Quinazolines and 1,4-Benzodiazepines. XXVII.[1] Mechanism of Ring Enlargement of Quinazoline 3-Oxides with Alkali[2] to 1,4-Benzodiazepin-2-one 4-Oxides

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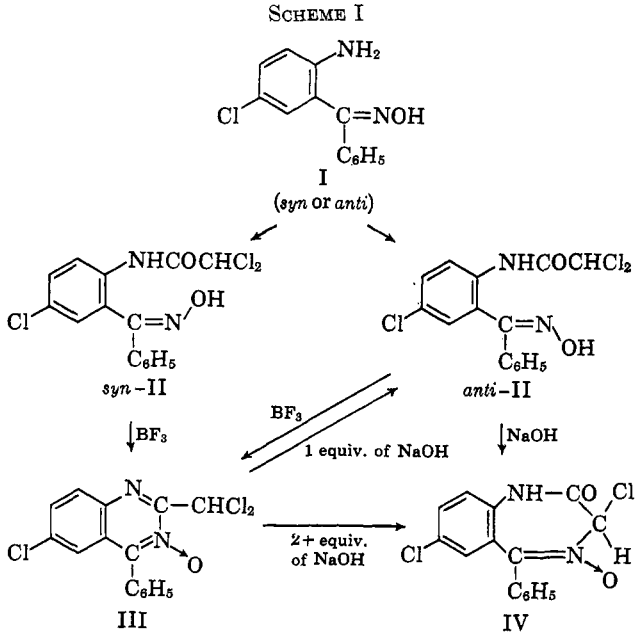
The mechanism of the ring enlargement of 2-halomethylquinazoline 3-oxides with alkali to 1,4-benzodiazepin-2-one 4-oxides was investigated. The synthesis of 3-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxides (IV) and their transformation to other 3-substituted benzodiazepin-2-ones is described.

The continuing interest of these laboratories in the synthesis of 1,4-benzodiazepines has led to an investigation of methods of synthesis of 3-substituted 1,4-benzodiazepin-2-ones where the substituent is other than a hydrocarbon residue. Compounds of this type have usually been prepared by Polonovski rearrangement of a 1,4-benzodiazepine 4-oxide on treatment with an acid chloride or anhydride,[3] and subsequent transformations of the 3-acyloxy derivative. This report describes a new approach leading to similar compounds based on the ring enlargement of a 2,2-dihalomethylquinazoline 3-oxide on treatment with alkali to a 3-halo-1,4-benzodiazepin-2-one 4-oxide. As a result of this work, the mechanism of this ring enlargement[4] has been established.

The key intermediate in this synthesis, the 2-dichloromethylquinazoline 3-oxide (III, Scheme I) was readily prepared from either the *syn*- or *anti*-oxime[5] of 2-amino-5-chlorobenzophenone (I) *via* the

SCHEME I



dichloroacetamido derivative II (*syn* and *anti*). Cyclization with hydrogen chloride in acetic acid afforded the desired intermediate III, but the product obtained was

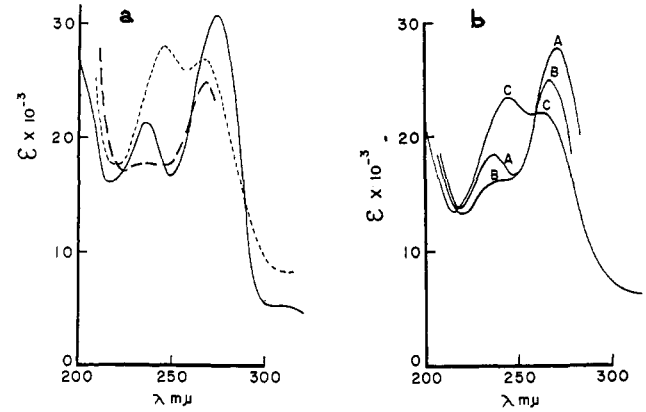


Figure 1.—Ultraviolet spectra (a) of III in isopropyl alcohol, ———; of *anti*-II in isopropyl alcohol and alkali (20 sec.), — — — —; and of IV in isopropyl alcohol and alkali, - - - - -; and (b) of III (2×10^{-5} *M*) plus an excess of 3.3×10^{-4} *N* KOH in 98% isopropyl alcohol: A, 20 sec.; B, 5 min.; and C, 3.5 hr.

difficult to purify and was isolated in rather low yield. Ring closure was readily effected, however, by the use of boron trifluoride to give a high yield of pure quinazoline 3-oxide (III).

The reaction of III with 2 or more equiv. of alkali in dimethoxyethane led to the formation of the 3-chloro-1,4-benzodiazepin-2-one 4-oxide (IV) in almost quantitative yield. However, when just 1 equiv. of alkali was used, under the same conditions, only 17% of IV and 48% of the dichloroacetamido-*anti*-oxime (*anti*-II) were obtained. Further treatment of *anti*-II with alkali afforded IV in high yield. Since these results seemed to indicate that *anti*-II was an intermediate in the conversion of III to IV, a more intensive study of this reaction was undertaken which resulted in a clearer understanding of its mechanism.

By observing the changes in the ultraviolet spectrum of a dilute solution of III in isopropyl alcohol containing a tenfold excess of alkali (Figure 1b), it was readily apparent that the reaction pathway was III → II → IV.

Since the spectra changed rapidly, particularly soon after mixing, the normal rate of scanning was increased and limited to the wave lengths (200–300 mμ) where the most significant changes occurred. A comparison showed that curve A representing the ultraviolet absorption after 20 sec. was very similar to that of the starting material III (Figure 1). Curve B (5 min.) was almost identical with that of the open amide (*anti*-II) in alkali shortly after mixing, and finally curve C was that of the benzodiazepine IV in alkali.

Further corroboration was obtained when III was treated with 2 equiv. of alkali at 0° in dimethoxyethane and aliquots were removed at intervals and quenched in

(1) Paper XXVI: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).

(2) Presented before the Division of Medicinal Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(3) (a) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1961 (1962). (b) L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *ibid.*, **29**, 332 (1964).

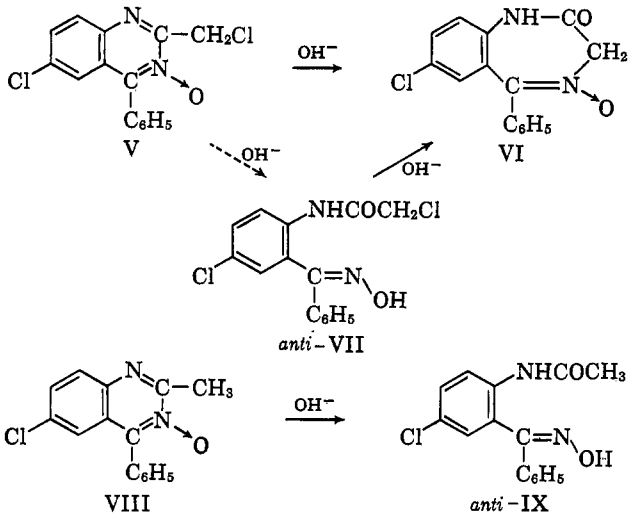
(4) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(5) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

dilute acid. Infrared spectra of the isolated crude product were measured in chloroform solution. The quinazoline 3-oxide (III) opened readily, and after 5 min. the infrared spectrum showed a very characteristic strong, sharp OH band at 3550 cm.$^{-1}$ (=NOH), the amide carbonyl band at 1710 cm.$^{-1}$, and the amide II at 1515 cm.$^{-1}$ indicative of the presence of the open amide oxime (*anti*-II). In addition, we followed the disappearance of the N-oxide band at 1300 cm.$^{-1}$ as the ring opened. As the seven-membered ring formed, the carbonyl band shifted to 1725 cm.$^{-1}$ and the amide II band at 1515 cm.$^{-1}$ disappeared. After 70 sec. quinazoline III and the acetamido oxime *anti*-II could be isolated, after 10 min. both acetamido oxime (*anti*-II) and benzodiazepine (IV), and after 30 min. only benzodiazepine IV could be isolated.

Sternbach and Reeder,[4] studying the analogous 2-chloromethylquinazoline 3-oxide (V), reported that treatment of V (Scheme II) with alkali resulted in ring expansion to product VI in good yield. It was also demonstrated that VI could be obtained by the reaction of the chloroacetamido *anti*-oxime (*anti*-VII) with alkali.

SCHEME II



In an attempt to show that *anti*-VII was an intermediate in the transformation of V to VI, several experiments analogous to those described above for the sequence III → *anti*-II → IV were carried out. When V was treated for 30 min. with less than 1 equiv. of alkali at 0° in dimethoxyethane, the only products isolated were VI and unreacted starting material (V). Similarly, following the reaction spectrophotometrically, the transformation of V to VI was so rapid that an ultraviolet spectrum measured at room temperature 5 min. after addition of a tenfold excess of alkali to a dilute solution (2×10^{-5} *M*) of V in isopropyl alcohol showed the absorption spectrum of VI only. The spectrum was also measured at shorter intervals, but at no time was an absorption spectrum similar to that of VII observed. In a third study, samples withdrawn from a reaction of V with 2 equiv. of alkali in dimethoxyethane at 0° were quenched with acid and the infrared spectra of the crude isolated products were then determined. The results were again the same. At no time was there any band attributable to an OH or amide II absorption which would indicate the presence of VII. This led to the conclusion that cyclization of *anti*-VII to VI was extremely rapid, and that the rate of ring closure (*anti*-VII → VI) was possibly even greater than the rate of hydrolytic cleavage (V → *anti*-VII). Compound *anti*-VII presumably existed for so short a time in both these experiments that its presence could not be demonstrated.

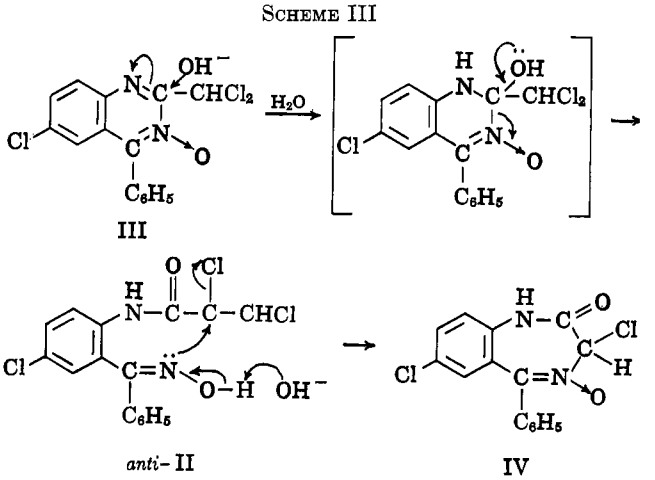
The extreme ease with which the quinazoline 3-oxide ring could be cleaved by alkali was demonstrated when 6-chloro-2-methyl-4-phenylquinazoline 3-oxide (VIII) was hydrolyzed to *anti*-IX in practically quantitative yield when treated with 2 equiv. of alkali in ethanol at room temperature. By following the change in ultraviolet spectrum, it could be seen that the ring opening was complete in less than 80 min.

A comparison of the infrared and n.m.r. spectra of the product with authentic samples prepared by acetylation of the *syn*- and *anti*-oximes of 2-amino-5-chlorobenzophenone showed that the product obtained by hydrolysis was indeed a derivative of the *anti*-oxime.[6]

The infrared spectrum in very dilute solution (0.2% in $CHCl_3$) showed intramolecular hydrogen bonding in the *anti*-oxime and little or none in the *syn*-oxime. In the n.m.r. spectrum, the NH proton of the *syn*-oxime appeared at $\delta = 9.72$ p.p.m. while the NH proton of the *anti* isomer was shifted to lower field ($\delta = 10.78$ p.p.m.) because of hydrogen bonding in the latter compound. These results were consistent with other observations of *syn*- and *anti*-oximes in these laboratories.[7]

Based on this evidence, the first step in the reaction of a 2-haloquinazoline 3-oxide (III) with alkali would be a nucleophilic attack by hydroxyl ion at carbon 2 (Scheme III). Ring opening to the 2-haloacetamido

SCHEME III



anti-oxime (*anti*-II) then occurs. This compound in turn, in the presence of more alkali then undergoes intramolecular N-alkylation with displacement of a chloride ion and cyclization to the 1,4-benzodiazepin-2-one derivative. In the case of the monohaloquinazoline 3-oxide, the facile displacement of the reactive halogen in the intermediate, the *anti*-oxime of the amide, results in only a transient existence for this

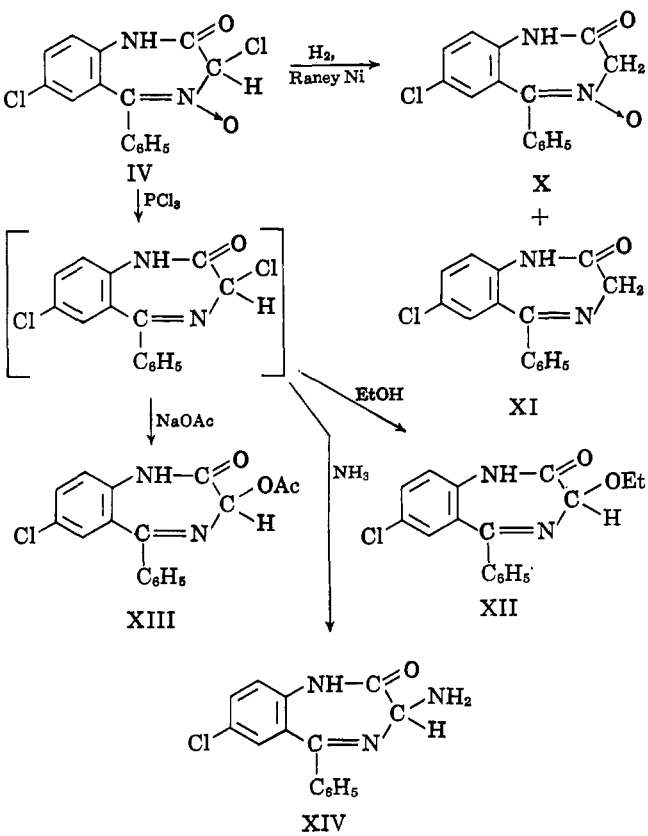
(6) The melting and mixture melting points were not very conclusive, possibly owing to transformation of the *anti*-oxime derivative into the acetamido *syn*-oxime while being heated.

(7) J. G. Pritchard, G. F. Field, K. Koch, G. Reymond, L. H. Sternbach, V. Toome, and S. Traiman, submitted for publication.

compound. The open amide cyclizes as rapidly as it is formed. Therefore, in the ultraviolet and preparative studies, the presence of only the benzodiazepin-2-one and unchanged quinazoline 3-oxide could be demonstrated. With the dichloroacetamido *anti*-oxime, the chlorine is less reactive and is therefore displaced at a slower rate. Since, in this case, the rate of cyclization is slower than the rate of open amide formation, it is possible to isolate the intermediate. In the reaction of the 2-methylquinazoline 3-oxide with alkali, the extreme ease with which the first step in the reaction, ring opening to an amido *anti*-oxime, occurs under relatively mild conditions could be seen.

The structural assignment for compound IV was based on the following evidence. The substance had an infrared spectrum (in KBr) characteristic of benzodiazepin-2-one 4-oxides: a strong carbonyl band at 1725 cm.$^{-1}$, a band at 1265 cm.$^{-1}$ generally associated with N-oxides, and the lack of any amide II bands. Conclusive evidence for the seven-membered lactam structure of IV was obtained by catalytic hydrogenation with Raney nickel catalyst (Scheme IV). The extremely labile chlorine in position 3 was removed first followed by hydrogenolysis of the oxygen in position 4. The two products isolated were the known benzodiazepin-2-ones X[4] and XI.[4]

SCHEME IV



Assignment of the 3-position for chlorine was based on the fact that reaction of IV with phosphorus trichloride to remove the 4-oxide followed by heating with ethanol gave the 3-ethoxy compound XII,[3a] reaction with sodium acetate yielded the corresponding 3-acetoxy derivative XIII,[3a] and reaction with ammonia gave the 3-amino derivative XIV.[8]

(8) American Home Products, French Patent 1,363,973 (April 16, 1962).

Compounds analogous to III and IV, but containing NO_2 or CF_3 in position 6 or 7, respectively, were also prepared in the same manner as shown in Scheme I.

Experimental Section[9]

2′-Benzoyl-2,2,4′-trichloroacetanilide *syn*-Oxime (*syn*-II).—To a solution of 100 g. (0.406 mole) of 2-amino-5-chlorobenzophenone *syn*-oxime (I) in 2 l. of ether, 500 ml. of water was added and the stirred mixture was cooled in an ice bath to 5°. Then 44 ml. (67.3 g., 0.455 mole) of dichloroacetyl chloride was added slowly, maintaining the temperature below +10° and keeping the reaction slightly alkaline by the simultaneous addition of 10% sodium hydroxide. The mixture was stirred for 30 min. in the cold after all of the dichloroacetyl chloride had been added. The ether layer was then separated, washed twice with 500-ml. portions of cold water, and dried over sodium sulfate. Most of the solvent was distilled off at atmospheric pressure and 100 ml. of benzene was added to the residue. The solvent was evaporated *in vacuo* to remove any water that remained. The residue was crystallized from benzene to give 122 g. (84%) of *syn*-II melting at 134–136°: ν^{CHCl_3} 3530 (OH), 3350 (broad, NH), 1705 (C=O), 1515 (amide II) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_2O_2$: C, 50.38; H, 3.11; Cl, 29.74. Found: C, 50.18; H, 3.12; Cl, 29.76.

This compound is polymorphic. In earlier work, a crystalline form melting at 108–109.5° was obtained. The infrared spectrum in solution was identical with that of material melting at 134–136°.

Anal. Found: C, 50.40; H, 3.48; Cl, 29.41.

2′-Benzoyl-2,2,4′-trichloroacetanilide *anti*-Oxime (*anti*-II).—*anti*-II was prepared from 100 g. (0.406 mole) of 2-amino-5-chlorobenzophenone *anti*-oxime in the same manner as above. It crystallized from benzene as colorless needles melting at 159–160°: yield 63.5 g. (43%); ν^{CHCl_3} 3550 (OH), 3380 (broad, NH), 1710 (C=O), 1520 (amide II) cm.$^{-1}$.

Anal. Found: C, 50.68; H, 3.13; Cl, 29.59.

2′-Benzoyl-2,2-dichloro-4′-nitroacetanilide *syn*-oxime (*syn*-NO_2-II) was prepared as above in 48% yield, m.p. 145–146°, as light yellow plates when crystallized from benzene.

Anal. Calcd. for $C_{15}H_{11}Cl_2N_3O_4$: C, 48.93; H, 3.01; N, 11.41. Found: C, 49.32; H, 3.24; N, 11.58.

2′-Benzoyl-2,2-dichloro-4′-trifluoromethylacetanilide *syn*-oxime (*syn*-CF_3-II) was prepared as above in 70% yield as colorless plates when crystallized from a mixture of benzene and hexane, m.p. 129–131°.

Anal. Calcd. for $C_{16}H_{11}Cl_2F_3N_2O_2$: C, 49.12; H, 2.83; N, 7.16. Found: C, 49.26; H, 2.70; N, 6.91.

6-Chloro-2-dichloromethyl-4-phenylquinazoline 3-Oxide (III). A. BF_3 as Condensing Agent.—To a solution of 122 g. (0.34 mole) of 2′-benzoyl-2,2,4′-trichloroacetanilide *syn*-oxime (*syn*-II) in 2 l. of benzene at about 50°, 60 ml. of boron trifluoride etherate was added slowly with stirring. The mixture was protected from atmospheric moisture with a calcium sulfate drying tube and heated to reflux. Within a few minutes white crystals began to appear. After refluxing for 6 hr. the reaction mixture was cooled and stirred with 1 l. of water. The benzene layer was separated and washed once with 1 l. of water and then twice with 500 ml. of 5% sodium bicarbonate. The aqueous layers were discarded and the organic phase was dried over sodium sulfate. Benzene was distilled off under reduced pressure and the yellow crystalline residue was stirred with 500 ml. of anhydrous ether and chilled, and the solid which was separated by filtration was dried in a vacuum oven at 40°. This gave 89.5 g. (77%) of III melting at 150–151°. Recrystallization from methanol or a mixture of methylene chloride and hexane gave yellow plates melting at 153–154°: ν^{CHCl_3} 1610 (w), 1545 (w), 1480 (m), 1300 (s, N→O) cm^{-1}.

6-Chloro-2-dichloromethyl-4-phenylquinazoline 3-oxide (III) was also prepared from the *anti*-oxime (*anti*-II) described above.

Anal. Calcd. for $C_{15}H_9Cl_3N_2O$: C, 53.05; H, 2.67; Cl, 31.32. Found: C, 53.20; H, 3.14; Cl, 31.64.

2-Dichloromethyl-6-nitro-4-phenylquinazoline 3-oxide (NO_2-III) was prepared from *syn*-NO_2-II by method A in 63% yield

(9) All melting points are corrected. The identity of compounds was determined by mixture melting point and comparison of infrared spectra. Structural changes were established by infrared, ultraviolet, and n.m.r. spectra. All infrared spectra were run in chloroform solution unless otherwise stated.

as yellow needles, m.p. 194–195°, when crystallized from a mixture of tetrahydrofuran and hexane.

Anal. Calcd. for $C_{15}H_9Cl_2N_3O_3$: C, 51.60; H, 2.60; Cl, 20.31. Found: C, 51.87; H, 2.77; Cl, 20.31, 20.28.

2-Dichloromethyl-4-phenyl-6-trifluoromethylquinazoline 3-oxide (CF_3-III) was prepared from *syn*-CF_3-II by method A in 56% yield and crystallized as yellow prisms from hexane, m.p. 163–165°.

Anal. Calcd. for $C_{16}H_9Cl_2F_3N_2O$: C, 51.50; H, 2.43; N, 7.51. Found: C, 51.18; H, 2.75; N, 7.54.

B. HCl as Condensing Agent.—A solution of 98 g. of 2′-benzoyl-2,2,4′-trichloroacetanilide *syn*-oxime (*syn*-II) in 1 l. of acetic acid was heated on a steam bath for 1.5 hr. while hydrogen chloride was bubbled through the solution. The reaction mixture was kept at room temperature for 16 hr. and then concentrated to dryness at reduced pressure. The residue thus obtained was dissolved in methylene chloride. This solution was washed with dilute sodium bicarbonate and water and then dried over sodium sulfate, and the solvent was distilled. On stirring the residue with ether, it crystallized to give 29 g. of crude III melting at 105–135°. The crude product was purified by passing a methylene chloride solution through a column of 250 g. of neutral alumina. Elution with methylene chloride gave a fraction which was recrystallized from a mixture of methylene chloride and hexane to give pure III melting at 153–154°.

3,7-Dichloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide (IV). A. From III.—A solution of 15 ml. of 2 *N* sodium hydroxide in 100 ml. of 1,2-dimethoxyethane was chilled to 0–5° and 5.0 g. (14.7 mmoles) of III was added. After 30 min. at this temperature, 100 ml. of water was added slowly while keeping the temperature below 10°. Then 3 *N* hydrochloric acid was added dropwise until the solution was neutral. The crystalline product was separated by filtration, washed with water, and dried over phosphorus pentoxide at reduced pressure to give 4.1 g. (87%) of IV melting at 194–195° dec. Recrystallization from a mixture of tetrahydrofuran and hexane gave colorless needles melting at 210–211° dec.: ν 3200 (NH), 3140 (NH), 1725 (C=O), 1490, 1270 (N→O) cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O_2$: C, 56.10; H, 3.14; Cl, 22.08; N, 8.72. Found: C, 55.93; H, 3.06; Cl, 21.30, 21.02; N, 8.67.

3-Chloro-1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (NO_2-IV) was prepared by method A from NO_2-III. It crystallized as light yellow plates from a mixture of tetrahydrofuran and hexane, m.p. 215–216°.

Anal. Calcd. for $C_{15}H_{10}ClN_3O_4$: C, 54.31; H, 3.04; N, 12.67. Found: C, 54.63; H, 3.03; N, 12.27.

Similarly, **3-chloro-1,3-dihydro-5-phenyl-7-trifluoromethyl-2H-1,4-benzodiazepin-2-one 4-oxide** (CF_3-IV) was obtained from CF_3-IV as colorless plates melting at 222–223° dec. when crystallized from a mixture of dimethoxyethane and hexane.

Anal. Calcd. for $C_{16}H_{10}ClF_3N_2O_2$: C, 54.17; H, 2.84; N, 7.89. Found: C, 54.17; H, 2.93; N, 7.90.

B. From *anti*-II.—A solution of 15 ml. of 2 *N* sodium hydroxide in 100 ml. of 1,2-dimethoxyethane was cooled to 0–5° and 5.0 g. (14.0 mmoles) of 2′-benzoyl-2,2,4′-trichloroacetanilide *anti*-oxime (*anti*-II) was added. After 30 min. at this temperature, the solution was diluted with 100 ml. of water and neutralized by the addition of 3 *N* hydrochloric acid. The crystalline product was filtered and dried over phosphorus pentoxide at reduced pressure to give 4.7 g. of crude IV melting at 206–207°. The infrared spectrum was identical with that of material prepared by method A.

Preparation of *anti*-II and IV from III.—A solution containing 5.0 g. (14.7 mmoles) of III in 100 ml. of dimethoxyethane was cooled to 0° and 15 ml. of 1 *N* sodium hydroxide was added slowly. After 40 min., 100 ml. of water was added and the reaction mixture was made slightly acidic by the addition of 3 *N* hydrochloric acid. The crystalline product was separated by filtration, washed with water, and dried over phosphorus pentoxide under reduced pressure. The product (4.8 g., m.p. 151–152° dec.) was stirred for 20 min. with 200 ml. of methylene chloride and filtered to remove 600 mg. of IV melting at 197–199° dec. An additional 200 mg. melting at 200–202° was recovered from the mother liquors (a total yield of 17%). The infrared spectra (in KBr) of both samples were identical with that of authentic IV. The methylene chloride filtrate was concentrated to dryness and the residue was crystallized from a mixture of benzene and hexane to yield 2.5 g. (48% yield) of *anti*-II melting at 150–152°. Recrystallization from benzene raised the melting point to 156–157° and gave a product identical with an authentic sample of *anti*-II as shown by mixture melting point, infrared spectrum, and R_f value on t.l.c.

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide (X) and 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XI).—A solution of 15 ml. of 2 *N* sodium hydroxide in 100 ml. of 1,2-dimethoxyethane was chilled to 0–5° and 5.0 g. (14.7 mmoles) of III was added. After 30 min. at this temperature, about 10–25 g. of Raney nickel was added and the mixture was hydrogenated at room temperature and atmospheric pressure. After about 15 mmoles of hydrogen had been absorbed, the reaction was stopped. The catalyst was separated by filtration and the filtrate was neutralized by the addition of 3 *N* hydrochloric acid. Most of the solvent was removed by concentration under reduced pressure and the residue was partitioned between methylene chloride and water. The organic layer was separated, dried over sodium sulfate, and concentrated to dryness. The residue crystallized from a mixture of acetone and hexane to give 1.55 g. (37%) of X as colorless plates melting at 228–230° dec. Recrystallization from ethanol gave a product melting at 234–235°, identical with an authentic sample.[3] The mother liquors obtained above were concentrated to dryness and the residue was crystallized from a mixture of acetone and hexane to give 150 mg. of material melting at 217–218°. This mother liquor was again taken to dryness and the residue was crystallized from ethyl acetate to give 400 mg. (10%) of XI melting at 207–209°. Recrystallization from ethyl acetate gave a product melting at 212–213.5° identical with an authentic sample.[4]

7-Chloro-1,3-dihydro-3-ethoxy-5-phenyl-2H-1,4-benzodiazepin-2-one (XII).—To a suspension of 4.7 g. of IV in 100 ml. of chloroform, 10 ml. of phosphorus trichloride was added. The mixture was stirred and heated to reflux for 30 min. and then concentrated to dryness under reduced pressure. The residue was partitioned between chloroform and ice-cold dilute sodium bicarbonate solution. After drying the organic layer over sodium sulfate, the solvent was distilled under reduced pressure. The residue was dissolved in 25 ml. of ethanol; the solution was refluxed for 5 min. and then concentrated to dryness. Crystallization of the residue from acetonitrile gave 800 mg. of product melting at 201–203° dec. The infrared spectrum (KBr) indicated the presence of an amine salt. The product was then partitioned between chloroform and dilute sodium bicarbonate, dried over sodium sulfate, and concentrated to dryness. Crystallization of the residue from acetonitrile gave 350 mg. of 7-chloro-1,3-dihydro-3-ethoxy-5-phenyl-2H-1,4-benzodiazepin-2-one melting at 221–223°. The material was identical with an authentic sample.[3a]

3-Acetoxy-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XIII).—A solution of 5.0 g. (15.5 mmoles) of IV in 100 ml. of chloroform and 10 ml. of phosphorus trichloride was allowed to react as described above. The crude deoxygenated product thus obtained was dissolved in 100 ml. of acetic acid containing 3.0 g. of anhydrous sodium acetate and the solution was heated at 80–90° for 10 min. Acetic acid was distilled at reduced pressure and the residue was partitioned between chloroform and water. The chloroform layer was washed with water and dilute sodium bicarbonate and dried over sodium sulfate, and solvent was then distilled. Crystallization of the residue from a mixture of methylene chloride and hexane gave 3.3 g. (65%) of crude XIII melting at 230–236° dec. Recrystallization from a mixture of methylene chloride and hexane gave a pure product identical with an authentic sample.[3a]

3-Amino-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (XIV).—The crude deoxygenated product obtained by the reaction of 15 g. of IV with phosphorus trichloride in chloroform as described above was dissolved in 500 ml. of dimethoxyethane and added slowly to 200 ml. of liquid ammonia at about −40°. The mixture was stirred and allowed to warm to room temperature overnight. The solid that had formed was separated by filtration, and the filtrate was concentrated to dryness at reduced pressure. The residue was partitioned between methylene chloride and dilute sodium carbonate. The organic layer was separated, washed with water, and dried over sodium sulfate. On concentration to a small volume, 2.0 g. of XIV crystallized (m.p. 195–197° dec.). The product, after recrystallization from acetonitrile, was identical with an authentic sample of XIV.[5]

2′-Benzoyl-4′-chloroacetanilide *anti*-Oxime (*anti*-IX) from VIII.—To a solution of 2.7 g. (10 mmoles) of VIII[5] in 180 ml. of

ethanol, 10 ml. of 2 *N* sodium hydroxide was added. After 20 hr. at room temperature, the solution was chilled, diluted with an equal volume of water, and neutralized by the addition of 10 ml. of 2 *N* hydrochloric acid. The crystalline product was removed by filtration and dried to give 2.4 g. (83%) of *anti*-IX melting at 186–186.5°. Recrystallization from methylene chloride did not alter the melting point. The product was identical with material prepared by the reaction of 2-amino-5-chlorobenzophenone *anti*-oxime with acetyl chloride as described below for the *syn* form.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54. Found: C, 62.56; H, 4.29.

2′-Benzoyl-4′-chloroacetanilide *syn*-Oxime (*syn*-IX) and 2′-Benzoyl-4′-chloroacetanilide *syn*-Oxime Acetate (XV).—A solution of 24.6 g. (0.1 mole) of 2-amino-5-chlorobenzophenone *syn*-oxime in 500 ml. of ether was stirred with 100 ml. of water and cooled to 0–5°. Acetyl chloride (14.2 g., 12.9 ml., 0.18 mole) was added dropwise over 40 min. while keeping the reaction slightly alkaline by the simultaneous addition of 10% sodium hydroxide. The ether layer was separated and washed with water. An insoluble crystalline material (XV) was separated by filtration of the ether layer. The crude product (5.4 g., m.p. 155–164°) was crystallized several times from chloroform to give colorless rods of XV, melting at 171–172.5°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_3$: C, 61.72; H, 4.57; N, 8.46. Found: C, 61.93; H, 4.61; N, 8.50.

The ether filtrate was dried over sodium sulfate and, on concentration, 16.8 g. of a mixture of *syn*-IX and XV melting at 152–176° crystallized. Recrystallization from chloroform gave mainly *syn*-IX (m.p. 179–182°, 6.9 g.). Further recrystallization from acetonitrile gave colorless plates of *syn*-IX melting at 182–184°. A mixture melting point with *anti*-IX showed a slight depression.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.54; N, 9.70. Found: C, 62.69; H, 4.47; N, 9.65.

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Reaction of α-Pinene Oxide with Zinc Bromide and Rearrangement of 2,2,3-Trimethyl-3-cyclopentene Products Derived Therefrom[1]

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Studies of zinc bromide catalyzed isomerization of α-pinene oxide resulted in formation of principally 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde in accordance with the report of Arbusow in 1935. Epoxides of esters of 2,2,3-trimethyl-3-cyclopentene-1-ethanol obtained from reduction of the aldehyde moiety were rearranged readily by acids to esters of 4-hydroxy-2,3,3-trimethyl-1-cyclopentene-1-ethanol.

In studies on isomerization of α-pinene epoxide (I) Arbusow[3] reported better than 90% yield of α-campholene aldehyde, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (II) by action of zinc bromide on the oxide. King and Farber noted the presence of 2,2,4-trimethyl-3-cyclopentene-1-acetaldehyde in addition to the 2,2,3 isomer II when the epoxide I was treated in quinaldine solution with *p*-toluenesulfonic acid (see Chart I). Hartshorn and collaborators[5] have recently reported on the acid-catalyzed rearrangement of I using boron trifluoride, zinc bromide, and hydrogen fluoride. With each catalyst they report a substantial yield of the 2,2,4 isomer. In reactions of the aldehyde II, no one apparently has observed rearrangement of this aldehyde by methyl group migration from the C-2 to the C-3 positions although Tiemann[6] reported such a rearrangement in the synthesis of α-campholenic acid, 2,2,3-trimethyl-3-cyclopentene-1-acetic acid (VII) from camphoroxime or campholenonitrile. The 2,2,3-trimethyl analog is readily converted to 2,3,3-trimethyl-1-cyclopentene-1-acetic acid (VIII). In fact, in repeating this work, it was difficult to avoid transformation of this sort.

In the course of studies of terpenes in this laboratory, an investigation on reactions of aldehyde II was undertaken to find new uses for turpentine. In order to duplicate the results of Arbusow,[3] this research involved a study of the reaction of zinc bromide on α-pinene epoxide (I). An important phase was the characterization of the reaction product or products since the results of earlier workers suggested three possible isomeric cyclopentene derivatives represented by III, IX, and XII (see Chart II). The aldehyde function of the principal product, 2,2,3-trimethyl-3-cyclopentene-1-acetaldehyde (II), was reduced to 2,2,3-trimethyl-3-cyclopentene-1-ethanol (III). For the purpose of characterization, alcohol III was compared with IX and XII. The alcohol III was considered an attractive intermediate since esters of mono- and polybasic acids might yield useful mono- and polyepoxides. In reactions of the epoxide XIII, formed by epoxidation of the acetate III, molecular rearrangements resulted in XIV and XVI.[7] The structural relationship of the cyclopentene compounds were confirmed by n.m.r. and infrared spectral analyses.

The reaction of α-pinene epoxide with freshly fused zinc bromide proceeded essentially in accordance with the results reported by Arbusow. Examination of the aldehyde by gas–liquid partition chromatography (g.l.p.c.) indicated it to be 96% pure. A second material was present to the extent of about 4%. Meerwein–Ponndorf and lithium aluminum hydride reductions of the aldehyde gave principally 2,2,3-trimethyl-3-cyclopentene-1-ethanol (III). G.l.p.c. analyses indicated the presence of two alcohols in a ratio of about

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(7) While this paper was being reviewed for publication, an article appeared which described essentially the same rearrangement: see D. J. Goldsmith and C. J. Cheer, *J. Org. Chem.*, **30**, 2264 (1965).