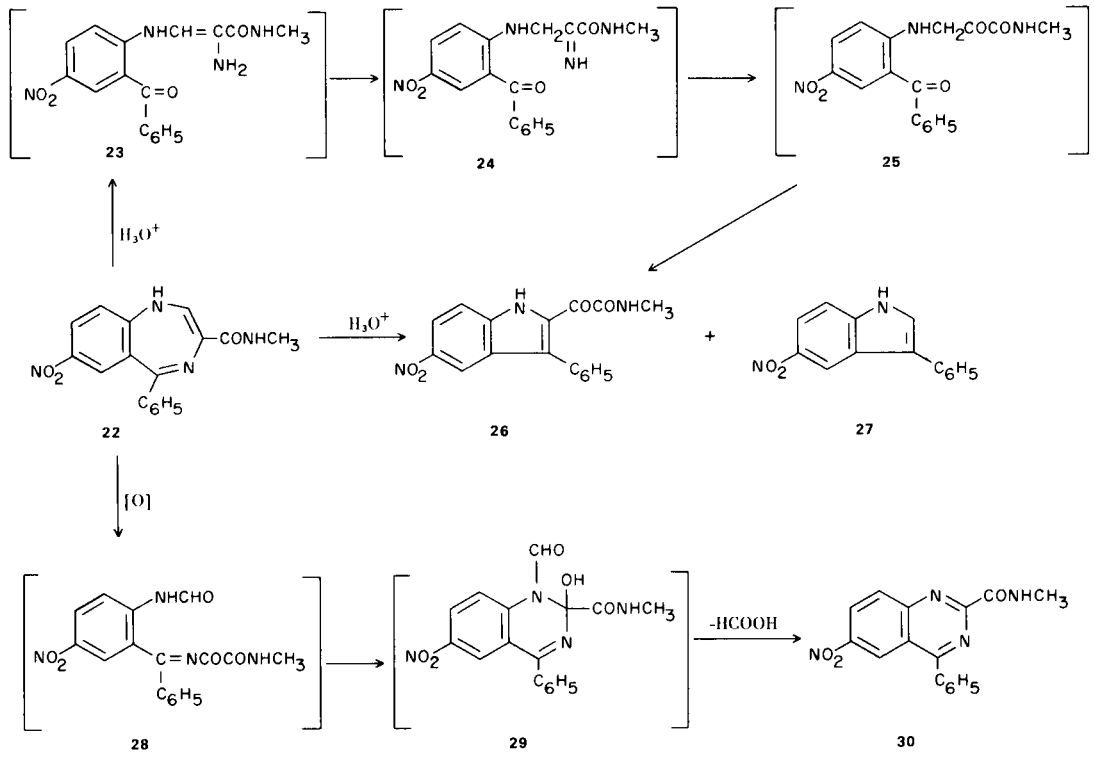
by the observation that compound **17** is converted to compound **21** by treatment with aqueous tetrahydrofuran. Here, the 3-hydroxymethyl quinazoline which is postulated as an intermediate (**18**, R = H) would yield compound **21** by loss of formaldehyde and water.

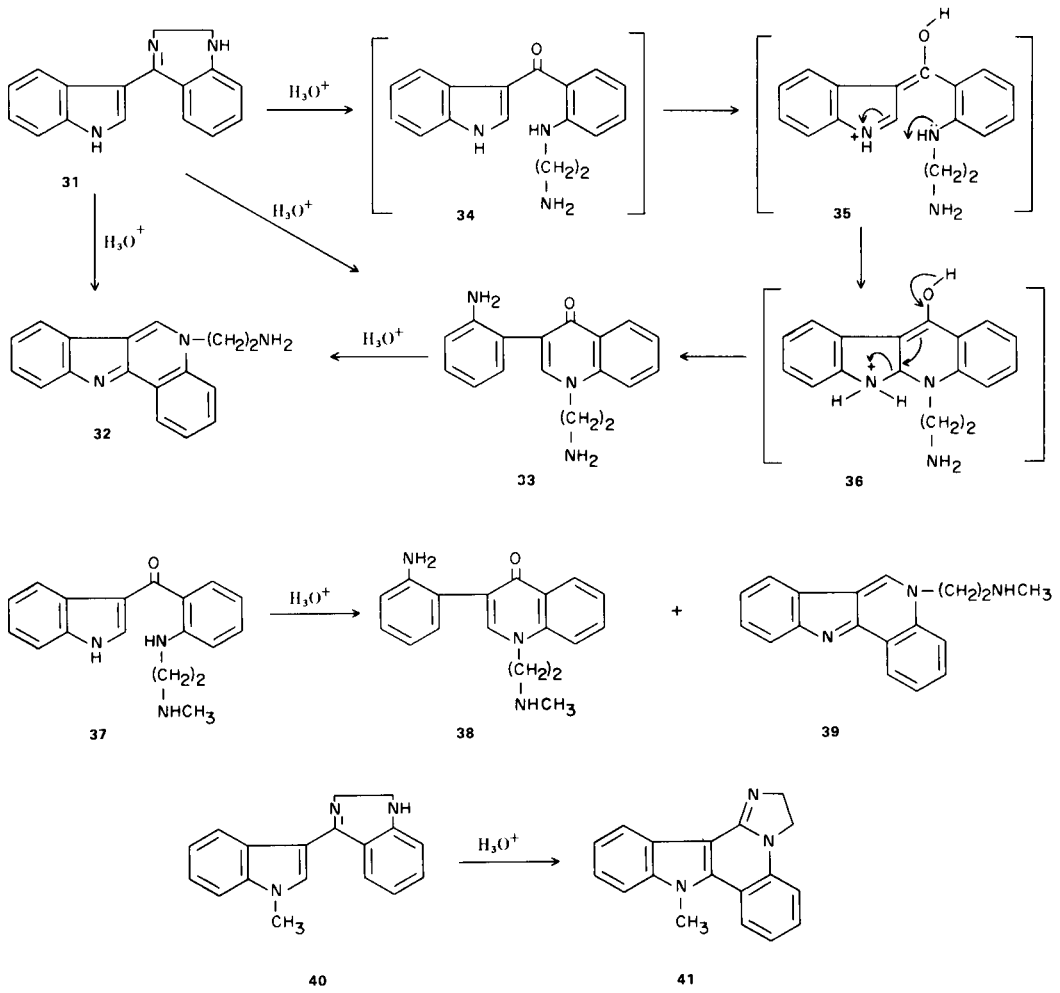


The 1*H*-1,4-benzodiazepine **22** was found to undergo ring contraction to the indoles **26** and **27** on treatment with acid (17). The formation of **26** is relatively easy to justify. If it is assumed that hydrolysis of the azomethine bond is the first step in the rearrangement, **23** would be the resultant intermediate and hydrolysis of the enamine would give the ketone **25**. The activated methylene group could then condense with the benzophenone carbonyl to give the indole. The formation of the other indole (**27**) appears to involve, besides rearrangement, subsequent hydrolysis, oxidation and decarboxylation steps. Oxidation of **22** with chromic acid led to the formation of the quinazoline derivative **30**. This reaction probably proceeds *via* the dicarbonyl intermediate **28** which could then cyclize to the quinazoline **29**. Loss of formic acid would then give the observed product.

An unusual rearrangement of a 1,4-benzodiazepine was observed in which, not only the diazepine nucleus, but also the 5-substituent took part.

Because of the pharmacological interest in 5-phenyl or 5-substituted phenyl-1,4-benzodiazepines, most of the investigations in this class of compounds were carried out on these derivatives. One of the exceptions was the 5-(3-indolyl)-1,4-benzodiazepine, compound **31** (18). Acid treatment of this compound resulted in the formation of either the indoloquinoline **32** or the quinolone **33**, depending on the conditions used. Compound **32** was shown to be an artifact derived from **33**. The mechanism given, proposed initial hydrolytic cleavage of the azomethine bond to give **34** as an intermediate. This would be followed by protonation at the carbonyl oxygen to





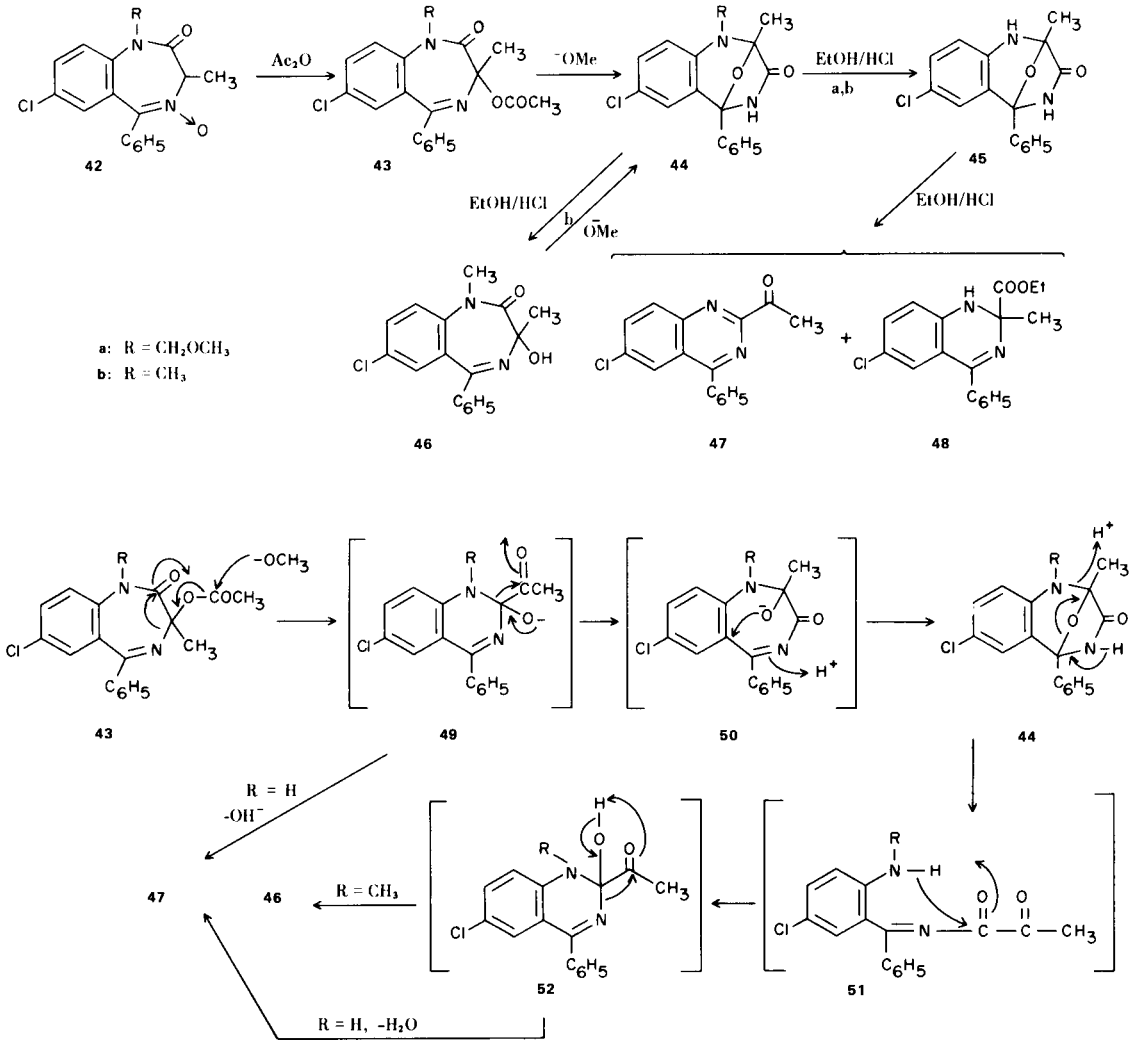
give the indolenine **35**. Nucleophilic addition of the anilino N-H function to the polarized C=N bond, would then lead to **36**. Cleavage of the C-N bond of the 5-membered ring, in an irreversible step as shown would give the observed quinolone **33**. The formation of **32** from **33** simply involves condensation of the anilino amine with the quinolone carbonyl group.

That an intermediate such as **34** was involved in the rearrangement was demonstrated by treating **31** with methyl iodide. This gave the 4-methyl quaternary salt which could be opened with base to give the corresponding *N*-methyl derivative of **34**, compound **37**. The compound when treated with hot mineral acid resulted in the formation of the quinolone **38**. The indoloquinoline **39** was also isolated from this reaction in low yield.

An analogous rearrangement in this series was observed when the *N*-methylindole derivative **40** was treated with acid. In this instance, only the imidazoindolquinoline **41** was isolated.

The 3-acetoxy-3-methylbenzodiazepinone, compound **43** (R = H) prepared from the corresponding *N*-oxide (**42**) was reported to undergo rearrangement to the acetylquinazoline **47** on treatment with acid or base (19). If however, the nitrogen in the 1-position was substituted by a methyl group, the 3-hydroxy derivative could be obtained by the unusual rearrangement shown below (20).

Treatment of **43** (R = CH_3 or CH_2OCH_3) with base afforded the corresponding, rearranged epoxy compounds **44** (R = CH_3 or CH_2OCH_3). When **44** (R = CH_3) was treated with ethanolic hydrogen chloride, an additional rearrangement gave the 1,3-dimethyl-3-hydroxy derivative, compound **46**. This rearrangement was found to be reversible and thus treatment of **46** with base led to the recovery of compound **44** (R = CH_3). Mild treatment of **44** (R = CH_2OCH_3) with ethanolic hydrogen chloride resulted in the cleavage of the methoxymethyl group and gave compound **45**. More vigorous treatment of **45** with

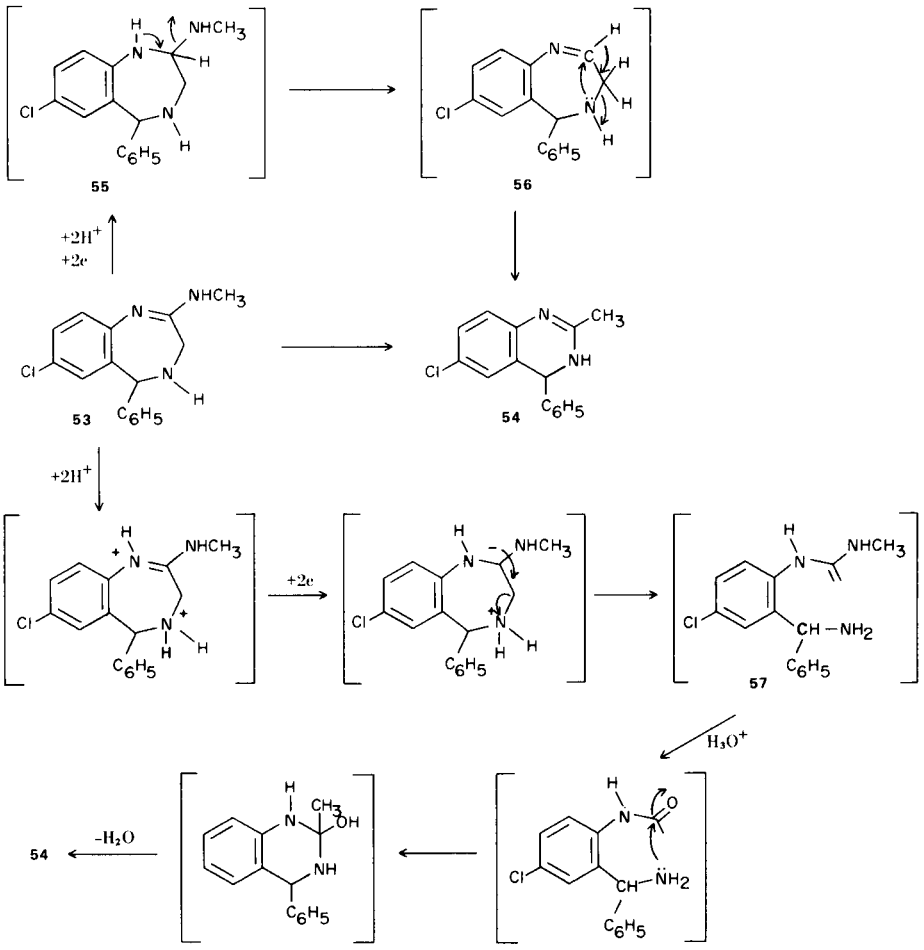


the same reagent gave the expected acetylquinazoline **47** and the 2-carbethoxy-2-methyldihydroquinazoline, compound **48**.

The proposed mechanisms are envisioned as preceeding by the initial attack of methoxide ion on **43** which would lead to the quinazoline intermediate **49**. This would then ring expand and epoxidize to **44** *via* the intermediate **50** as shown. Acid treatment of **44** would cleave the epoxide to give the diketone **51** as an intermediate and this in turn could recyclize to the quinazoline derivative **52** (the protonated form of **49**). When R = CH_3, ring expansion to the observed product **46** would occur. However, when R = H, the intermediate **52** would be expected to dehydrate to the acetylquinazoline **47**. Compound **47** could also arise from intermediate **49** by loss of hydroxyl ion. The rearrangement of compound **46** to compound **44** is envisioned as simply the reverse process, *i.e.* again, *via* the quinazoline intermediate **49**. The formation of compound **48**, the other rearrangement product from **44**, could arise by cleaving the epoxide in the opposite manner, ethanolysis of the amide bond followed by recyclization between positions 2 and 4 of the benzodiazepine ring.

It has been reported (21) that the electrochemical reduction of the amidine **53** gives an excellent yield of the dihydroquinoline, **54**. The mechanism shown involves the addition of two electrons and two hydrogen ions across the 1,2-position of the expected reduction product (intermediate **55**). It is then proposed that loss of methylamine followed by a hydride shift would occur as indicated in **56** to give the observed product.

An alternate mechanism which obivates the need for this very unlikely hydride shift is shown schematically below and would proceed *via* the open intermediate **57**.



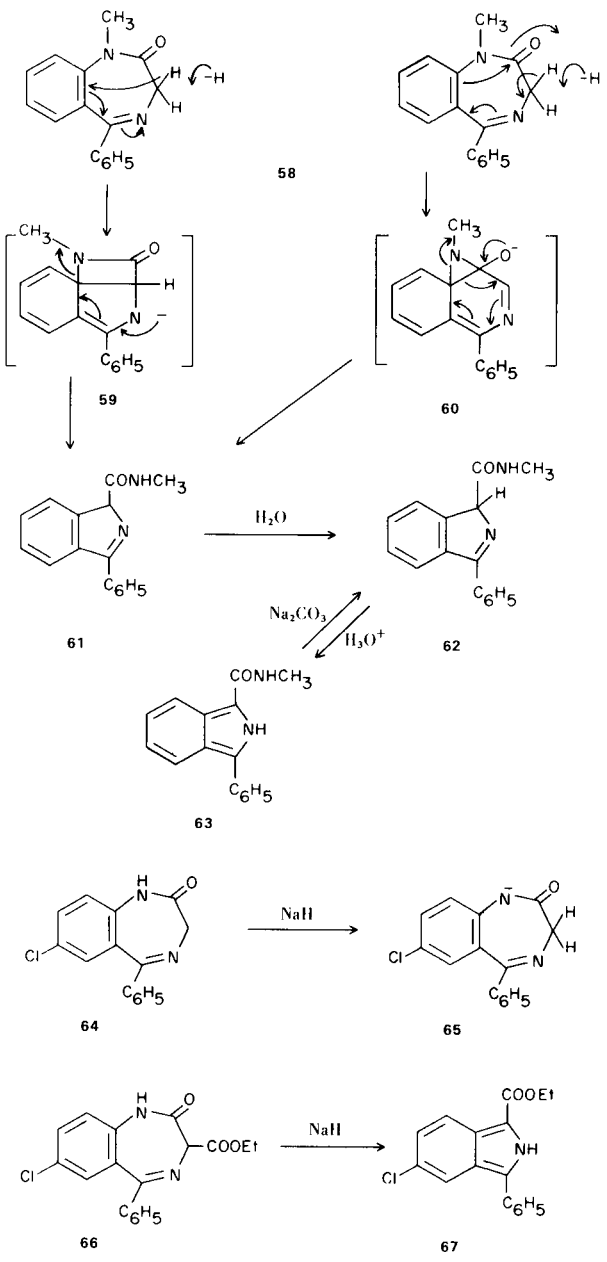
Rearrangements Involving Bridged Intermediates.

The treatment of 1-substituted 1,4-benzodiazepin-2-ones, -2-thiones and tetrahydropyrimido[1,2-*a*]-1,4-benzodiazepines with strong base resulted in the formation of isoindole derivatives in high yield (22,23). Two plausible mechanisms were proposed, both of which involved bridged intermediates. Thus, when the 1-methyl-1,4-benzodiazepinone **58** is treated with sodium hydride in *N,N*-dimethylformamide it has been shown that the initial step is removal of a proton from the 3-position to give the sodium salt of the corresponding anion (23). The anion could ring contract as shown to give either of the tricyclic intermediates **59** or **60**. Either intermediate could then undergo further ring contraction to give the salt of the isoindole carbanion **61**. Acidification of **61** would lead either to the isoindolenine **62** or the isoindole **63**. In one case, these were shown to be interconvertible (22).

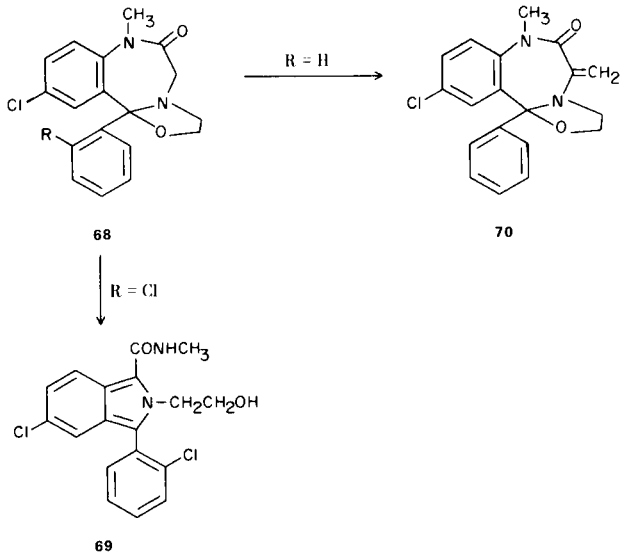
Simple benzodiazepines which are unsubstituted in the 1-position, *e.g.* compound **64** do not undergo this rearrangement since the first anion formed has been shown to be at the amide nitrogen (**65**) (24). While the dianion can be formed, rearrangement does not occur since this would require a double negative charge on the lactam nitrogen which is a very unlikely species.

If, however, the 3-carbethoxybenzodiazepine **66** is treated with sodium hydride in DMF, rearrangement to **67** does occur since the relative acidities of the 1 and 3 protons are now reversed (25).

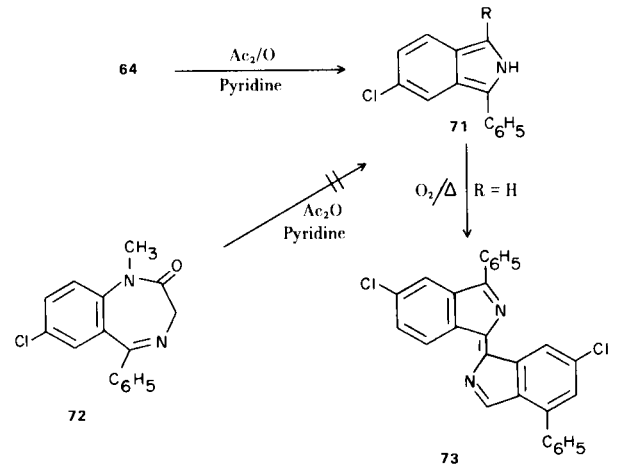
A closely related rearrangement was that of the oxazolobenzodiazepine **68**. When R was halogen, treatment with sodium hydride gave the isoindole **69** (26). A similar mechanism to that of **58** → **63** was proposed. However, when R = H, **68** was converted *via* a postulated Vilsmeier reaction, reduction and dehydration to the methylene derivative **70**.



Treatment of the 1,4-benzodiazepine, unsubstituted at the 1-position (**64**), with acetic anhydride in pyridine resulted in the formation of the acetylisoindole **71** (R = $COCH_3$) (27). Since the 1-alkyl derivative **72** did not react under these conditions, it was postulated that this reagent first acylated the 1-nitrogen. The $-OCOCH_3$ ion could then attack the proton at the 3-position as before (**58** → **63**) leading to ring contraction and formation of the isoindole **71** (R = H) by loss of acetylisocyanate. Compound **71** (R = H) was shown to acylate under the reaction conditions to give the observed product **71** (R = $COCH_3$). The bisisoindolylidene, **73** also isolated

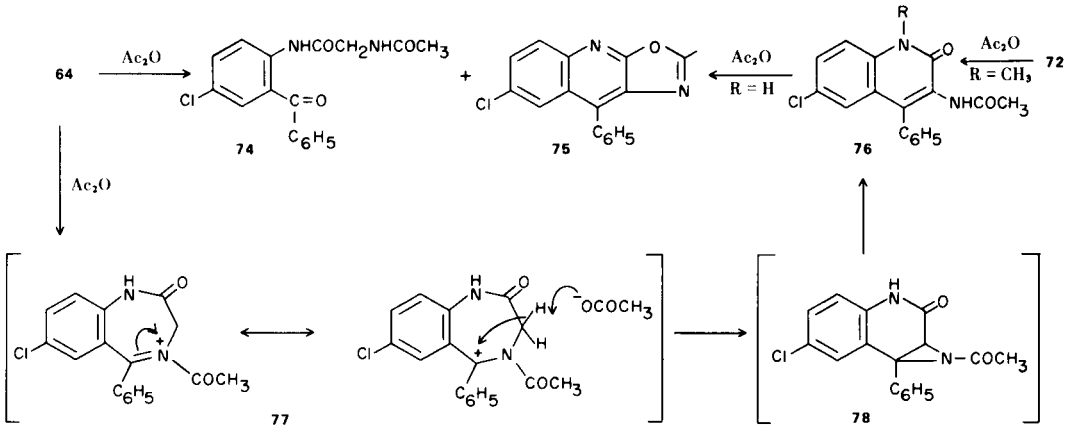


in the rearrangement was shown to be an artifact derived from **71** (R = H).

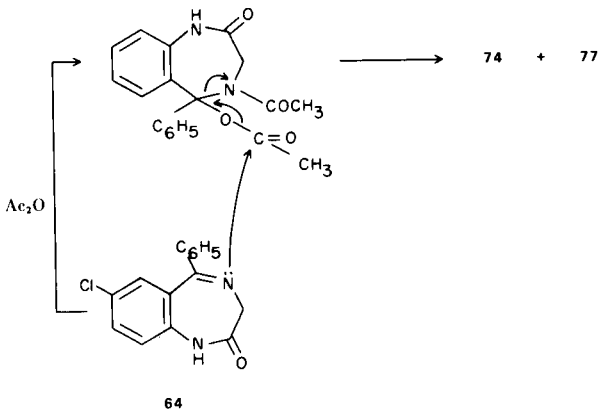


Contrasted with the acetic anhydride-pyridine rearrangement, the reaction took another course when either **64** or **72** was heated with acetic anhydride and a few drops of sulfuric acid or with acetic anhydride in the presence of sodium acetate. Thus, from **64** a mixture of the anilide **74** and the quinoline derivative **75** was isolated (28). Compound **72** gave **76** (R = CH_3), the carbostyril corresponding to **75**.

Here the mechanism was visualized as proceeding *via* the acetylated ion **77**. The anion from acetic acid could then abstract one of the acidic protons at the 3-position, ring contraction to the tricyclic intermediate **78** would follow and with aromatization as the driving force **78** would collapse to the carbostyril **76** (R = H). Under the reaction conditions **76** (R = H) has been shown to dehydrate to **75**.

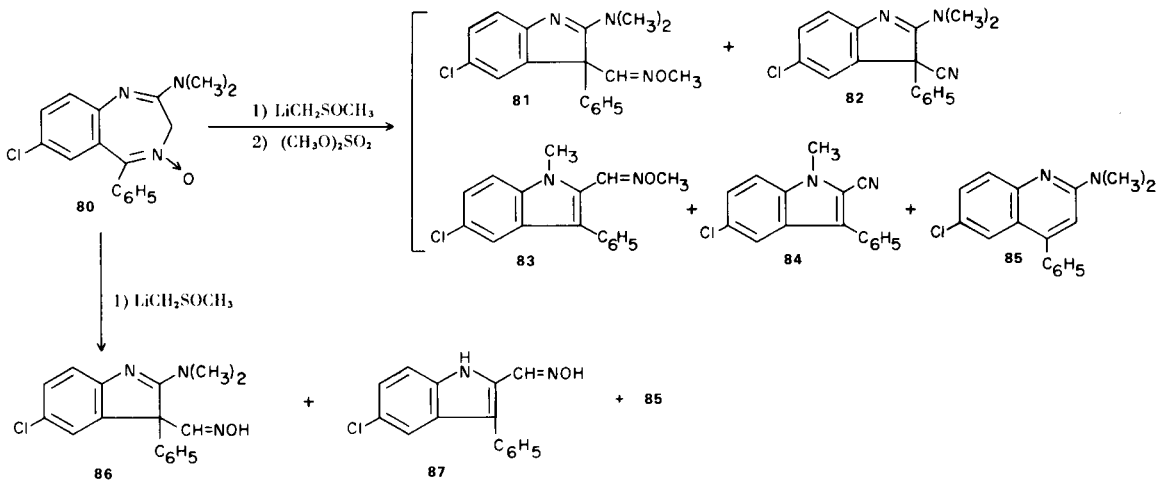


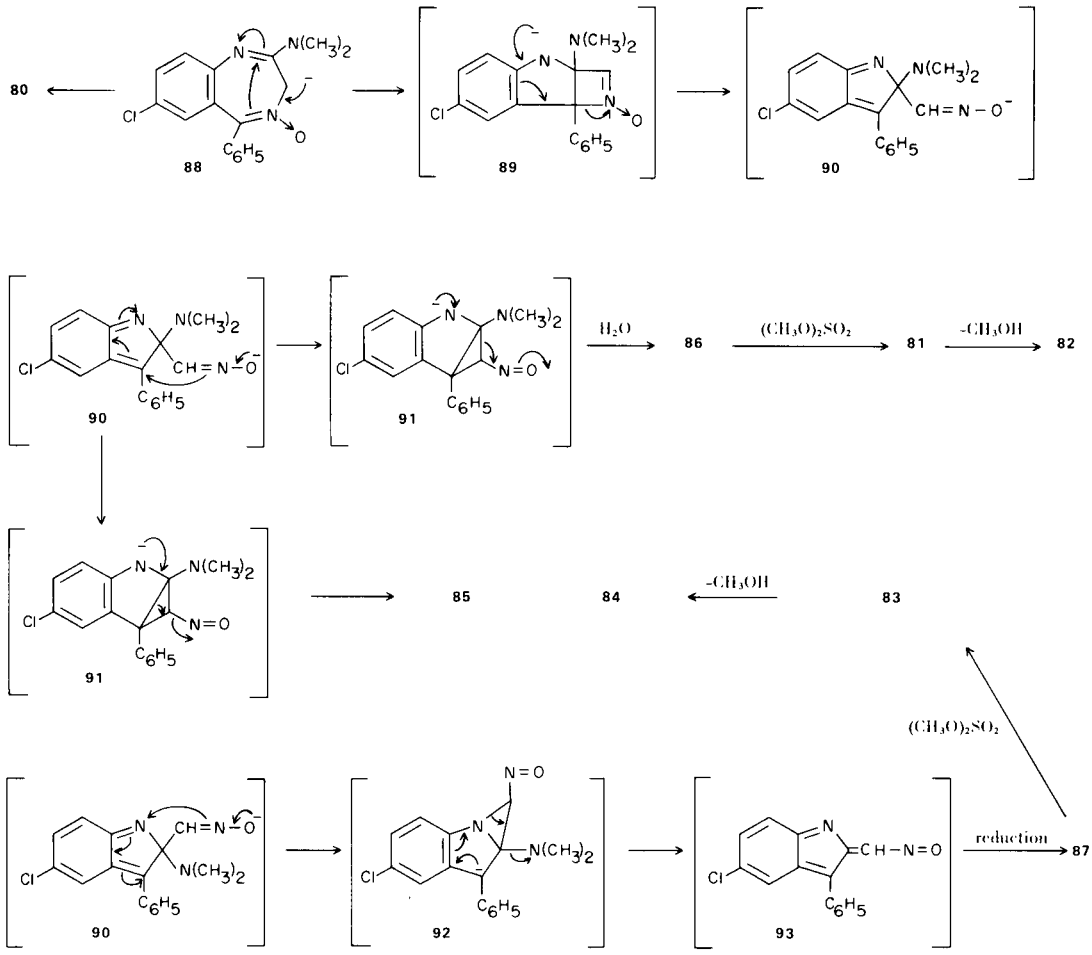
The anilide **74** was always found in the reaction mixture (low yield) even when non-aqueous conditions were used in the workup. It was proposed that **74** could be formed by an addition compound of type **79**, which would parallel the "normal" reaction product obtained when a Schiff base is treated with acetic anhydride. A compound such as **79** would itself be a strong acylating agent and could acylate additional **64** to give both the observed minor product **74** and the ion **77**.



Attempts to further alkylate the 2-dimethylaminobenzodiazepine **80** with dimethyl sulfate in the presence of the lithium anion of dimethyl sulfoxide led to a complex mixture of the rearrangement products **81**, **82**, **83**, **84**, and **85** (29). In order to determine whether or not the methylating agent had any effect on these rearrangements, **80** was treated with lithium dimsyl anion in dimethylsulfoxide. Workup afforded the indole derivatives **86** and **87** together with the quinoline **85**.

A plausible mechanism for the formation of these compounds has been proposed (29) in which all of the end products are derived from the common intermediate **90**. Thus, removal of the proton at the 3-position would





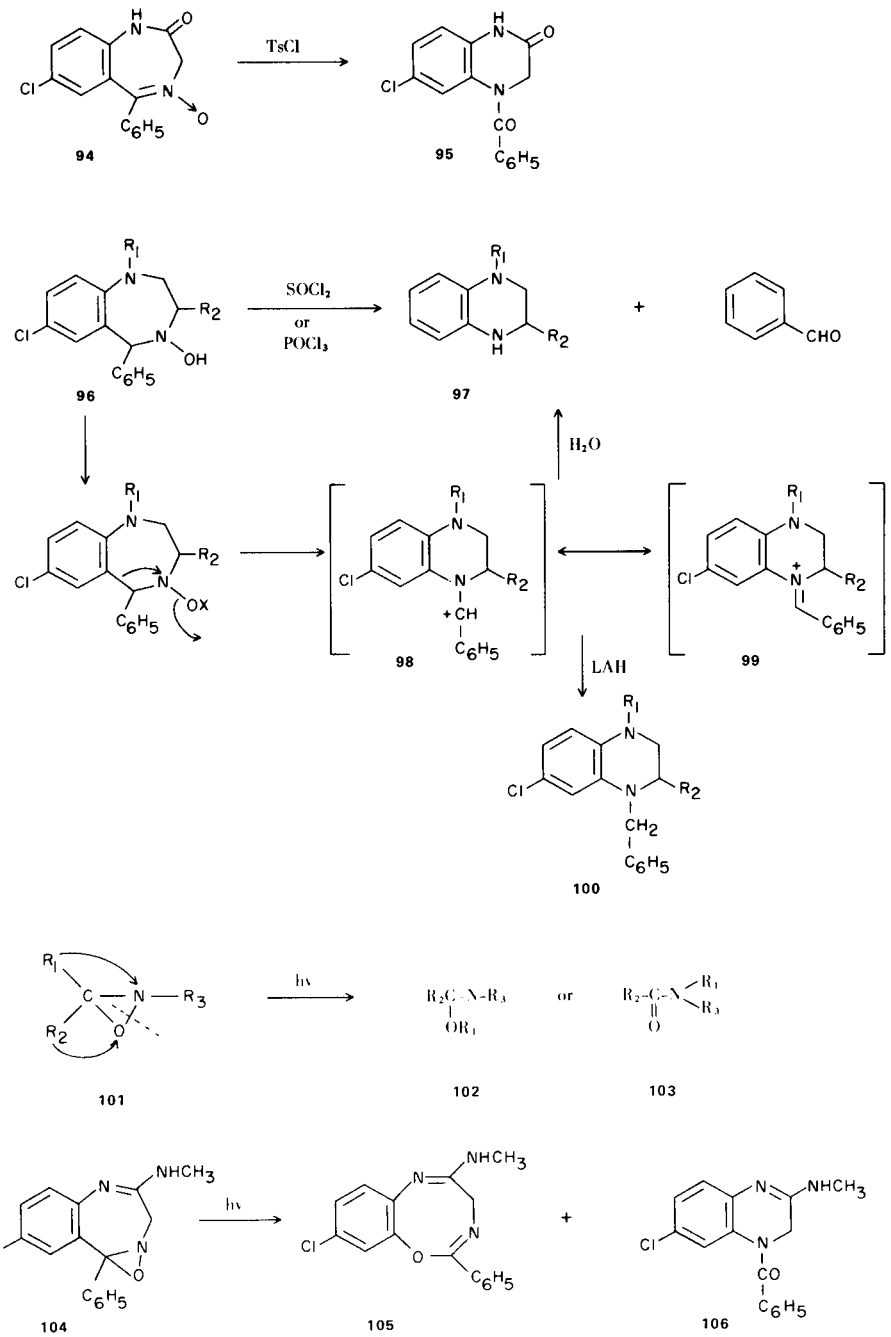
give the anion **88**. Ring-closure to **89** occurs by way of nucleophilic attack on the amidine double bond. Ring opening of **89** gives **90** as shown.

Cyclization of the azomethine bond in **90** to the 3-position of the indole would lead to the cyclopropane derivative **91**. Ring opening as shown followed by protonation would then give **86**. Methylation of **86** followed by loss of methanol would give **81** and **82**, respectively. The cyclopropane ring in intermediate **91** could also cleave in another sense. Thus, the quinoline **85** would result from cleavage of the bond bridging the six-membered ring in **91** together with simultaneous loss of nitrous oxide. Similarly, the azomethine bond of **90** could cyclize to the 1-position of the indole, rather than the 3-position and would result in the formation of the tricyclic intermediate anion **92**. Loss of dimethylamine in the manner indicated would give the indoleisocyanate **93**. Reduction of **93** in the reaction medium (the exact reducing species is not known) would then lead to the observed product **87**. Methylation of **87** gives **83**, which on loss of methanol, would give compound **84**.

Miscellaneous Rearrangements.

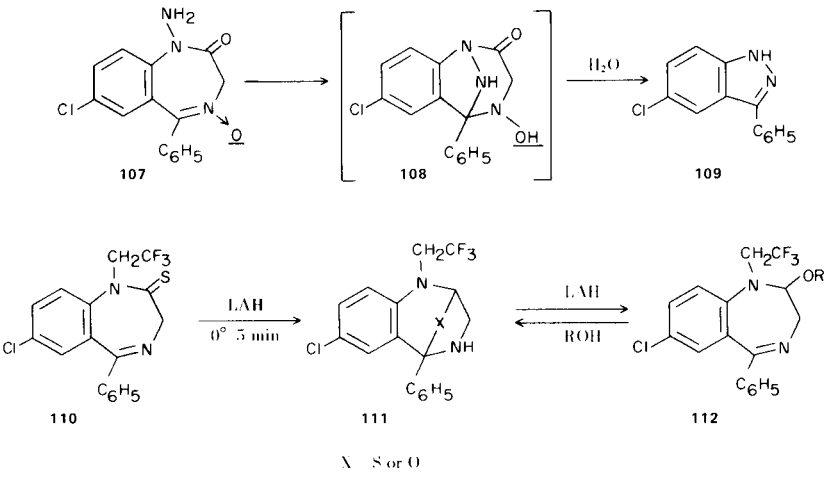
These rearrangements generally fall into two groups. The first class comprises those which involve skeletal changes, but either do not easily fall into the two categories previously discussed or in which the benzodiazepine ring system itself does not constitute the driving force for the rearrangement. The second type consists of those in which no skeletal rearrangement takes place, *e.g.* a simple bond migration. This latter class is included in this review only for the sake of completeness.

A Beckmann type of rearrangement of a 1,4-benzodiazepine 4-oxide has been reported (12). Thus, compound **94** on treatment with *p*-toluenesulfonyl chloride was shown to give the quinoxalone derivative **95** (12). A somewhat related rearrangement (in this case, an extension of the Stieglitz rearrangement) was shown to be a potentially useful synthetic method for the preparation of unsymetrically substituted quinoxalines (30). The hydroxylamine derivatives **96** were found to undergo rearrangement on treatment with either thionyl chloride or phosphorus oxychloride to give benzaldehyde and the



quinoxoline **97**. The mechanism of this ring contraction would involve esterification of the 4-OH group as the first step. The resulting increase in the electron deficiency of the 4-nitrogen would promote cleavage of the N-O bond together with concerted migration of the C_5-C_{11} bond. This would generate the carbonium ion **98** stabilized by the immonium ion **99**. The existance of the intermediate ions **98**, **99** was confirmed by the isolation of the 4-benzyltetrahydroquinoxaline **100** from a reductive workup of the reaction mixture. Normal, hydrolytic workup led to the isolation of **97** and benzaldehyde.

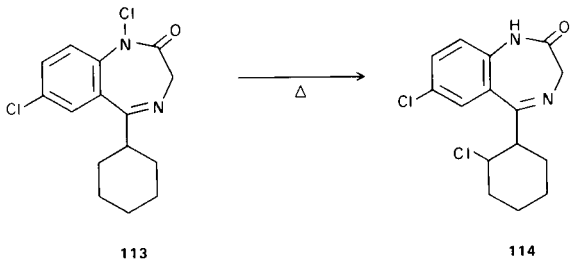
The photolylis of nitrones to oxaziridines has been mentioned earlier (15). It is also known that oxaziridines undergo, on further irridiation, cleavage of the nitrogen-oxygen bond followed by rearrangement of one of the groups attached to the carbon atom of the oxaziridine to either the nitrogen or the oxygen atom. Thus, cleavage of **101** would lead to compounds of type **102** and **103** as shown (31). It was, therefore, not surprising that irridiation of the oxaziridine **104** gave both types of rearrangement products, the benzoxadiazocine **105** and the quinoxaline **106** (32).



When the amide **17**, corresponding to the amidine **104** was photolized, the same rearrangement occurred to give the corresponding amide of compound **105** together with the quinoxalinone **95** (31).

The facile hydrolysis of 1-aminobenzodiazepines of type **107** to 5-phenyl-3-chloroindazole (**109**) was postulated to be due to the formation of the bridged intermediate **108** (33).

The Polonovski type of rearrangement of 1,4-benzodiazepine 4-oxides to give the corresponding 3-acetoxy derivatives has been extensively reported. The further rearrangement of these products has been discussed in the first section of this review. Bridged benzodiazepines of type **111** have been reported to have been prepared from compounds of type **110** and **112** by lithium aluminum hydride reduction (34).



The simple migration of the 3,4-bond in 1,5-dihydro-1,4-benzodiazepines to the more stable 1,3-dihydro derivatives has been reported (35), as has the migration of 1-halo-1,4-benzodiazepinones to the corresponding 3-halo derivatives (36). In the preparation of a 3-ethoxybenzodiazepine by this method, 2-carbethoxy-6-chloro-4-phenylquinazoline was also isolated. This ring contraction is probably analogous to that of **4** → **6** or **4** → **7**, the only difference being that an oxidation takes place under the reaction conditions (37). A related rearrangement of a 1-chloro-5-cycloalkyl-1,4-benzodiazepine has been reported for compound **113** in which the halogen migrates to the cycloalkyl group **114** (38). If the 5-substituent is methyl, this rearrangement can be repeated 3 times to give either the corresponding chloromethyl, dichloromethyl, or trichloromethyl derivative (39).

A rather unusual rearrangement of an oxaziridine has also been observed. When compound **17** was treated with ferrous sulfate in the presence of aqueous tetrahydrofuran, the product isolated was the corresponding 3-hydroxy derivative, compound **4** (40).

REFERENCES

(1) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, 53, 577 (1964).

(2) L. H. Sternbach, L. O. Randall, and S. Gustafson, "Psychopharmacological Agents", Vol. 1, Academic Press, New York, N. Y., 1964, p. 137.

(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) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, 68, 747 (1968).

(6) A. V. Bogatskii and S. A. Andronati, *Russian Chem. Rev.*, 39, 1064 (1970).

(7) A. Bracken, A. Pocker, and H. Raistrick, *Biochem. J.*, 57, 587 (1954).

(8) J. H. Birkinshaw, M. Luckner, Y. S. Mohammed, K. Mothes, and C. E. Stickings, *ibid.*, 89, 196 (1963).

(9) Y. S. Mohammed and M. Luckner, *Tetrahedron Letters*, 1953 (1963).

(10) S. C. Bell and S. J. Childress, *J. Org. Chem.*, 27, 1691 (1962).

(11) L. H. Sternbach, E. Reeder, A. Stempel, and A. I.

Rachlin, *ibid.*, 29, 332 (1964).

(12) S. C. Bell and S. J. Childress, *ibid.*, 29, 506 (1964).

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

(14) A. M. Felix, J. V. Earley, R. I. Fryer, and L. H. Sternbach, *J. Heterocyclic Chem.*, 5, 731 (1968).

(15) L. H. Sternbach, B. A. Koechlin, and E. Reeder, *J. Org. Chem.*, 27, 4671 (1962).

(16) R. Y. Ning, I. Douvan, and L. H. Sternbach, *ibid.*, 35, 2243 (1970).

(17) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *ibid.*, 32, 3798 (1967).

(18) E. E. Garcia, J. G. Riley, and R. I. Fryer, *ibid.*, 33, 2868 (1968).

(19) S. C. Bell, R. J. McCaully, C. Gochman, S. J. Childress, and M. I. Gluckman, *J. Med. Chem.*, 11, 457 (1968).

(20) A. Walser, G. Silverman, J. Blount, and R. I. Fryer, *J. Org. Chem.*, 36, 1465 (1971).

(21) H. Oelschlager and H. Hoffmann, *Arch. Pharm.*, 300, 817 (1967).

(22) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Am. Chem. Soc.*, 88, 3173 (1966).

(23) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, 34, 649 (1969).

(24) R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Med. Chem.*, 7, 386 (1964).

(25) A. Walser and J. Hellerbach, unpublished results.

(26) A. Terada, Y. Yabe, T. Migadera and R. Tachikawa, 3rd International Congress of Heterocyclic Chemistry, The Tohoku University, Sendai, Japan, August 23-27, 1971, p. 542.

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

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

(29) N. W. Gilman, J. F. Blount, and L. H. Sternbach, *ibid.*, 37, in press (1972).

(30) A. Walser, G. Silverman, R. I. Fryer, L. H. Sternbach, and J. Hellerbach, *ibid.*, 36, 1248 (1971).

(31) See R. Y. Ning, G. F. Field and L. H. Sternbach, *J. Heterocyclic Chem.*, 7, 475 (1970) and cited references.

(32) G. F. Field and L. H. Sternbach, *J. Org. Chem.*, 33, 4438 (1968).

(33) W. Metlesics, R. F. Tavares, and L. H. Sternbach, *ibid.*, 30, 1311 (1965).

(34) M. Steinman, R. Alekel, Yee-Shing Wong, E. F. York, and J. G. Topliss, 162nd American Chemical Society meeting, Washington, D. C., Sept. 12-17, 1971, Fluo. 021.

(35) R. I. Fryer, D. Winter, and L. H. Sternbach, *J. Heterocyclic Chem.*, 4, 355 (1967).

(36) R. I. Fryer, E. E. Garcia, and L. H. Sternbach, U. S. Patent, 3,371,083 (1968).

(37) E. E. Garcia, R. I. Fryer, unpublished results.

(38) J. Schmitt, P. Comoy, M. Suquet, J. Birtard, J. LeMeur, J. J. Basselier, M. Brunaud and J. Salle, *Chim. Ther.*, 254 (1967).

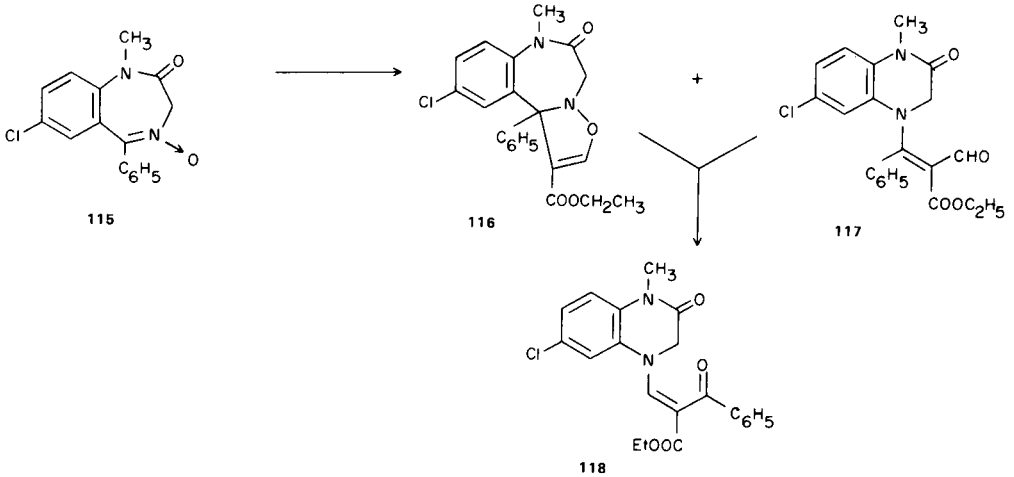
(39) J. Schmitt, U. S. Patent, 3,551,412 (1970).

(40) R. Y. Ning, W. Y. Chen, and L. H. Sternbach, unpublished results.

(41) C. G. Chidester, D. J. Duchamp and J. Szmuskovicz, American Crystallographic Association, Winter Meeting, University of New Mexico, Alburquerque, N.M., April 3-7, 1972; Abstract E9.

Note added in proof:

Since this review was prepared it has been reported (41) that the treatment of the benzodiazepine **115** with ethyl propiolate resulted in the formation of the anticipated product **116** together with the rearranged quinoxalone, compound **117**. Further treatment of **116** or **117** with ethanol gave a new quinoxalone, compound **118**. Structures were established from three dimensional X-ray diffraction data. Mechanisms were not presented, but the rearrangement would seem to be related to the Beckmann type reported above (12).



115 116 117 118