TABLE I

PER CENT YIELD IN BROMINATION OF QUINOLINE–ALUMINUM CHLORIDE COMPLEX

Bromination process	5-Bromo-[a]	5,6-Dibromo-	5,8-Dibromo-	5,6,8-Tribromo-
Mono-	46	3	8	
Di-		9	62	
Tri-		10	41	9

[a] Appreciable amounts of 8-bromoquinoline were noted.

To demonstrate that the introduction of gaseous bromine gave better selectivity the following two compounds were synthesized.

5,8-Dibromoquinoline.—The complex of quinoline (0.56 mole) and aluminum chloride (1.7 moles) was brominated at 80° with bromine vapor (0.6 mole) for 6 hr. and at 110° with more bromine vapor (0.6 mole). The usual isolation gave 144 g. (86%) of 5,8-dibromoquinoline, m.p. 120–125°. Purification by the countercurrent extraction procedure gave the pure compound, m.p. 126–128°, in approximately 70% yield.

5,6,8-Tribromo- and 5,6,7,8-Tetrabromoquinoline.—The complex of 5,8-dibromoquinoline (0.07 mole) and aluminum chloride (0.21 mole) was brominated at 145° with gaseous bromine (0.08 mole) over a period of 2 hr. The usual isolation procedure gave the crude tribromo compound in 78% yield, m.p. 145–150°. The crude compound was sublimed. Since the compound did not dissolve in benzene, the finely ground crystals were leached with a series of 5% hydrochloric acid solutions, followed by a series of 10% hydrochloric acid solutions. The extracted samples of m.p. 157–159° obtained by neutralization of the acid and filtration were combined. The reported melting point of 5,6,8-tribromo[20] is 159° and of 5,7,8-tribromoquinoline[21] is 141°. The remaining crude product from the extraction was leached with 20% hydrochloric acid and yielded a new compound which was probably 5,6,7,8-tetrabromoquinoline, recrystallized from amyl acetate, m.p. 241–243°.

Anal. Calcd. for $C_9H_3NBr_4$: Br, 71.85. Found: Br, 71.37.

5,6,7,8-Tetrachloroquinoline.—The complex of 5,8-dichloroquinoline (m.p. 97–98°, 0.09 mole, made by the swamping catalyst method) and aluminum chloride (0.27 mole) was chlorinated at 150° with chlorine (0.18 mole) over a period of 4 hr. The usual isolation followed by sublimation gave 22 g. (91%) of white crystals, m.p. 185–187°. The usual absorption band for the three adjacent hydrogen atoms at 12.7 μ was found in the infrared.

Anal. Calcd. for $C_9H_3NCl_4$: Cl, 53.10. Found: Cl, 52.93.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this work.

(20) A. Claus, *J. prakt. Chem.*, [2] **53**, 30 (1896).

(21) A. Claus and A. Ammelburg, *ibid.*, [2] **50**, 35 (1894).

Quinazolines and 1,4-Benzodiazepines. XVIII.[1] The Acetylation of Chlordiazepoxide[2] and Its Transformation into 6-Chloro-4-phenyl-2-quinazolinecarboxaldehyde[3]

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Acetylation of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide gave three products, the normal N-acetyl derivative (II), a 3-acetoxy compound (III) produced by rearrangement of the N-oxide, and the diacetyl compound (IV). In acidic medium, 1,4-benzodiazepines bearing an oxygen in position 3 rearranged to the corresponding 2-quinazolinecarboxaldehyde. The structures of these compounds were proved and the general applicability of the reactions is discussed.

A study of the acetylation of chlordiazepoxide[2] (I) led to the discovery that under varying reaction conditions three different products could be obtained, the normal N-acetylated reaction product,[4] described earlier, an isomeric monoacetyl derivative, and a diacetyl derivative, respectively.

Acetylation of I with acetic anhydride in pyridine at room temperature yielded the N-acetylated product (II), while reaction with acetyl chloride in DMF[5] gave an isomeric monoacetyl derivative which has been found to be 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III), formed by rearrangement of the N-oxide to a compound bearing an oxygen on the adjacent carbon atom. Under more energetic reaction conditions (heating with acetic anhydride, with or without pyridine), the diacetyl compound (IV) was obtained. (See p. 333, col. 1.)

The rearrangement of I to III is analogous to the Polonovski rearrangement of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide to the corresponding 3-acetoxy compound VI.[6]

Assignment of structures II, III, and IV was readily made on the basis of the characteristic infrared spectra of the three compounds.[7] The absence of any bands in the NH region and the presence of an amide carbonyl band at 1683 cm.$^{-1}$ confirmed the chemical structural proof[4,8] of II, while a strong NH stretching band[9] at 3480 cm.$^{-1}$ and a typical ester carbonyl band at 1758 cm.$^{-1}$ were consistent with the structure postulated for III. The diacetyl derivative (IV) showed both an amide carbonyl band at 1680 cm.$^{-1}$ and an ester carbonyl band at 1758 cm.$^{-1}$.

The structure of the rearrangement products was confirmed by hydrolysis of the diacetyl derivative IV with one equivalent of acid to VI.[6] Hydrolysis of compound IV with 2 moles of alkali at room temperature led to the hydroxy derivative V [ν (cm.$^{-1}$) 3550 (OH), 3440 (NH)]. This compound could be reacetylated to yield compound III.

(1) Paper XVII, R. I. Eryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, in press.

(2) Generic name for 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (Librium(R)).

(3) (a) While this paper was being prepared, an abstract of a paper by S. C. Bell, C. Gochman, and S. J. Childress appeared in Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963, p. 37-O, indicating that its contents probably overlap, in part, the material described in this paper. (b) NOTE ADDED IN PROOF.—See S. C. Bell, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **28**, 3010 (1963).

(4) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

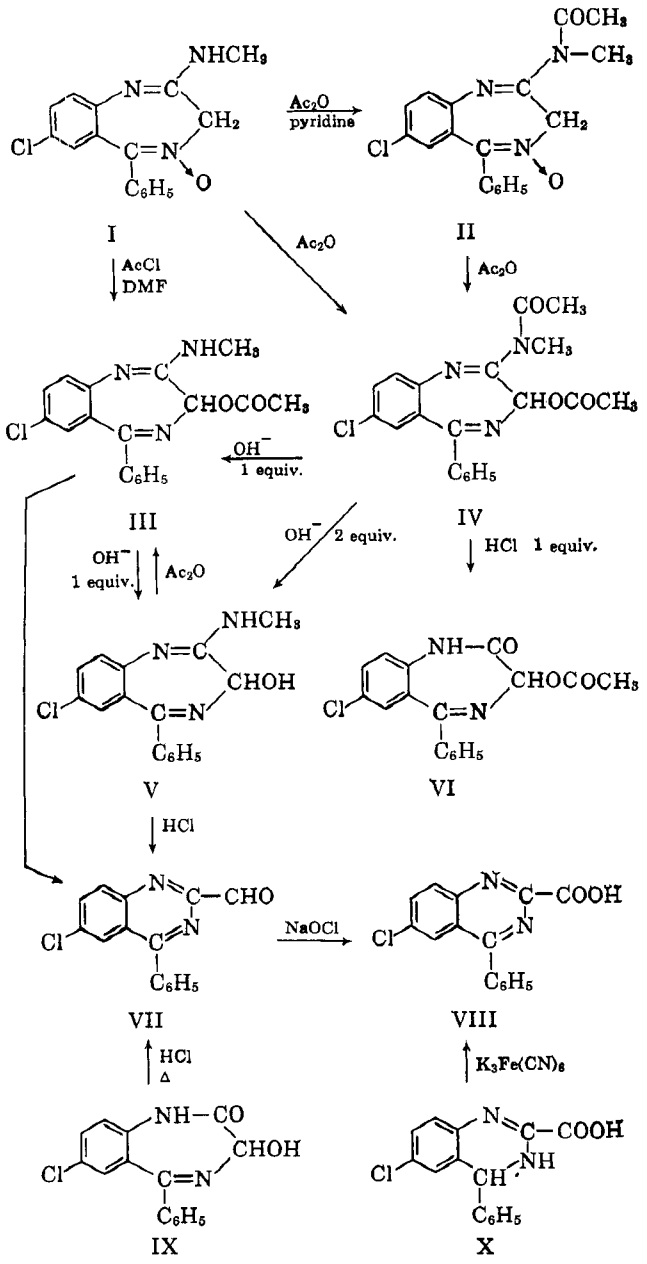
(5) DMF is N,N-dimethylformamide.

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

(7) All infrared spectra were determined in 3% solution in chloroform unless otherwise noted.

(8) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

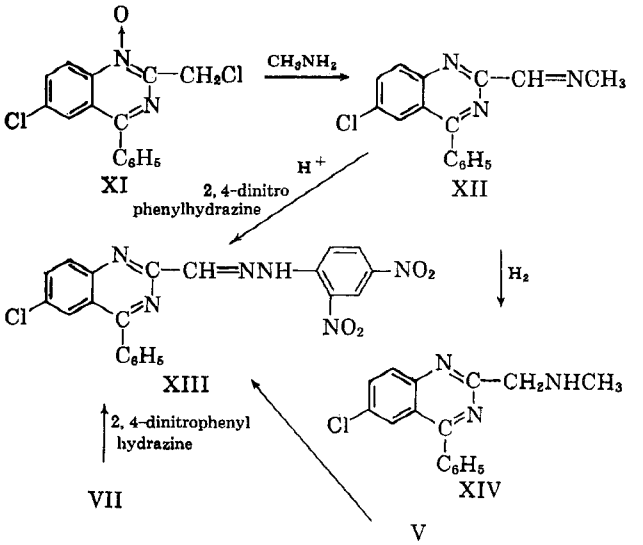
(9) Chlordiazepoxide (I) itself shows a weak band in this region (3474 cm.$^{-1}$). The intensity of this absorption band increases with dilution (3% → 0.3%) indicating intermolecular bonding.



An interesting rearrangement, confirming the potential aldehyde character of C-3 in III, V, and IX,[6] occurred on treatment of these compounds with mineral acid. The methylamino group was lost in III and V and a ring contraction occurred, resulting in the formation of quinazoline aldehyde VII (strong carbonyl stretching band at 1728 cm^{-1}). Under the same conditions compound IX yielded the same aldehyde (VII). When the hydrolysis was carried out in alcohol, VII was isolated as the hemiacetal. The structure of the aldehyde (VII) was proved by its oxidation to the quinazoline carboxylic acid (VIII) ,which was shown to be identical with the one obtained by oxidation of the 3,4-dihydro derivative (X).[6]

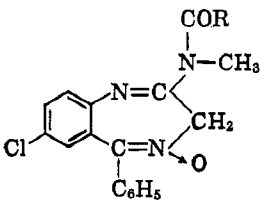
A second proof of structure of the quinazoline aldehyde (VII) was based on the rearrangement of XI[10] with methylamine to the methylimine (XII), a compound which also could be obtained from VII by treatment with methylamine. The rearrangement of XI to XII is reminiscent of the reaction of α-picoline

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

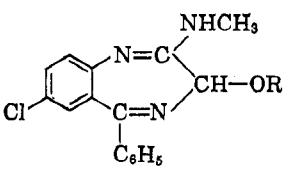


N-oxide with acetic anhydride.[11] However, the fact that it occurs under basic conditions suggests that a different mechanism may be involved. On catalytic reduction of XII, the known compound XIV[12] was isolated thus proving the structure of XII. Treatment of XII with 2,4-dinitrophenylhydrazine in an acidic medium gave the hydrazone (XIII). This compound was identical with the hydrazone prepared from VII and V.

Further study of the acylation of chlordiazepoxide (I) showed that on acylation with various acylating agents, depending on the reaction conditions, the N-acyl or O-acyl derivatives were obtained.[13] The propionyl and butyryl compounds (XVa,b and XVIa,b) were prepared in the same way as the corresponding acetyl derivatives. However, benzoyl chloride in pyridine or DMF gave only the ester XVIc.



XVa,b



XVIa,b,c
a, R = propionyl
b, R = butyryl
c, R = benzoyl

Walker,[14] on acetylation of 7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-oxide, obtained a product to which he ascribed the N-acetyl structure (XVII). Since no experimental data were given and, since his infrared data [λ^{Nujol} 3.05, 5.74, 6.14, 6.23 μ = ν^{Nujol} ($cm.^{-1}$) 3279, 1742, 1629, 1605] suggested this compound to be the 3-acetoxy derivative, we studied this acetylation and found that as in the earlier discussed cases two acetylation products could be obtained. Using acetic anhydride in pyridine as acetylating agent we obtained the normal N-acetyl

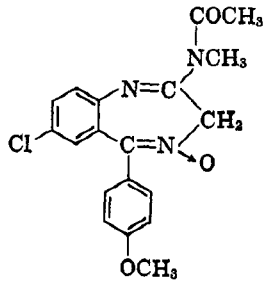
(11) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954).

(12) Described as the hydrochloride by S. C. Bell, C. Gochman, and S. J. Childress, *J. Med. Pharm. Chem.*, **5**, 63 (1962).

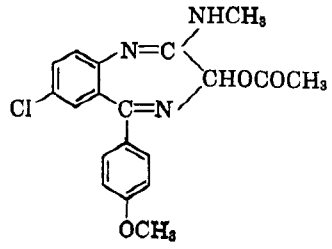
(13) The structure assignment was based on the presence of the characteristic ester carbonyl band at 1760–1740 $cm.^{-1}$, the amide carbonyl band at 1690–1680 $cm.^{-1}$, and the NH band at 3480–3410 $cm.^{-1}$ in the infrared spectrum.

(14) G. N. Walker *J. Org. Chem.*, **27**, 1930 (1962).

derivative (XVII) [ν^{CHCl_3} (cm.$^{-1}$) 1680, 1620, 1605]. On acetylation with acetyl chloride in DMF we obtained the 3-acetoxy derivative (XVIII), which showed the same infrared absorption bands as reported by Walker for his acetyl derivative[14,15] [ν^{CHCl_3} (cm.$^{-1}$) 3410, 1745, 1620, 1598 and ν^{Nujol} (cm.$^{-1}$) 3270, 1745, 1623, 1605]. This indicates that the compound reported by Walker is in fact the 3-acetoxy derivative (XVIII).



XVII



XVIII

The study of the acetylation of other 2-methylamino-5-phenylbenzodiazepine 4-oxides has led to the finding that the course of this reaction is quite general; acetic anhydride in pyridine at room temperature yields the normal N-acetyl derivatives, whereas acetyl chloride in DMF leads to the rearranged 3-acetoxy compounds.

Experimental

All melting points are corrected and were determined in a Thomas–Hoover melting point apparatus. The infrared spectra were determined in 3% chloroform solution unless otherwise indicated. Identity of compounds was established by mixture melting point and comparison of infrared spectra.

3-Acetoxy-7-chloro-2-(N-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine (IV). A.—A solution of 31 g. (0.103 mole) of I[4] in a mixture of 360 ml. of pyridine and 180 ml. of acetic anhydride was heated to 50° for 20 min. then left at room temperature for 4 days. After concentration *in vacuo* to a small volume, the residue was treated with ether and petroleum ether,[16] which caused the precipitation of crystals. The first fraction isolated (19.1 g., 54%) consisted of almost pure 7-chloro-2-(N-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (II).[4] After the addition of more petroleum ether a second fraction (11.8 g.) was obtained which melted below 140°. Repeated recrystallization from ether or a mixture of methylene chloride, ether, and petroleum ether, gave 8.7 g. (34%) of pure 3-acetoxy-7-chloro-2-(N-methylacetamido)-5-phenyl-3*H*-1,4-benzodiazepine (IV). The product was dimorphic and formed colorless prisms melting at 145–146° or at 159–160° [ν (cm.$^{-1}$) 1758, 1680].

B.—A solution of 10 g. (29.3 mmoles) of II[4] in 25 ml. of acetic anhydride was heated for 10 min. to 80°. The solution was concentrated *in vacuo* and the residue recrystallized from a mixture of acetone and petroleum ether. The first fraction consisted of 3.6 g. of unchanged starting material. After the addition of more petroleum ether, 4.7 g. (42%) of crude crystalline IV was obtained. The product was purified as described previously.

Anal. Calcd. for $C_{20}H_{18}ClN_3O_3$: C, 62.58; H, 4.73; O, 12.51; acetyl, 22.43. Found: C, 62.56; H, 4.47; O, 12.91; acetyl, 22.81.

3-Acetoxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (III) Hydrochloride.—To a solution of 64 g. (0.214 mole) of I in 600 ml. of dimethyl formamide, 25.2 ml. (0.354 mole) of acetyl chloride was added with cooling. Crystallization began after a short time and after about 1 hr. 44 g. (54%) of III hydrochloride was separated by filtration. After recrystallization from a mixture of ethanol and petroleum ether the product formed colorless needles melting at 212–213°.

Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O_2$: C, 57.15; H, 4.53. Found: C, 56.99; H, 4.80.

Free Base (III). A.—The free base prepared from III crystallized from a mixture of methylene chloride and ether to yield colorless prisms melting at 202–203° [ν (cm.$^{-1}$) 3480, 1758].

B.—A solution of 3.8 g. (0.01 mole) of IV in 50 ml. of dioxane was treated with 10 ml. of 1 *N* sodium hydroxide. After 1.5 hr. at room temperature, the mixture was concentrated *in vacuo* to a small volume and diluted with water and ether. The ether layer was separated, dried, concentrated to a small volume, and the precipitated crystals filtered off. Thus, 1.3 g. (34%) of colorless prisms were obtained, which after recrystallization from acetone proved to be identical with the material prepared by method A.

Anal. Calcd. for $C_{18}H_{16}ClN_3O_2$: C, 63.25; H, 4.72: N, 12.30; acetyl, 12.6. Found: C, 63.12; H, 4.77; N, 12.46; acetyl, 12.94.

7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepin-3-ol (V). A.—A solution of 3.4 g. (0.01 mole) of III in a mixture of 50 ml. of dioxane and 10 ml. of 1 *N* sodium hydroxide was stirred at room temperature for 4 hr. and then concentrated *in vacuo* to a small volume. Water was added and the reaction product was extracted with methylene chloride. The organic layer was dried, concentrated *in vacuo*, and the residual oil was crystallized from ether. After recrystallization from a mixture of methylene chloride and petroleum ether, 2.6 g. (87%) of colorless needles melting at 184–186° were obtained. The product is dimorphic and when recrystallized from dilute dimethylformamide forms colorless prisms melting at 191–192° dec. [ν (cm.$^{-1}$) 3550, 3440]. The product (V) could be reconverted into the O-acetyl derivative (III) by treatment at room temperature with an excess of acetic anhydride in pyridine.

B.—Compound V also was obtained by the same procedure from the diacetyl derivative (IV) using 2 moles of alkali for the hydrolysis.

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; N, 14.02. Found: C, 64.11; H, 4.98; N, 13.58.

3-Acetoxy-7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (VI).—A solution of 1.9 g. (0.005 mole) of IV in a mixture of 50 ml. of dioxane and 5 ml. of 1 *N* hydrochloric acid was heated within 5 min. to 50°. The reaction mixture was cooled to room temperature, concentrated *in vacuo* to a small volume, neutralized with 5 ml. of 1 *N* sodium hydroxide, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo*. Crystallization of the residue from ether yielded 0.3 g. (17%) of crude VI. On recrystallization from acetone, the pure product was obtained and proved to be identical with a sample prepared as described in the literature[6] [ν^{KBr} (cm.$^{-1}$), 3230, 1750, 1723].

7-Chloro-2-(N-methylpropionamido)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (XVa).—Treatment of I with propionic anhydride in pyridine, as described for the acetyl derivative[4], gave the N-propionyl derivative (XVa) as colorless prisms, recrystallized from a mixture of methylene chloride and acetone, melting at 213–214° [ν (cm.$^{-1}$) 1685].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 64.13; H, 5.10; Cl, 9.97. Found: C, 64.76; H, 5.12; Cl, 9.98.

7-Chloro-2-methylamino-5-phenyl-3-propionoxy-3*H*-1,4-benzodiazepine (XVIa).—To a solution of 12 g. (0.04 mole) of I in 100 ml. of dimethylformamide, 5.5 g. (0.06 mole) of propionyl chloride was added. The solution was cooled, left at room temperature for 1 hr., then diluted with ice–water and dilute sodium hydroxide. The mixture was extracted with methylene chloride, the organic layer washed with water, dried, and concentrated *in vacuo*. Crystallization from ether or from a mixture of ether and petroleum ether gave 3.5 g. (25%) of XVIa as colorless prisms melting at 197–198° [ν (cm.$^{-1}$) 3480, 1760].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_2$: C, 64.12; H, 5.10; N, 11.81. Found: C, 64.15; H, 5.38; N, 11.70, 11.71.

7-Chloro-2-(N-methylbutyramido)-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (XVb).—Six grams (0.02 mole) I was treated with 3 ml. (0.029 mole) of butyryl chloride in 75 ml. of pyridine. The reaction mixture was worked up as described for XVa and yielded colorless prisms of XVb melting at 169–170°, when crystallized from ether or acetone [ν (cm.$^{-1}$) 1685]. The compound gave a melting point depression with isomeric XVIb.

Anal. Calcd. for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.45. Found: C, 65.07; H, 5.48.

3-Butyryloxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XVIb).—Compound XVIb was prepared, using butyryl chloride as acylating agent, in the same manner as described

(15) The melting point of our product is 202–203° and not as reported by Walker 218.5–219.5°. This could possibly be due to dimorphism.

(16) In all cases petroleum ether indicates a fraction boiling at 30–60°.

for XVIa. It formed colorless crystals melting at 171–172°. The compound gave a melting point depression with the isomeric XVb [ν (cm.$^{-1}$) 3470, 1750].

Anal. Calcd. for $C_{20}H_{20}ClN_3O_2$: C, 64.95; H, 5.45. Found: C, 64.87; H, 5.34.

3-Benzoyloxy-7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (XVIc).—This compound was prepared in the same manner described earlier for XVIa, using benzoyl chloride as acylating agent. The use of pyridine as solvent gave the same reaction product. After recrystallization from acetone, the product formed prisms melting at 215–216° [ν (cm.$^{-1}$) 3480, 1740].

Anal. Calcd. for $C_{23}H_{18}ClN_3O_2$: C, 68.40; H, 4.49. Found: C, 68.47; H, 4.11.

7-Chloro-5-(4-methoxyphenyl)-2-(N-methylacetamido)-3*H*-1,4-benzodiazepine 4-Oxide (XVII).—Acetylation of 7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-oxide,[14] as described in the literature[4] for the 5-phenyl derivative, gave the N-acetyl derivative, crystallizing as colorless plates from a mixture of methylene chloride and hexane and melting at 188–190° [ν (cm.$^{-1}$) 1680].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.37; H, 4.88; acetyl, 11.58. Found: C, 61.57; H, 4.93; acetyl, 11.40.

3-Acetoxy-7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine (XVIII).—The product XVIII was prepared from 7-chloro-2-methylamino-5-(4-methoxyphenyl)-3*H*-1,4-benzodiazepine 4-oxide[14] and acetyl chloride in the same manner as compound XVIa. Crystallization from acetonitrile followed by recrystallization from a mixture of tetrahydrofuran and hexane gave colorless crystals melting at 202–203° [ν (cm.$^{-1}$) 3410, 1745].

Anal. Calcd. for $C_{19}H_{18}ClN_3O_3$: C, 61.37; H, 4.88; acetyl, 11.58. Found: C, 61.29; H, 4.93; acetyl, 12.09.

6-Chloro-4-phenyl-2-quinazoline Carboxaldehyde (VII). A. From III.—A suspension of 3.4 g. (0.01 mole) of III in 140 ml. of water and 10 ml. of 1 *N* hydrochloric acid was stirred and heated to 85° for 10 min. The precipitate was then separated by filtration and dissolved in ether. The ether solution was dried, concentrated to a smaller volume, and 1.3 g. (49%) of almost pure crystalline VII was separated by filtration. Recrystallization from ether gave slightly yellow prisms melting at 177–178° [ν (cm.$^{-1}$) 3000, 1728].

Anal. Calcd. for $C_{15}H_9ClN_2O$: C, 67.04; H, 3.37; N, 10.42; Cl, 13.19. Found: C, 67.14; H, 3.07; N, 10.48; Cl, 13.22.

B. From V.—A solution of 2.9 g. (0.01 mole) of V in a mixture of 640 ml. of water and 20 ml. of 1 *N* hydrochloric acid was left at room temperature for 72 hr. The crystalline reaction product (1.2 g., 45%, m.p. 177–178°) was separated by filtration.

C. From IX.—A suspension of 5.6 g. (0.02 mole) of IX[6] in a mixture of 200 ml. of dioxane, 200 ml. of water, and 40 ml. of 1 *N* hydrochloric acid was heated on the steam bath for 15 min., cooled to room temperature, and concentrated *in vacuo* to a smaller volume. Methylene chloride and 40 ml. of 1 *N* sodium hydroxide were added and some undissolved starting material was removed by filtration. The organic layer was separated, dried, and concentrated *in vacuo*. Crystallization of the residue from ether yielded 3.2 g. of crude VII. After recrystallization from ether, 1.2 g. (22%) of the pure product was obtained.

6-Chloro-4-phenyl-2-quinazoline Carboxaldehyde Ethyl Hemiacetal. A.—A solution of 3 g. (0.01 mole) of V in 50 ml. of ethanol and 10 ml. of 1 *N* hydrochloric acid was heated on the steam bath for 10 min. The solution was concentrated *in vacuo* to a smaller volume and the crude crystalline product (2.7 g., 86%) was separated by filtration. After recrystallization from ethanol the pure product crystallized, as colorless needles which melted at 101–103° then resolidified and melted at the melting point of VII [ν (cm.$^{-1}$) 3480, 1725 (w), 1078].

The very weak aldehyde carbonyl band (1725 cm.$^{-1}$) indicating the presence of about 6% of aldehyde may be due to decomposition in solution.

The instability of this compound was shown by the following experiment. A solution of 0.7 g. of the hemiacetal in 25 ml. of benzene was refluxed for 7 min. with azeotropic distillation of the solvent. The solution was concentrated *in vacuo* to dryness and the residue crystallized from ether to give 0.3 g. of the aldehyde (VII).

B.—A suspension of 2.7 g. (0.01 mole) of VII in 100 ml. of ethanol containing 0.1 ml. of concentrated hydrochloric acid was stirred at room temperature for 20 min. The solution thus obtained was concentrated *in vacuo* to a small volume and yielded 2.5 g. (76%) of crystalline hemiacetal.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; EtO, 14.32. Found: C, 65.08; H, 4.99; EtO, 14.00.

6-Chloro-4-phenyl-2-quinazolinecarboxylic Acid (VIII). A. From VII.—A suspension of 1.0 g. (36 mmoles) of VII in 50 ml. of 10% sodium hydroxide and 20 ml. of sodium hypochlorite (16.7% active chlorine) was stirred and heated on a steam bath for 2.5 hr. During this time there was a change in the crystal form. After cooling, the solid was separated by filtration and partitioned between chloroform and dilute hydrochloric acid. The chloroform layer was separated, washed with water, and concentrated to dryness after drying over sodium sulfate. The residue of 900 mg. was crystallized from a mixture of acetone and hexane to give 350 mg. (32%) of VIII melting at 207–209° dec. Further crystallization from benzene raised the melting point to 212.5–213.5° dec. [ν (cm.$^{-1}$) 3300 (OH), 1775 (carboxyl C=O)]. In a chloroform solution containing piperidine, amine salt bands appeared in the 2500-cm.$^{-1}$ region and a strong COO^- band at 1615 cm.$^{-1}$.

B. From X.—To a suspension of 1.0 g. of X[6] in 50 ml. of 2.5 *N* sodium hydroxide, a solution of 2.1 g. of potassium ferricyanide in 50 ml. of water was added. After stirring at room temperature for 1 hr., the reaction mixture was acidified with acetic acid and the crystalline precipitate separated by filtration. The crude material was partitioned between chloroform and dilute hydrochloric acid and the organic layer then washed with water and dried over sodium sulfate. After filtration and evaporation of solvent, a residue of 900 mg. was obtained. Crystallization from a mixture of chloroform and hexane gave 600 mg. (60%) of colorless needles of VIII.

Anal. Calcd. for $C_{15}H_9ClN_2O_2$: C, 63.27; H, 3.19; N, 9.84. Found: C, 63.15; H, 3.24; N, 9.65.

6-Chloro-2-(N-methylformimidoyl)-4-phenylquinazoline (XII). A. From XI.—A suspension of 6.4 g. (0.021 mole) of 2-chloromethyl-4-phenyl-6-chloroquinazoline 1-oxide[10] in 100 ml. of methanolic methylamine (37%) was stirred at room temperature. After 2.5 hr. the solid had dissolved and the resulting solution was allowed to stand for 20 hr. The solvent was evaporated *in vacuo* and the solid residue was partitioned between 200 ml. of methylene chloride and 75 ml. of water. The organic layer, after washing with water, drying over sodium sulfate, and evaporation *in vacuo*, yielded 5.4 g. of crude product. Recrystallization from ethyl acetate gave 3.3 g. (56%) of XII melting at 155–156°.

B. From VII.—A solution of 0.5 g. (1.8 mmoles) of VII in 25 ml. of a 14.5% solution of methylamine in methanol was kept at room temperature for 3.5 hr. After removal of solvent *in vacuo* and crystallization from ether, 0.2 g. (40%) of XII, identical with the previous material, was obtained.

Anal. Calcd. for $C_{16}H_{12}ClN_3$: C, 68.20; H, 4.29; N, 14.91; Cl, 12.58. Found: C, 68.54; H, 4.29; N, 14.95; Cl, 12.33.

6-Chloro-2-methylaminomethyl-4-phenylquinazoline (XIV).—A solution of 1.0 g. (0.0036 mole) of XII in 50 ml. of methanol was hydrogenated under atmospheric pressure in the presence of 1.0 g. of Lindlar's catalyst. Hydrogen uptake was rapid and 0.0036 mole of hydrogen was absorbed. After filtration of catalyst and evaporation of the solvent *in vacuo*, crude XIV was obtained. Recrystallization from a mixture of ether and petroleum ether gave material melting at 93–95°, which was identical with a sample liberated from the hydrochloride prepared according to Bell, *et al.*[12]

Anal. Calcd. for $C_{16}H_{14}ClN_3$: C, 67.72; H, 4.97. Found: C, 67.82; H, 4.82.

XIV Hydrochloride.—This salt was identical with the product prepared as described in the literature.[12]

2,4-Dinitrophenylhydrazone of 6-Chloro-4-phenyl-2-quinazolinecarboxaldehyde (XIII) A. From XII.—A sample of 0.4 g. (1.4 mmoles) of XII was converted to the 2,4-dinitrophenylhydrazone as described by Shriner, *et al.*[17] The crude product (0.6 g.) was recrystallized from dimethylformamide and formed yellow needles melting at 275–276°.

B. From VII.—Treatment of VII with dinitrophenylhydrazine as described before gave a product identical with material prepared from XII.

(17) R. L. Shriner, R. C. Fuson, and D. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1959, p. 219.

C. From V.—To a solution of 5 g. (0.025 mole) of 2,4-dinitrophenylhydrazine in 25 ml. of concentrated sulfuric acid, 36 ml. of water, and 125 ml. of ethanol, 3 g. (0.01 mole) of V was added. The reaction mixture was stirred at room temperature for 16 hr. The crystalline reaction product, formed in almost quantitative yield, was separated by filtration. After recrystallization from dimethylformamide, yellow needles of XIII were obtained.

Anal. Calcd. for $C_{21}H_{13}ClN_6O_4$: C, 56.20; H, 2.92; N, 18.72; Cl, 7.90. Found: C, 55.84; H, 3.12; N, 18.34; Cl, 7.77.

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Heterocyclic Studies. X. A Steroidal 1,2-Diazepin-4-one[1]

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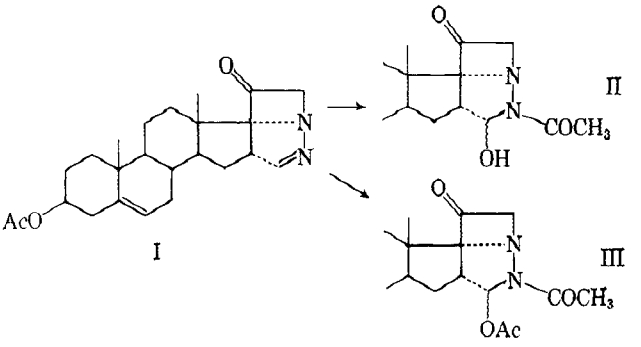
Acylation of the diazabicyclic ketone system (I) results in addition of acid or anhydride to the C=N bond. I is isomerized to the diazepinone (IV) by heating in acetic acid with sodium acetate. The steroidal diazepinone differs greatly in reactivity from the methylphenyldiazepinone (VI) and fails to undergo the characteristic ring contractions and transannular reaction of the latter.

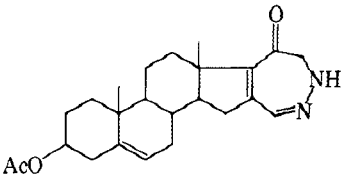
In a previous article we recorded the preparation of a series of nitrogenous steroid derivatives in which the 1,2-diazabicyclo[3.2.0]heptene ring system is fused to the pregnane D-ring.[2] The compounds in this series are of interest, *per se*, as an addition to the growing catalog of nitrogen-containing steroids, some of which have proven to be of pharmacological importance.[3] From a chemical standpoint, however, the steroid nucleus represents a convenient framework to which the heterocyclic rings can be attached in a sterically restricted way, providing an opportunity to expand our knowledge of the 1,2-diazabicyclo[3.2.0]heptane and 1,2-diazepine systems.

A number of nuclear transformations of the bicyclic ketone (I) have been described in which the heterocyclic system remained intact, and it was observed that the compound displays the high carbonyl reactivity characteristic of four-membered cyclic ketones.[2] We now report the results of further study on the heterocyclic chemistry of I.

The diazabicycloheptenone system in I is resistant to mild hydrolysis or oxidation, but reaction occurs with acetyl chloride or, under forcing conditions, with acetic anhydride. With both reagents two products can be isolated which involve the addition of the elements of acetic acid in one case and of acetic anhydride in the other. The infrared spectra of these derivatives contain three and four carbonyl bands, respectively; in both cases the characteristic low wave-length band at 5.56–5.57 μ indicates retention of the four-membered cyclic ketone group. A band at 6.01–6.06 μ in both spectra must be due to an amide carbonyl, and the structures of these products can be assigned as II and III, resulting from addition to the azomethine bond in the pyrazoline ring of I. Similar additions have been observed in the indolenine series[4]; benzoyl chloride in aqueous alkali leads to the 1-benzoyl-2-indolinol, and acetic anhydride to the N-acetylcarbinolamine acetate. The formation of III with acetyl chloride is rather surprising, however, and this reaction, as well as the transformations of the adducts, is being studied further.



One of the primary aims of this work has been the conversion of I to the diazepinone (IV) and a comparative study of the reactions of this compound with those of



IV

the counterpart (VI) in which methyl and phenyl substituents replace the ring D residues. The chemistry of the latter compound has been explored extensively,[5] and a number of ring-contraction and transannular reactions have been encountered. Some of these transformations that are of importance in connection with the present work are recapitulated in Scheme I. The reactions of the steroid series have revealed a much diminished tendency for rearrangement and interconversion of the bicyclic and seven-membered ring systems.

In the previous paper[2] it was noted that the conditions sufficient for the conversion V → VI (Scheme I), namely treatment with very mild acid or base, were without effect on the steroidal bicyclic ketone (I). A number of attempts to bring about a parallel isomerization by employing more vigorous acid or basic condi-

(1) Supported by Grant A-3629 from the National Institute of Arthritis and Metabolic Diseases.

(2) J. A. Moore, W. F. Holton, and E. L. Wittle, *J. Am. Chem. Soc.*, **84**, 390 (1962).

(3) M. Alauddin and M. Martin-Smith, *J. Pharm. Pharmacol.*, **14**, 325, 469 (1962).

(4) H. Leuchs, A. Heller, and A. Hoffmann, *Ber.*, **62**, 871 (1929), and earlier references cited there.

(5) (a) J. A. Moore and R. W. Medeiros, *J. Am. Chem. Soc.*, **81**, 6026 (1959); (b) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959); (c) J. A. Moore, F. J. Marascia, R. W. Medeiros, and E. Wyss, *ibid.*, **84**, 3022 (1962).