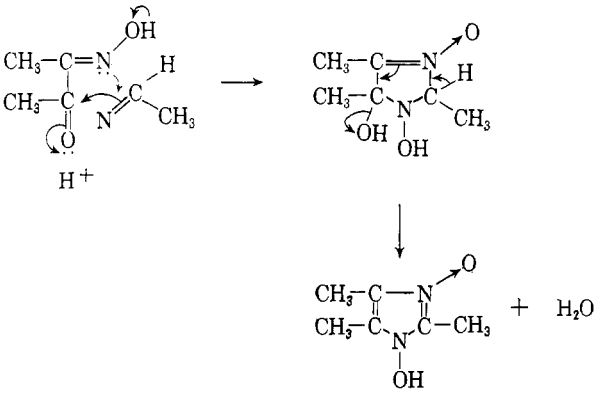
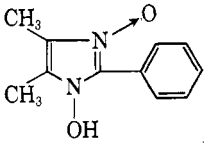
reduction product showed no depression in melting point when mixed with an authentic sample of 2,4,5-trimethylimidazole and the infrared spectra of the two were identical. The melting point of the hydrochloride of the reduction product showed no depression when mixed with 2,4,5-trimethylimidazole hydrochloride and their infrared spectra were also identical.

A possible mechanism for the formation of these compounds is as follows.



The only examples of 1-hydroxyimidazole 3-oxides in the literature appear in a publication by LaParola.[4] This author investigated the reaction between dimethylglyoxime and benzaldehyde, as well as other aromatic aldehydes, and obtained a substance possessing the formula $C_{11}H_{12}N_2O_2$. To this product he assigned the structure VI. The assignment of structure was based upon the fact that upon reduction with zinc and hydrochloric acid there was obtained 2-phenyl-4,5-dimethylimidazole.[5]



VI

Thus it would appear that 1-hydroxyimidazole 3-oxides can be prepared either by reaction of 2,3-butanedione monoxime with aldehyde oximes or by the reaction of dimethylglyoxime with aldehydes. The first step in these reactions may well be exchange of the oxime grouping between the aldehyde and the α-diketone.

Experimental[6,7]

1-Hydroxy-2,4,5-trimethylimidazole 3-Oxide.—A mixture of 20.0 g. (0.34 mole) of acetaldoxime and 34.2 g. (0.34 mole) of 2,3-butanedione monoxime was warmed to obtain a homogeneous solution. After standing at room temperature for 2 days, the mixture was refluxed 1 hr. and then diluted with 500 ml. of ether. The tan solid removed by filtration weighed 30.42 g. (63%), m.p. 194° dec. Two recrystallizations from 95% ethanol gave material melting constantly at 198° dec.

Anal. Calcd. for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.81; H, 6.87; N, 19.56.

Two grams of the product obtained above was dissolved in chloroform and the hydrochloride precipitated by the addition of an ethereal hydrochloric acid solution. There was obtained 2.14 g. of a tan solid melting at 131.5–133° and showing no depression when mixed with the material prepared by the action of hydrochloric acid on 2,3-butanedione monoxime. The infrared spectra of the two samples were also identical.

1-Hydroxy-2,4,5-trimethylimidazole 3-oxide hydrochloride was prepared in 38% yield by treated 2,3-butanedione monoxime with dry hydrogen chloride according to the procedure for Diels and Van der Leeden.[1] Recrystallization from butanone-2 gave prisms melting at 129.5–131.5°.

Anal. Calcd. for $C_6H_{10}N_2O_2 \cdot HCl$: Cl, 19.85; N, 15.69. Found: Cl, 20.06; N, 15.80.

Reduction of 1-Hydroxy-2,4,5-trimethylimidazole 3-Oxide with Sodium Hydrosulfite.—To 2.84 g. (0.02 mole) of 1-hydroxy-2,4,5-trimethylimidazole 3-oxide in 50 ml. of water was added 17.413 g. (0.1 mole) of sodium hydrosulfite. The mixture was heated under reflux for 3.5 hr. The solution was allowed to cool and was saturated with potassium carbonate and extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, and the ether was removed. There was obtained 0.76 g. of a white solid melting at 131.5–134.5°. Recrystallization from ether gave material melting at 133.5–133.5°. A mixture melting point with authentic 2,4,5-trimethylimidazole[8] (m.p. 134.5 135.5°) showed no depression. Addition of an ethereal hydrogen chloride solution to a solution of the reaction product in ether gave the hydrochloride, melting at 315° and showing no depression when mixed with an authentic sample of 2,4,5-trimethylimidazole hydrochloride (m.p. 314°).

1-Hydroxy-2-ethyl-4,5-dimethylimidazole 3-Oxide.—A mixture of 7.3 g. (0.1 mole) of propionaldoxime and 10.11 g. (0.1 mole) of 2,3-butanedione monoxime was warmed to 40° to obtain a homogeneous solution. After standing overnight, the mixture was refluxed for 3 hr. The viscous oil was triturated with ether and the resulting solid was removed by filtration. There was obtained 10.10 g. (65%) of a cream-colored solid melting at 190.5° dec. Recrystallization from 95% ethanol gave 8.20 g. of colorless prisms melting at 195° dec.

Anal. Calcd. for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.92; H, 7.46; N, 17.82.

(4) G. LaParola, *Gazz. chim. ital.*, **75**, 216 (1945).

(5) Very recently F. Miniscki, *et al.* [*Tetrahedron Letters*, 785 (1963)], described the preparation of 1-hydroxybenzimidazole 3-oxides by the reaction between nitrile oxides and aromatic nitroso derivatives. The properties of these compounds appear to be quite similar to those of 1-hydroxyimidazole 3-oxides; that is, they form a monohydrochloride salt readily, dissolve in aqueous alkali, and are reduced readily to benzimidazoles.

(6) Melting points are corrected.

(7) The author is indebted to Dr. George Slomp and Mr. Forest MacKellar for the n.m.r. spectral studies, to Dr. Gerald Umbreit and his coworkers for the pK_a data and for the microanalytic data, and to Miss Lorraine Pschigoda for infrared spectral studies. He is indebted also to Mr. Albert Lallinger for technical assistance.

(8) R. W. Cowgill and W. M. Clark, *J. Biol. Chem.*, **198**, 36 (1952).

Quinazolines and 1,4-Benzodiazepines. XX.[1] The Formation of 3-Phenylindole-2-carboxaldehydes from 2,3-Dihydro-1*H*-1,4-benzodiazepine 4-Oxides

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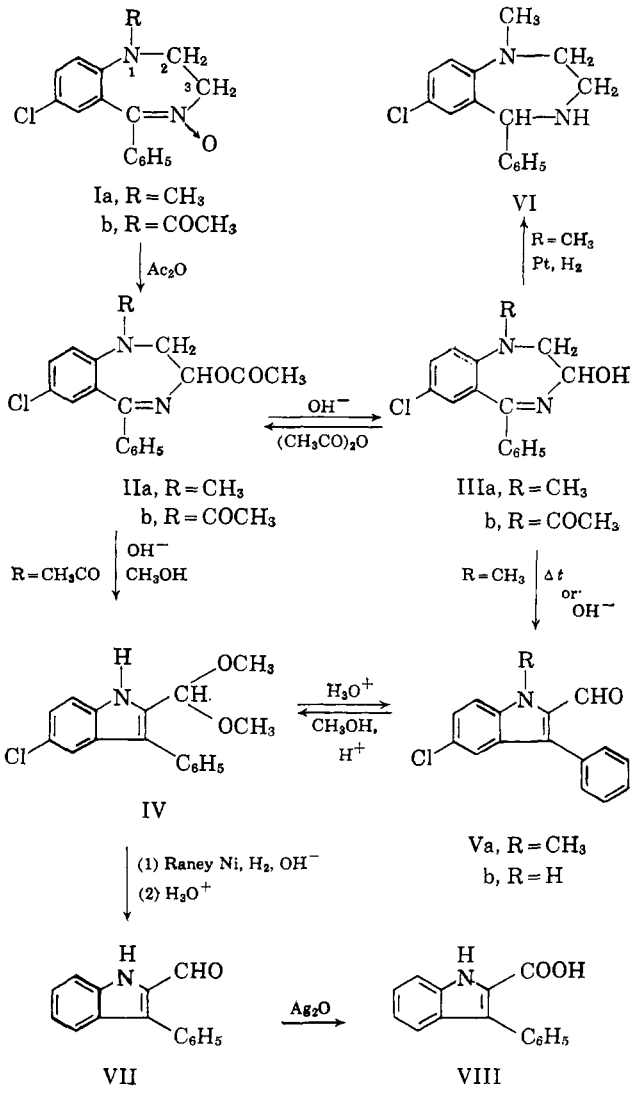
Recent interest in nitrones of type I[2] led us to investigate the rearrangement of these compounds with acetic anhydride. The products isolated contained an oxygen function in position 3 of the 1,4-benzodiazepine system. Their structure is in accordance with that postulated for intermediates in the Polonovski reac-

(1) Paper XVIII: L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *J. Org. Chem.*, **29**, 332 (1964); paper XIX: R. I. Fryer, B. Brust, J. Earley, and L. H. Sternbach, *J. Med. Chem.*, **7**, 386 (1964).

(2) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **28**, 2150 (1963); W. Metlesics, G. Silverman, and Leo H. Sternbach, *ibid.*, **28**, 2459 (1963).

SCHEME I



tion.[3] As in previously reported cases,[1,4] these rearrangement products could be isolated and their reactions are shown in Scheme I.

Alkaline hydrolysis of the rearrangement product IIb under mild conditions gave IIIb which could be reacetylated to IIb. The methyl derivative IIa could not be crystallized, and in a purification attempt on a basic alumina column the hydroxy derivative IIIa was isolated. The seven-membered ring structure of compound IIIa was proved by catalytic hydrogenation to VI.[5]

In an attempt to dehydrate IIIa by distillation *in vacuo* an almost quantitative yield of Va was obtained. This ring contraction showed that the hydroxy group in IIIa was in position 3.

The ring contraction of benzodiazepines of type II or III to indolecarboxaldehydes was also observed under a variety of hydrolytic conditions. These reactions led to the indolecarboxaldehyde derivatives IV, Va, and Vb. Alkaline hydrolysis of IIb in methanol gave a 70% yield of IV and a small amount of the corresponding aldehyde Vb. These ring contractions involve the loss of ammonia and the condensation of the methylene group (C-2) with the carbon bearing the phenyl group (C-5 in II or III). Since the acetal IV could not be obtained from V under the same conditions, it must be a product of direct solvolysis.

The structure of IV was proved by dehalogenation to VII which was oxidized with silver oxide to give the corresponding carboxylic acid VIII. This was identical with a sample prepared as reported in the literature.[6]

(3) R. Huisgen, F. Bayerlein, and W. Heydkamp, *Chem. Ber.*, **92**, 3223 (1959).

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

(5) For the preparation of this compound see L. H. Sternbach, E. Reeder, and G. A. Archer, *ibid.*, **28**, 2456 (1963).

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra of the compounds described were determined to establish structural changes. Identity was proved by mixture melting point and comparison of infrared spectra. The ultraviolet spectra were determined in isopropyl alcohol using a Cary Model 14 spectrophotometer.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine 4-Oxide (Ia).—A solution of 5.4 g. (0.02 mole) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine 4-oxide[2] in 100 ml. of dimethylformamide was prepared under dry nitrogen. To this solution 3.18 g. (0.066 mole) of a 50% suspension of sodium hydride in mineral oil was added with stirring and the bath temperature was raised to about 50°. After 1 hr. the mixture was cooled in an ice bath and 6 ml. (about 0.1 mole) of methyl iodide was added. The solution was kept at 25° for 18 hr. and poured into ice–water. After extraction with dichloromethane, an oil was obtained which crystallized on addition of a mixture of ether and petroleum ether (b.p. 30–60°) to give 3.9 g. of crystals melting at 133–139°.

Recrystallization from a mixture of methylene chloride and petroleum ether yielded 3 g. (53%) of yellow prisms melting at 140–143°. The product was also obtained in a second crystalline form melting at 169–172°, which showed identical spectral properties: λ_{max} 241 mμ (ε 23,000), 268 (16,000), and 306 (11,000).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27; N, 9.77. Found: C, 66.79; H, 5.40; N, 9.61.

3-Acetoxy-1-acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (IIb). A. From Ib.—A solution of 7.0 g. (0.022 mole) of Ib[2] in 60 ml. of acetic anhydride was refluxed for 7 hr. After evaporation of the acetic anhydride *in vacuo* the residue on addition of ether gave crystals which, after recrystallization from a mixture of methylene chloride and hexane, yielded 4.7 g. (59%) of white prisms melting at 177–179°, λ_{infl} 223 mμ (ε 30,000), λ_{max} 254 mμ (ε 13,000).

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3$: C, 63.96; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 63.70; H, 4.75; Cl, 10.00; N, 7.99.

B. From IIIb.—A solution of 0.05 g. of IIIb in 2 ml. of acetic anhydride was kept at 25° for 17 hr. The acetic anhydride was evaporated *in vacuo* and the residue crystallized from ether to give white prisms melting at 170–175° which were identified with IIb.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepin-3-ol (IIIa).—A solution of 3.5 g. (0.012 mole) of Ia in 12.5 ml. of acetic anhydride was heated for 110 min. at a bath temperature of *ca.* 115°. The acetic anhydride was removed *in vacuo*, and the residue was dissolved in a mixture of 15 ml. of 2 *N* sodium hydroxide and 100 ml. of acetone. After 10-min. standing at 25° the acetone was removed *in vacuo* (bath temp. *ca.* 50°), and the aqueous phase was extracted with methylene chloride. The methylene chloride solution was dried with sodium sulfate and evaporated to give a crystalline residue which, after recrystallization from a mixture of methylene chloride and petroleum ether, melted at 155–157° dec. The yield was 1.2 g. (34%), λ_{max} 228 mμ (ε 19,000) and 249 (17,000).

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.01; H, 5.27; N, 9.77. Found: C, 67.16; H, 5.66; N, 9.73.

1-Acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepin-3-ol (IIIb).—To a solution of 1.78 g. (0.005 mole) of IIb in 50 ml. of methanol 10 ml. of 1 *N* aqueous sodium hydroxide was added dropwise over a period of 10 min. The solution was concentrated *in vacuo* without heating and extracted with dichloromethane. On concentration of the methylene chloride and addition of ether,

(6) R. Manske, W. Perkin, and R. Robinson, *J. Chem. Soc.*, 1 (1927).

1.0 g. (63%) of white prisms was obtained which melted at 170–171° dec., λ_{infl} 220 mμ (ε 38,000), λ_{max} 253 mμ (ε 13,000).

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 65.44; H, 5.22; N, 8.87.

5-Chloro-3-phenylindole-2-carboxaldehyde Dimethylacetal (IV).—A solution of 4.5 g. (0.13 mole) of IIb in 150 ml. of methanol and 50 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 3 hr. The solution was concentrated *in vacuo* and extracted with methylene chloride. The methylene chloride was removed and on addition of petroleum ether 3.1 g. of crystals were obtained which, on recrystallization from a mixture of ether and petroleum ether gave 0.1 g. of yellow needles melting at 231–237° (see Vb below).

From the mother liquor, 2.6 g. (69%) of white prisms was obtained which melted at 134–137°, λ_{max} 229 mμ (ε 35,000) and 267 (11,000).

Anal. Calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64; CH_3O, 20.6. Found: C, 68.11; H, 5.80; N, 4.68; CH_3O, 20.9.

This compound was also obtained from Vb by heating in methanol with *p*-toluenesulfonic acid as catalyst.

5-Chloro-1-methyl-3-phenylindole-2-carboxaldehyde (Va). A. From Vb.—To a solution of 0.5 g. (0.002 mole) of Vb in 10 ml. of dimethylformamide was added 0.2 g. (0.004 mole) of a 50% suspension of sodium hydride in mineral oil. The mixture was kept for 15 min. at 36–40°, cooled to 25°, and 0.28 ml. of methyl iodide was added. After 15 min. the solution was poured into water and filtered from the precipitate, which was recrystallized from a mixture of methylene chloride and petroleum ether to give 0.23 g. (43%) of yellow needles melting at 156–159°, λ_{max} 252 mμ (ε 30,000) and 318 (22,500).

Anal. Calcd. for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.42; H, 4.72; N, 5.04.

B. From IIIa.—Hydrolysis of IIIa under basic conditions gave Va in moderate yield. However, an almost quantitative yield of Va was obtained in an attempt to distil IIIa in a bulb tube (0.1 mm., bath temp. *ca.* 150°).

5-Chloro-3-phenylindole-2-carboxaldehyde (Vb). A. From IIIb.—A solution of 0.5 g. (0.0016 mole) of IIIb in 10 ml. of methanol, 1 ml. of water, and 2 ml. of 1 *N* aqueous sodium hydroxide was refluxed for 2.5 hr., and evaporated. The residue was taken up in methanol, and hydrochloric acid was added. A yellow precipitate which formed was collected on a filter and recrystallized from methylene chloride to give 0.2 g. of yellow needles (Vb) melting at 237–240°, λ_{max} 251 mμ (ε 31,000) and 320 (24,000).

Anal. Calcd. for $C_{15}H_9ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.56; H, 3.96; N, 5.49.

B. From IV.—A solution of 0.5 g. of IV in 15 ml. of methanol and 15 ml. of 1 *N* hydrochloric acid was heated to reflux for 5 min. Yellow crystals precipitated which melted at 235–240° and were identified with Vb.

7-Chloro-2,3,4,5-tetrahydro-1-methyl-1*H*-1,4-benzodiazepine (VI).—A solution of 1.7 g. (0.006 mole) of IIIa in 50 ml. of acetic acid was hydrogenated at 25° and 1 atm. using 0.2 g. of platinum oxide as catalyst. After an uptake of 335 ml. (*ca.* 0.014 mole) the hydrogen absorption had slowed down to a rate of *ca.* 20 ml. per hr. The solution was poured on ice, made basic with aqueous sodium hydroxide, and extracted with ether. The ether solution was evaporated, and the residue was extracted with boiling heptane. Addition of hydrogen chloride in ether precipitated crystals which, after recrystallization from a mixture of ethanol and ether, melted at 240–250° (VI).[5]

3-Phenylindole-2-carboxaldehyde (VII).—A solution containing 2.4 g. (0.008 mole) of IV and 8 ml. of 1 *N* sodium hydroxide in 100 ml. of ethanol was hydrogenated at atmospheric pressure and 25° using *ca.* 5 g. of Raney nickel as catalyst. The uptake stopped after the consumption of 170 ml. (*ca.* 0.007 mole) of hydrogen. The solution was filtered from the catalyst and evaporated *in vacuo*. The residue was shaken with dilute hydrochloric acid and extracted with ether. The ether solution on evaporation gave a crystalline residue which, after recrystallization from a mixture of methylene chloride and methanol, gave pale yellow needles melting at 195–197°. The yield was 1 g. (56%); λ_{max} 230 mμ (ε 16,500), 250 (22,500), and 320 (21,000).

Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01. Found: C, 81.51; H, 4.95.

3-Phenylindole-2-carboxylic Acid (VIII).—To a solution of 0.11 g. of VII in a mixture of 30 ml. of ethanol and 20 ml. of acetone was added 0.17 g. of silver nitrate and 15 ml. of 0.1 *N* aqueous sodium hydroxide. The solution was stirred at 25° for 17 hr. and filtered, and the filtrate was concentrated *in vacuo*. The residue was dissolved in dilute sodium hydroxide, and the solution was extracted with ether. On acidification of the aqueous layer a precipitate formed which was collected on a filter, dried, and recrystallized from a mixture of ether and petroleum ether. White prisms melting at 188–190° were obtained in *ca.* 34% yield (*ca.* 0.04 g.) and found to be identical with an authentic specimen.[6]

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Dr. V. Toome and Mr. S. Traiman for the determination of ultraviolet and infrared spectra.

Formation of 3-Substituted 2-Thio-4-oxo-hexahydro-1,3-diazines and 2-Substituted Imino-6-oxo-1,3-thiazanes from 1-Substituted 3-Carboxyethylthioureas and Interconversion of Both Cyclic Systems

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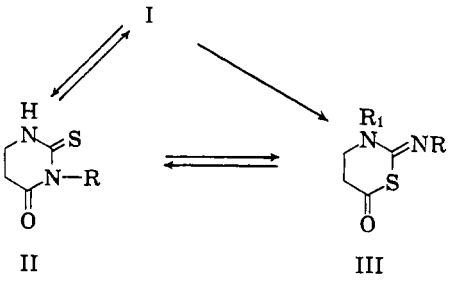
Recently we have described the cyclization of 3-carboxyethylthioureas (I),[1] and as a part of a continuing study we wish to report some further details and the interconversion of both cyclic systems, *e.g.*, 3-substituted 2-thio-4-oxo-hexahydro-1,3-diazines (II) to 2-substituted imino-6-oxo-1,3-thiazanes (III, $R_1 = H$) and *vice versa*.

$$R{-}NH{-}CS{-}NH{-}CH_2CH_2COOH$$



When the cyclization is carried out in acetic anhydride at 90–95°, the preponderant product is the thiazine derivative. From the mother liquor it is possible to isolate the diazine. Presented in Table I

TABLE I

SIMULTANEOUS FORMATION OF THIAZINE AND DIAZINE DERIVATIVES

R	Thiazines (III), yield, % $R_1 = H$	Thiazines (III), yield, % $R_1 = CH_3CO$	Diazines (II), yield, %	Ratio of III-II, mole
o-Tolyl	70		17	1:0.24
p-Methoxyphenyl		72.5	3.9	1:0.06
p-Ethoxyphenyl	68		7.6	1:0.11
o-Chlorophenyl	89.5		~1	1:0.01
m-Chlorophenyl		54.5	12.8	1:0.28
p-Chlorophenyl	90		8	1:0.10

(1) M. Derzaj-Bizjak, S. Oblak, and M. Tišler, *J. Org. Chem.*, **27**, 1343 (1962).