leads to the speculation that a common biogenetic intermediate such as **6** may explain the observed formation of both tetracycline and 5-hydroxytetracycline by various *Streptomyces* strains. Such an intermediate as **6** might be visualized as undergoing either fermentative reduction or hydration (peroxidation–reduction) in the final step of biogenesis. We feel this route to be an attractive possibility, although the conversion of 5a,6-anhydro-5-hydroxytetracycline to 5-hydroxytetracycline has been accomplished by an *S. aureofaciens* strain.[12b]

Experimental

Isolation of Dehydrochlorotetracycline.—A *Streptomyces aureofaciens* mutant was grown on a medium similar to that used for the production of chlorotetracycline.[2] This medium included 75 g. of cornstarch, 25 g. of corn steep liquor, and 10 ml. of soybean oil per liter, plus the usual organic salts and calcium carbonate. After a 2-day inoculum incubation, a 250-gal. tank was run for 5 days at 26° with 12 cu. ft. of sterile air/hr./gal.; terminal pH, 7.3.

The broth, 157 gal., was adjusted to pH 2 with sulfuric acid; 75 lb. of Supercel was added, filtered, and filtrate adjusted to pH 8.5 with sodium hydroxide. The precipitate which formed was filtered on a press and washed with water to yield 16 kg. of wet cake. This cake contained small amounts of chlortetracycline as well as dehydroaureomycin, as a metal complex. The wet broth precipitate (16 kg.) was slurried in isopropyl alcohol (17 l.). After the slurry was acidified to pH 1.9 with concentrated hydrochloric acid, sodium chloride (3 kg.), butanol (34 l.), and Supercel (650 g.) were added. The mixture was filtered and the phases were separated. To the aqueous phase was added the filtration residue, isopropyl alcohol (8.5 l.), butanol (17 l.), and sufficient concentrated hydrochloric acid to adjust the pH to 1.5. After filtration the phases were separated. The combined organic phases were concentrated under reduced pressure to a volume of 15 l. and filtered from precipitated solids. To the filtrate were added 0.01 *N* hydrochloric acid (3 l.) and hexane (34 l.). After separation of the phases the organic phase was extracted twice with 0.01 *N* hydrochloric acid (1.5 l.). The combined acid extracts were freeze dried; residue, 416 g., was dissolved in methanol (2.5 l.) and filtered from insolubles. On addition of ethyl acetate (1.1 l.) crystals formed on cooling and standing for 2 days. The crystals were collected and washed with ethanol; yield, 107 g. A small sample was recrystallized from methanol–ethanol. Its infrared spectrum was identical with that of an authentic sample.[5]

Anal. Calcd. for $C_{22}H_{22}N_2Cl_2O_8$: C, 51.48; H, 4.32; N, 5.46; Cl, 13.81. Found: C, 51.28; H, 4.58; N, 4.99; Cl, 13.05.

The ultraviolet absorption spectrum in methanol–hydrochloric acid showed λ_{max} 254, 383 mμ (log ε 4.3, 3.6), while in methanol–sodium hydroxide the absorption was shifted to 247, 260 (sh), 424 mμ (log ε 4.3, 4.3, 4.6), and in methanol–magnesium chloride to 238, 268, 410 mμ (log ε 4.47, 4.4, 4.04). The optical rotation was determined in 0.67% solution in 0.03 *N* hydrochloric acid. The value was found to change with time as follows: $[\alpha]^{25}D$ +6.8° (15 min.); +12.5° (105 min.); +1° (19 hr.). The pK_a's of another sample of dehydrochlorotetracycline hydrochloride were determined in 0.1 *N* potassium chloride solution.[13] The values found were *ca.* 3.3; 4.98 ± 0.10; 9.64 ± 0.10; neut. equiv., 528 (calcd. 512). Qualitative observations of ultraviolet absorption *vs.* pH taken in aqueous solution (*c* 4.10^{-5} *M*) indicate that an anion forms with increasing pH in the range pH 3.1 (λ_{max} 375 mμ) to pH 6.0 (λ_{max} 405 mμ); the pH at the inflection point is *ca.* 4.6. This furnished a qualitative corroboration of the pK_a 2 value.

Amphoteric Dehydrochlorotetracycline.—One gram of dehydrochlorotetracycline hydrochloride was slurried in 50 ml. of water and adjusted to pH 7.0. The solution so formed was filtered, then adjusted to pH 3.0. A light yellow crystalline solid separated (0.7 g.), which showed only a trace of 5.8-μ infrared absorption in either potassium bromide pellet or dioxane solution. This material (0.65 g.) was boiled in chloroform for 4.5 hr., filtered from a trace of insoluble residue, the filtrate reduced to dryness and recrystallized from 25 ml. of chloroform containing 4 ml. of hexane. The crystals so obtained were dried at 60° (0.01 mm.) for 18 hr. They showed very strong infrared absorption at 5.83 μ either in potassium bromide pellet or in chloroform solution. The crystals decomposed indefinitely above 181°.

Anal. Calcd. for $C_{22}H_{21}N_2O_8Cl$: C, 55.41; H, 4.44; N, 5.88. Found: C, 54.93; H, 4.65; N, 5.71; λ_{max} ($CHCl_3$) 366 mμ (log ε 3.58).

The n.m.r. spectrum of the ketonic tautomer was measured in octadeuteriotetrahydrofuran. No signal was observed in the region of 3.3–6 τ. The aromatic protons were indicated as doublets at 2.45 and 3.1 τ. The infrared spectrum of the solution used for n.m.r. measurements showed a strong peak at 5.82 μ.

Acid Degradation of Dehydrochlorotetracycline.—Ten milligrams of dehydrochlorotetracycline hydrochloride was dissolved in 5 ml. 1 *N* hydrochloric acid and heated at 95° for 24 min. An amorphous precipitate formed which showed an ultraviolet absorption spectrum of λ_{max} 248, 320, 373 mμ, reminiscent of apoterramycin.

5-Methoxy-7-chloroanhydrotetracyclines.—A 0.5% solution of 7-chlorodehydrotetracycline hydrochloride was heated under reflux in 0.1 *N* methanolic hydrochloric acid for 17 hr. The solution was concentrated under reduced pressure, filtered, and the crude product precipitated with ethyl acetate. Further purification was achieved by recrystallization from ethyl acetate. Paper chromatography showed the product to be homogeneous and different from anhydrochlorotetracycline or anhydrotetracycline; λ_{max} (MeOH·HCl) 229, 272, 337, 433 mμ; log ε 4.37, 4.58, 3.45, 3.86; $[\alpha]^{25}D$ −229° (*c* 0.2, MeOH).

Anal. Calcd. for $C_{23}H_{24}N_2O_8Cl_2 \cdot {}^1/_2H_2O$: C, 51.50; H, 4.70; N, 5.23; Cl, 13.18; OCH_3, 5.79; C-CH_3, 2.80. Found: C, 51.29; H, 4.81; N, 5.28; Cl, 15.10; OCH_3, 6.58; C-CH_3, 2.97.

5-Ethoxy-7-chloroanhydrotetracycline.—This compound was prepared by the procedure described before, substituting ethanol for methanol; λ_{max} (MeOH·HCl) 229, 274, 335, 438 mμ; log ε 4.39, 4.55, 3.55, 3.83; $[\alpha]^{25}D$ −181° (*c* 0.2, MeOH).

Anal. Calcd. for $C_{24}H_{26}N_2O_8Cl_2$: C, 53.24; H, 4.84; N, 5.18; OC_2H_5, 8.32. Found: C, 53.71; H, 5.25; N, 4.85; OC_2H_5, 9.1.

Other 5-alkoxy-7-chloroanhydrotetracyclines, including the isopropoxy and benzyloxy derivatives, were prepared in a similar manner by heating the reaction mixture under reflux or to 100° for several hours and were characterized by paper chromatography and by their ultraviolet absorption spectra.

Acknowledgment.—We are indebted to Mr. E. Tynan and Dr. F. W. Tanner, Jr., for the fermentation of the dehydroaureomycin. Drs. R. L. Wagner, Jr., Kotaro Murai, and their associates provided the physical measurement data.

(13) P. P. Regna, I. A. Solomons, K. Murai, A. E. Timreck, K. J. Brunings, and W. A. Lazier, *J. Am. Chem. Soc.*, **73**, 4211 (1951).

Quinazolines and 1,4-Benzodiazepines. XI.[1] Synthesis and Transformations of 7-Chloro-2,3-dihydro(and 2,3,4,5-tetrahydro)-5-phenyl-1*H*-1,4-benzodiazepine[2]

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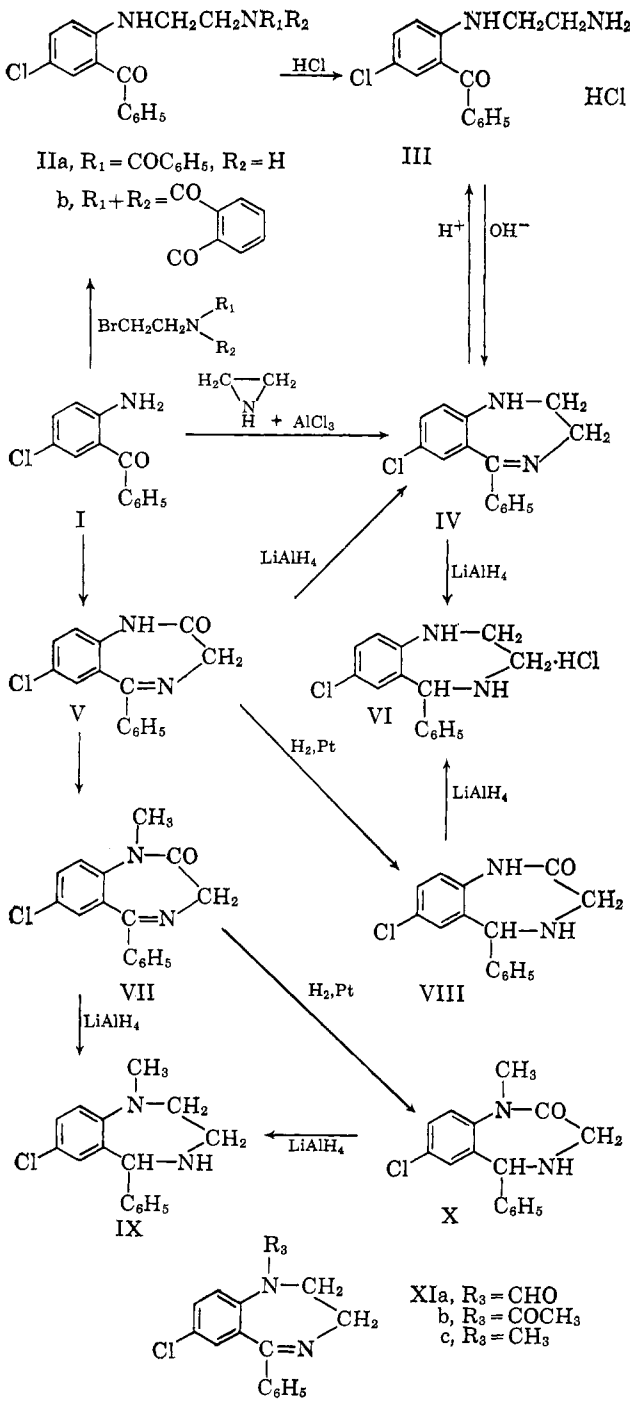
Our interest in benzodiazepine derivatives prompted us to study methods for the synthesis of 2,3-dihydro-5-

(1) Paper X, L. H. Sternbach, R. Ian Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, (3) 261 (1963).

(2) The material contained in this paper and the synthesis of analogs of IV, bearing in position 7, a hydrogen or bromine atom, a methyl, carboxy, or carbomethoxy group, are described in the Hoffmann-La Roche Belgian Patent 620773 (Derwent Abstracts of Feb. 8, 1963). This application also contains derivatives of IV bearing an additional substituent in the phenyl ring (2′-F, Cl, OCH_3) and analogs of XIc bearing an amino, dimethylamino, or cyano group in position 7. Part of this material will be described in a further communication.

phenyl-1*H*-1,4-benzodiazepines. Using 2-amino-5-chlorobenzophenone as starting material, we developed three methods leading to the desired 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (IV).[3a]

The most useful procedure was the reduction of the corresponding benzodiazepin-2-one (V)[3b] with lithium aluminum hydride[4] in tetrahydrofuran, which gave a good yield of the desired product (IV). Another approach was the conversion of the aminobenzophenone I into a benzamidoethylamino or phthalimidoethylamino derivative II, followed by hydrolysis to remove the protecting acyl group. This method was less advantageous since the intermediates of type II were obtained in low yield. The hydrolysis of IIa and b did not offer any particular difficulties; the initially formed aminoethylaminobenzophenone III cyclized spontaneously during the isolation procedure. The third method, in which the aminobenzophenone I was condensed with ethylenimine, gave only a 3.5% yield of the desired product.



Compound IV could be acylated or methylated to yield the corresponding 1-substituted derivatives XI. Acid hydrolysis of IV led to the aminoethylaminobenzophenone III, which was isolated in the form of its hydrochloride. Treatment of this compound with alkali resulted in its cyclization to IV.

The lithium aluminum hydride reduction method was also applied to the 1,3,4,5-tetrahydrobenzodiazepinone VIII,[3] which was readily converted into the corresponding tetrahydrobenzodiazepine VI[5]; this compound was isolated as the hydrochloride, since the free base could not be obtained in crystalline form. The same compound also was obtained by lithium aluminum hydride reduction of IV. The reduction of the 1-methyl derivative VII[3] with lithium aluminum hydride yielded mixtures,[6] from which was obtained a crystalline product to which structure IX was assigned. This structure was proved by the preparation of IX by lithium aluminum hydride reduction of X, which was prepared by catalytic hydrogenation of VII.

Experimental

All melting points are corrected. The infrared and ultraviolet absorption spectra of starting materials and reaction products were compared in order to establish structural changes. The infrared spectra were determined in 3% chloroform solutions or in potassium bromide pellets using a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet absorption spectra in isopropyl alcohol or in 0.1 *N* hydrochloric acid.

7-Chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (IV). A. From 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (V).—To a stirred suspension of 24 g. (0.63 mole) of lithium aluminum hydride in 400 ml. of tetrahydrofuran (freshly distilled over potassium hydroxide) was added during 1 hr. a solution of 86.4 g. (0.32 mole) of V in 1200 ml. of tetrahydrofuran. The mixture was refluxed until it turned deep brown (*ca.* 5 min.). It was then cooled and the excess reducing agent was destroyed by the addition of wet ether. The grey suspension which formed was filtered through Hy-flo and gave a clear yellow solution, which was dried over sodium sulfate and concentrated *in vacuo*. The residue was crystallized from a mixture of methylene chloride and petroleum ether[7] and gave 58.6 g. (71%) of yellow needles or prisms melting at 172–174°.

Anal. Calcd. for $C_{15}H_{13}ClN_2$: C, 70.17; H, 5.10. Found: C, 69.80; H, 5.01.

B. From 2-Amino-5-chlorobenzophenone (I) and Ethylenimine.—To a cooled, stirred suspension of 8.9 g. (0.067 mole) of anhydrous aluminum chloride in 100 ml. of dry benzene was added 20 g. (0.09 mole) of I. The reaction mixture was heated to reflux temperature, then the heating was stopped, and a solution of 1.9 g. (0.045 mole) of ethylenimine in 25 ml. of benzene was added in small portions. The reaction mixture was stirred for about 30 min. and poured onto ice. After the addition of 30 g. of potassium hydroxide, the organic layer was separated, extracted with 2 *N* hydrochloric acid, and discarded. The aqueous acid

(3) (a) The synthesis of the 7-nitro analog of IV by another method was first described by J. A. Hill, A. W. Johnson, and T. J. King, *J. Chem. Soc.*, 4430 (1961); (b) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(4) M. Uskoković, J. Iacobelli, and W. Wenner, *ibid.*, **27**, 3606 (1962), used the same method for the reduction of 3*H*-1,4-benzodiazepine-2,5-(1*H*,4*H*)-dione.

(5) The infrared spectra of tetrahydro and dihydro derivatives showed characteristic differences in the 1600-cm.$^{-1}$ region. The dihydro derivatives had a strong band at 1612–1615 cm.$^{-1}$, which can be ascribed to the 4,5-double bond, since it is not present in the tetrahydro derivatives.

(6) The infrared spectra of noncrystalline fractions obtained from the reaction indicated the presence of XIc.

(7) The petroleum ether had a boiling range of 30–60°.

layer was made alkaline and extracted with ether, and this extract was dried and concentrated *in vacuo*. The residue (1.7 g.) was crystallized from ether and yielded 0.8 g. (3.5%) of IV.[8]

C. *Via* **N-[2-(4-chloro-2-benzoylanilino)ethyl]benzamide (IIa).**—A solution of 2.3 g. of I (0.01 mole) and 2.3 g. of β-bromoethylbenzamide (0.01 mole) in 25 ml. of dimethylformamide was heated on a steam bath for 16 hr., diluted with water, and extracted with methylene chloride. The organic layer was dried and evaporated *in vacuo*. The residue was crystallized from a mixture of ether and petroleum ether, yielding 0.9 g. (23%) of crude reaction product. The analysis sample was crystallized from acetone–petroleum ether and formed yellow needles of N-[2-(4-chloro-2-benzoylanilino)ethyl]benzamide (IIa) melting at 143–144°.

Anal. Calcd. for $C_{22}H_{19}ClN_2O_2$: C, 69.75; H, 5.06; N, 7.39. Found: C, 69.46; H, 5.16; N, 7.61.

A solution of 1.1 g. of IIa in a mixture of 15 ml. of concentrated hydrochloric acid and 10 ml. of ethanol was refluxed for 56 hr. The reaction mixture was diluted with water and extracted with methylene chloride to remove starting material. The aqueous layer was made alkaline with 3 *N* potassium hydroxide and extracted with methylene chloride; the extract was dried and evaporated *in vacuo*. The residue was crystallized from ether and yielded 0.34 g. (45%) of crude IV.[8]

D. *Via* **N-[2-(4-Chloro-2-benzoylanilino)ethyl]phthalimide (IIb).**—A solution of 2.3 g. (0.01 mole) of I and 2.5 g. (0.01 mole) of β-bromoethylphthalimide in 30 ml. of dimethylformamide was refluxed for 16 hr., diluted with water, and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo to dryness. The residue was crystallized from* ether to give 0.6 g. (14%) of crude reaction product. The analysis sample was crystallized from ether and formed yellow prisms or needles of N-[2-(4-chloro-2-benzoylanilino)ethyl]-phthalimide (IIb) melting at 171–173°.

Anal. Calcd. for $C_{23}H_{17}ClN_2O_3$: C, 68.23; H, 4.23. Found: C, 68.03; H, 4.26.

To 30 ml. of 70% sulfuric acid, heated to 135°, was added 1 g. (2.4 mmoles) of IIb, and the temperature was raised to 179°. After 30 min., the solution was poured onto ice and extracted with methylene chloride to remove phthalic acid and unchanged starting material. The aqueous layer was made alkaline with 40% potassium hydroxide and extracted with methylene chloride. The organic layer was dried and concentrated *in vacuo* to dryness (0.5 g.). The residue was crystallized from ether and yielded 0.2 g. (32%) of crude IV.[8]

Hydrochloride.—The base IV was treated with an excess of methanolic hydrogen chloride, and the salt was crystallized by the addition of ether and petroleum ether. It formed yellow prisms melting at 245–247°.

Anal. Calcd. for $C_{15}H_{14}Cl_2N_2$: C, 61.45; H, 4.81. Found: C, 61.78; H, 4.65.

Formyl Derivative (XIa).—The mixed anhydride of formic acid and acetic acid was prepared by the addition of 6.8 ml. of 98% formic acid to 16.4 ml. of acetic anhydride cooled in an ice bath. This mixture was heated at 50° for 2 hr., then cooled, and added to a solution of 40 g. (0.156 mole) of IV in 300 ml. of methylene chloride. This solution was kept at 25° for 17 hr. and concentrated *in vacuo*. The residue was treated with aqueous ammonia and ether. The ether phase was dried and yielded crystals which, after recrystallization from a mixture of methylene chloride and petroleum ether, gave 15 g. (34%) of white prisms melting at 116–119°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.51; H, 4.54; N, 9.72.

Acetyl Derivative XIb.—A solution of 1 g. of IV in a mixture of 15 ml. of pyridine and 10 ml. of acetic anhydride was left at room temperature for 5 hr., and then concentrated *in vacuo* to dryness. The residue was crystallized from ether and then from a mixture of methylene chloride, ether, and petroleum ether, to form colorless prisms melting at 165–166° (92%).

Anal. Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06. Found: C, 68.41; H, 4.78.

2-(2-Aminoethylamino)-5-chlorobenzophenone Hydrochloride (III).—A solution of 2 g. of compound IV in a mixture of 20 ml. of ethanol and 20 ml. of 2 *N* hydrochloric acid was refluxed for 19 hr. and then concentrated *in vacuo* to dryness. The residue was crystallized from a mixture of methanol and ether to yield 0.4 g. of the crude hydrochloride. After recrystallization from the same solvent mixture, the product formed yellow needles which softened at 170° and melted at 172–174° dec.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2O$: C, 57.89; H, 5.18. Found: C, 58.16; H, 5.23.

Attempts to liberate the free base by treatment of the hydrochloride with alkali resulted in cyclization to IV.

7-Chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (XIc).—To a solution of 10.2 g. (0.04 mole) of IV in 100 ml. of dimethylformamide was added at 50°, with stirring, 2 g. of a 53% mineral oil dispersion of sodium hydride. The mixture was cooled, and 3.6 ml. of methyl iodide added. After stirring for 30 min. at room temperature, the reaction mixture was poured into ice–water and extracted with methylene chloride. The organic layer was separated, dried, and concentrated *in vacuo*. The residue (8.3 g.) was dissolved in a small amount of a mixture of ether and petroleum ether (1:1), and adsorbed on a chromatographic column (3.5-cm. diameter) prepared with 300 g. of Woelm grade I alumina. The column was eluted first with 2.8 l. of a 50% ether–petroleum ether mixture, then with 500 ml. of a 75% ether–petroleum ether mixture, followed by 500 ml. of absolute ether. The eluates were combined and concentrated *in vacuo*. The residue was crystallized from a small amount of a mixture of ether and petroleum ether to yield 2.8 g. (25%) of crude reaction product. After recrystallization from the same solvent mixture, or from pentane, the pure product was obtained as colorless prisms melting at 95–97°.

Anal. Calcd. for $C_{16}H_{15}ClN_2$: C, 70.97; H, 5.58; N, 10.35. Found: C, 70.75; H, 5.35; N, 10.12.

Further elution of the column with U.S.P. ether yielded unchanged starting material.

7-Chloro-2,3,4,5-tetrahydro-5-phenyl-1*H*-1,4-benzodiazepine Hydrochloride (VI). A.—To 6.9 g. (0.18 mole) of lithium aluminum hydride in 150 ml. of dry tetrahydrofuran was added a solution of 21 g. (0.077 mole) of 7-chloro-1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (VIII)[3] in 300 ml. of tetrahydrofuran. The addition was carried out with stirring, as rapidly as the foaming permitted. The mixture was heated to reflux, then cooled, and stirred at room temperature until the reaction subsided. It was then refluxed for 30 min., decomposed with ethyl acetate and wet ether, and filtered over Hy-flo. The organic layer was separated, dried, and concentrated *in vacuo*. The oily residue was dissolved in methanol and acidified with a slight excess of methanolic hydrogen chloride. On addition of acetone, the crude hydrochloride (16.4 g., 72%) crystallized and was separated by filtration. The analysis sample was recrystallized from a mixture of methanol and acetone; it formed slightly yellow plates melting at 259–260° dec.

Anal. Calcd. for $C_{15}H_{16}Cl_2N_2$: C, 61.03; H, 5.46. Found: C, 61.04; H, 5.24.

B.—To a stirred suspension of 1.5 g. (0.04 mole) of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran was added a solution of 5.1 g. (0.02 mole) of IV in 50 ml. of tetrahydrofuran. The reaction mixture was refluxed for 3 hr., cooled, decomposed with 200 ml. of wet ether, and filtered over Hy-flo. The filtrate was dried and concentrated *in vacuo*. The residue (5.5 g.) was crystallized from a mixture of ether and petroleum ether to yield 1.9 g. of starting material. The mother liquors were concentrated *in vacuo* to dryness. The residue was dissolved in methanol, and acidified with an excess of methanolic hydrogen chloride. Ether was added, and the precipitated hydrochloride (2.2 g., 60% yield) was filtered off.[8]

7-Chloro-2,3,4,5-tetrahydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (IX). A.—A solution of 7-chloro-1,3,4,5-tetrahydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (X)[9] (40 g.) in anhydrous tetrahydrofuran (500 ml.) was added dropwise over 2 hr. to a refluxing solution of lithium aluminum hydride (15.2 g.) in tetrahydrofuran (500 ml.). Refluxing was continued for a further 2.5 hr.; then the excess lithium aluminum hydride was decomposed by careful addition of saturated aqueous sodium sulfate (100 ml.). The solution was then dried with anhydrous sodium sulfate and filtered. Evaporation of the filtrate gave the crude product, which was dissolved in ether and extracted with 1 *N* hydrochloric acid. The acid extract was made basic with sodium hydroxide solution and extracted with methylene chloride. The extract was evaporated, and the residue was converted to

(8) The product was identified with an authentic sample by mixture melting point determination and comparison of the infrared spectra.

(9) Compound X was prepared in the same manner as VIII.[3] It crystallized from ether as prisms, melting at 144–145°.

Anal. Calcd. for $C_{16}H_{15}ClN_2O$: C, 65.57; H, 5.50. Found: C, 65.86; H, 5.27.

the monohydrochloride by treatment with the calculated amount of methanolic hydrochloric acid. The hydrochloride was crystallized by the addition of ether and separated (m.p. *ca.* 250°). It was then reconverted to the base IX, which on recrystallization from pentane formed pale yellow needles, m.p. 60–62° (52%).

Anal. Calcd. for $C_{16}H_{17}ClN_2$: C, 70.44; H, 6.28. Found: C, 70.33; H, 6.47.

B.—Reduction of VII with lithium aluminum hydride in tetrahydrofuran, by the same procedure as that used for reduction of X and purification of the product by the same methods, gave IX in 20% yield.[5]

The hydrochloride was prepared from the base and methanolic hydrochloric acid, as previously described, and was obtained as colorless needles (from methanol–ether), m.p. 258–259°.

Anal. Calcd. for $C_{16}H_{18}Cl_2N_2$: C, 62.14; H, 5.87; N, 9.06; Cl, 22.93. Found: C, 62.44; H, 6.10; N, 9.09; Cl, 22.56.

The monopicrate was prepared from the base and picric acid in ether and was obtained as yellow prisms, m.p. 202–204° (from ethanol).

Anal. Calcd. for $C_{22}H_{20}ClN_5O_7$: C, 52.64; H, 4.03; N, 13.95. Found: C, 52.89; H, 4.02; N, 14.17.

Acknowledgment.—We are indebted to Dr. A. Motchane, Mr. S. Traiman, and Dr. V. Toome for the the infrared and ultraviolet spectra, and to Dr. Al Steyermark and his staff for the microanalyses. Mr. L. A. Dolan was helpful in the preparation of larger amounts of starting materials and intermediates.

Quinazolines and 1,4-Benzodiazepines. XII.[1] Preparation and Reactions of 2,3-Dihydro-1*H*-1,4-benzodiazepine 4-Oxides

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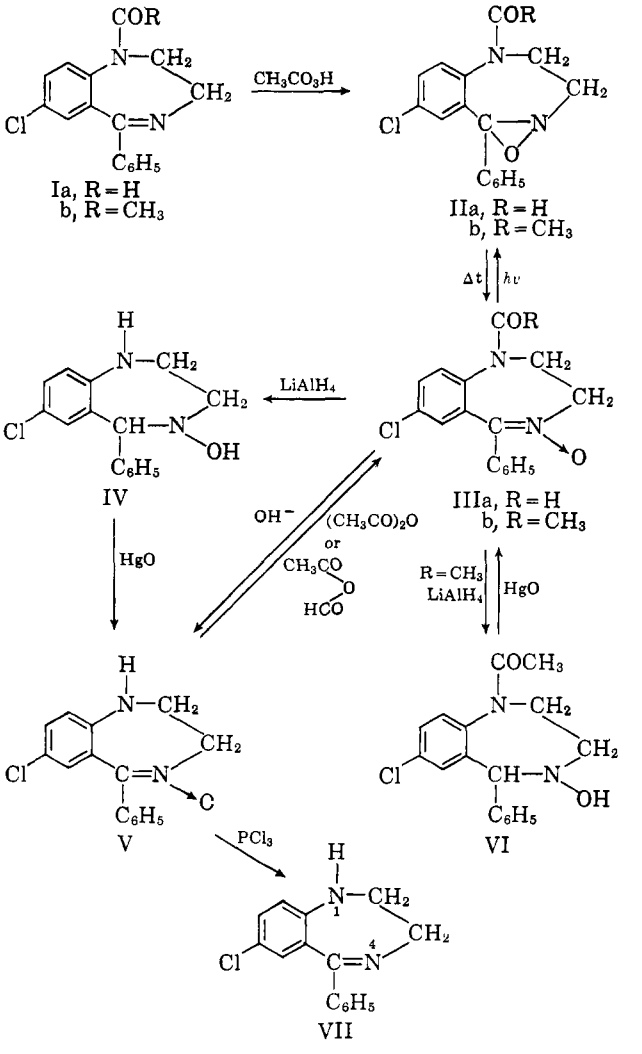
In order to obtain nitrones of type V the oxidation of the acylated 2,3-dihydrobenzodiazepines (Ia and b) with peracetic acid[2] was studied.

The primary oxidation products, the oxaziridines IIa and b, were obtained in good yield. They isomerized on heating to the nitrones IIIa and b which, in turn, rearranged to IIa and b on exposure of dilute solutions to daylight.[3] In contrast to the nitrones, the oxaziridines IIa and b liberated iodine from an acidic potassium iodide solution. According to expectation,[3,4] the ultraviolet spectra of the oxaziridines showed only an inflection at *ca.* 238 mμ, whereas the nitrones IIIa and b had maxima at *ca.* 234, 260, and 310 mμ.

These maxima, also shown by compound V, are characteristic of compounds containing a nitrone function in conjugation with a phenyl group.[4]

The acyl derivatives IIIa and b were hydrolyzed with alkali to the nitrone V, which could be reacylated to the starting materials III. This shows that under the chosen conditions the nitrones did not undergo any structural changes. Further proof was obtained by



treatment of V with phosphorus trichloride which gave the known diazepine VII.[1]

The reduction of III with lithium aluminum hydride did not yield 1-alkyl derivatives. Depending on reaction conditions, either the hydroxylamine IV or VI was obtained from IIIb.[5] Both products could be reoxidized with mercuric oxide to give the corresponding nitrones V and IIIb, respectively.

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-4,5-epoxy-1-formyl-2,3,4,5-tetrahydro-5-phenyl-1*H*-1,4-benzodiazepine (IIa).—Peracetic acid was prepared by dropwise addition of 2.5 ml. of acetic anhydride to a mixture of 3 ml. of methylene chloride, 0.6 ml. of 90% hydrogen peroxide, and 1 drop of concentrated sulfuric acid at 0°. This mixture was kept in an ice bath for 15 min., at 25° for 30 min., and then added to a solution of 5.3 g. (0.019 mole) of Ia[1] in 10 ml. of acetic acid. The solution was left at 25° for 17 hr. and then made alkaline by addition of ice and aqueous ammonia. Crystals separated which, after recrystallization from a mixture of methylene chloride and petroleum ether, formed 3.5 g. (63%) of white prisms melting at 150–152°.

(1) Paper XI, L. H. Sternbach, E. Reeder, and G. A. Archer, *J. Org. Chem.*, **28**, 2456 (1963).

(2) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957).

(3) See L. H. Sternbach, B. A. Koechlin, and E. Reeder, *J. Org. Chem.*, **27**, 4071 (1962), for comparison and for earlier references.

(4) M. J. Kamlet and L. A. Kaplan, *ibid.*, **22**, 576 (1957).

(5) Compound IIIa, on reduction with lithium aluminum hydride, also gave IV, which was not isolated but oxidized directly to V (over-all yield, *ca.* 25%).