Quinazolines and 1,4-Benzodiazepines. L.[1] The Ring Contraction of 4-Hydroxy-5-phenyltetrahydro-1,4-benzodiazepines to Tetrahydroquinoxalines

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Received September 18, 1970

4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines have been shown to dehydrate to the corresponding 2,3-dihydro derivatives or to ring contract to 1,2,3,4-tetrahydroquinoxalines. The extent of dehydration *vs.* ring contraction depends on the reagents used and on the substituents on the benzodiazepine nucleus. These effects and possible mechanisms are discussed.

In connection with other work, we were able to show that, by generating a carbanion at the 5 position of 4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepines[2] with base, imine formation occurs with elimination of hydroxyl ion to give the corresponding 2,3-dihydrobenzodiazepines[3] in good yield. In an attempt to effect this dehydration with other reagents, *e.g.*, the phosphorus halides and thionyl chloride, we observed cleavage of the hydroxylamine and rearrangement. Two products were isolated from the reaction mixture and were identified as benzaldehyde and 1,2,3,4-tetrahydroquinoxaline.

This ring contraction was applied to the preparation of a few unsymmetrically substituted racemic tetrahydroquinoxalines, compounds **3a–d**. The starting hydroxylamines **1**, of unknown stereochemistry, were obtained by reduction of the corresponding 1,4-benzodiazepin-2-one 4-oxides **9a–d** with lithium aluminum hydride. These compounds were prepared in turn by alkylating the 3-sodio derivative of the known compound **9b**[4] with the appropriate alkyl halide.

This reaction constitutes another novel C to N migration[5] and may be considered to be an extension of a Stieglitz-type of rearrangement.[6] A plausible mechanism is given in Scheme I, in which the first step is shown as esterification of the 4-hydroxy group. This would result in an increase in the electron deficiency of the 4-nitrogen. Rupture of the N–O bond with concerted migration of the C_5–C_{11} bond would generate the carbonium ion A stabilized through the corresponding immonium ion C. The existence of the intermediate ions B or C was confirmed by the isolation of the 4-benzyltetrahydroquinoxaline **4** from a reductive work-up of the reaction mixture. Hydrolytic work-up led to the tetrahydroquinoxaline **3** and benzaldehyde.

Interestingly, the electron-releasing aniline nitrogen is necessary for the success of this rearrangement. When 1-acetyl-7-chloro-4-hydroxy-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**6**) (Scheme II) was treated with phosphorus oxychloride, only dehydration was observed and compound **7** was isolated.

This fact may help explain the different extent of dehydration observed with compound **1a** *vs.* **1b** upon reaction with thionyl chloride. Chlorosulfination of the aniline nitrogen of **1a** would decrease its electron-donating capacity, thus favoring elimination rather than rearrangement. Chlorosulfination of the aniline nitrogen is not possible with **1b** and accordingly the amount of dehydration product observed is negligible.

The same ring contraction along with some dehydration could also be effected by phenyl isocyanate. When compound **1b** was refluxed in toluene with an excess of phenyl isocyanate, the urea derivative **8** was the major product obtained. A possible mechanism for this example is given in Scheme III.

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Experimental Section

Melting points were determined microscopically on a hot stage. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer; nmr spectra were recorded with a Varian A-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography. Petroleum ether refers to a fraction of bp 30–60°.

7-Chloro-1,3-dihydro-1,3-dimethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (9c).—Potassium *tert*-butoxide (23 g, 0.2 mol) was added to a solution of 50 g (0.167 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9b**)[4] in 250 ml of dry dimethylformamide cooled to 0°. The mixture was stirred for 5 min in a nitrogen atmosphere, 12.5 ml (28.6 g or 0.2 mol) of methyl iodide was added, and stirring was continued for 10 min without cooling. The reaction mixture was diluted with ice–water. The precipitated crystals were collected, washed with water, and recrystallized from ethanol to yield 38.6 g (73%) of product with mp 185–188°: nmr ($CDCl_3$) δ 1.68 (d, 3, J = 6.5 Hz, C_3 CH_3), 3.50 (s, 3, NCH_3), 4.43 (q, 1, J = 6.5 Hz, C_3 H); ir ($CHCl_3$) 1680 cm^{-1} (C=O); uv max 237 mμ (ϵ 30,000), 311 (11,200).

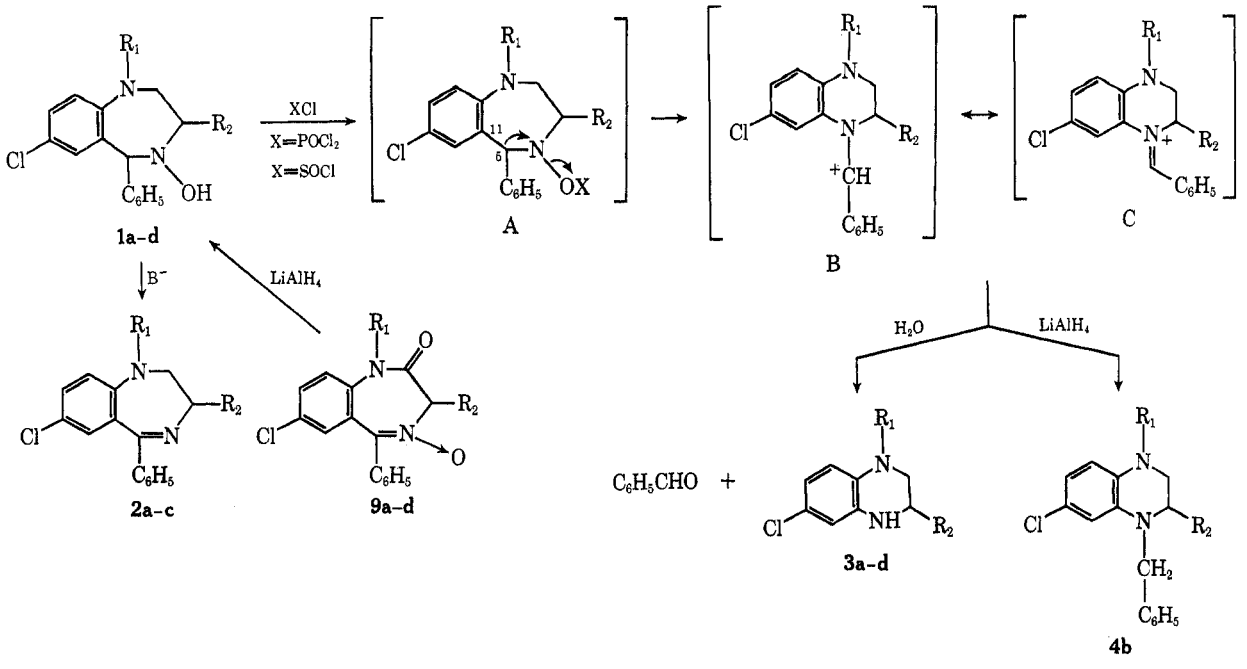
Anal. Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90. Found: C, 64.77; H, 4.85; N, 8.86.

3-Benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (9d).—A solution of 60 g (0.2 mol) of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9b**)[4] in 400 ml of dimethylformamide was cooled to −20°. Potassium *tert*-butoxide (28 g, 0.25 mol) was added with stirring under nitrogen. The mixture was stirred for 10 min and then cooled to −40° when 31.6 g (0.25 mol) of benzyl chloride was added. The temperature was allowed to rise to room temperature. After stirring for 2 hr, the reaction mixture was quenched with ice–water. The precipitate was collected, washed with water, and dissolved in methylene chloride. The solution was dried over sodium sulfate, filtered, and evaporated. Crystallization of the residue from ether yielded 46 g (59%) of product. The analytical sample was recrystallized from methanol and melted at 180–182°: nmr ($CDCl_3$) δ 3.46 (s, 3, NCH_3), 4.48 (t, 1, J = 6.5 Hz, C_3H).

Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C, 70.47; H, 5.09; N, 7.19.

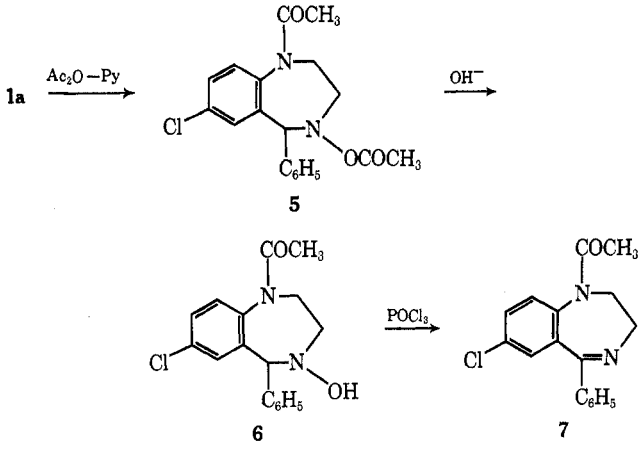
7-Chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (1b).—7-Chloro-1,3-dihydro-1-methyl-5-

SCHEME I

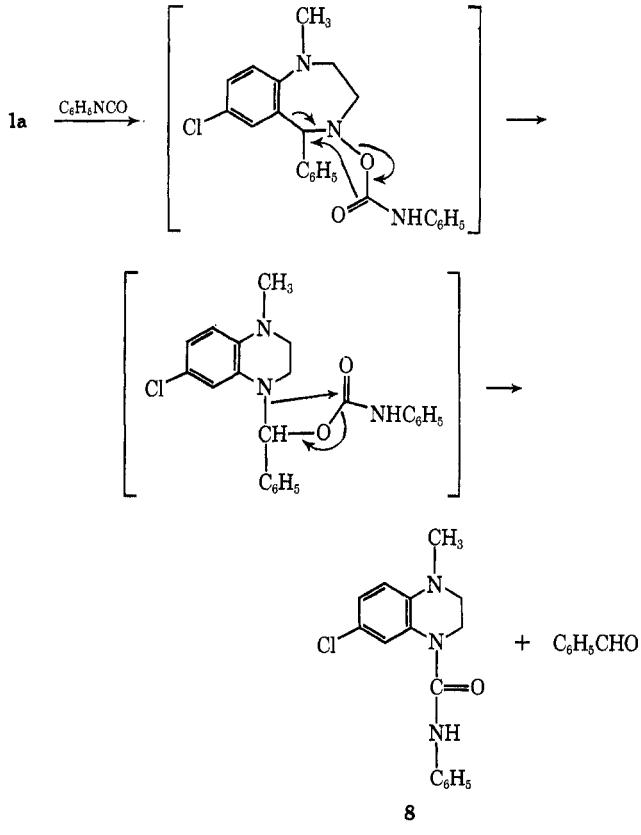


a, $R_1, R_2 = H$
b, $R_1 = CH_3$; $R_2 = H$
c, $R_1, R_2 = CH_3$
d, $R_1 = CH_3$; $R_2 = CH_2C_6H_5$

SCHEME II



SCHEME III



phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9b**)[4] (20 g, 0.066 mol) was added in portions to a suspension of 6 g of lithium aluminum hydride in 250 ml of ether. After addition, the mixture was refluxed for 4 hr and hydrolyzed by the careful addition of 30 ml of water. The inorganic material was filtered off and washed well with benzene. The filtrate was evaporated and the residue was crystallized from methanol with seeding to yield 10 g (52%) of product with mp 138–140°. Seeds were obtained by chromatographic purification of part of the crude product on a 30-fold amount of silica gel using 10% (v/v) ethyl acetate in methylene chloride for elution. Recrystallization from methanol raised the mp 141–143°.

Anal. Calcd for $C_{16}H_{17}ClN_2O$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.28; H, 5.88; N, 9.63.

7-Chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1c**).—7-Chloro-1,3-dihydro-1,3-dimethyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9c**) (50 g, 0.16 mol) was reduced as above with 17 g of lithium aluminum hydride in 800 ml of ether. The usual work-up followed by crystallization from ether–petroleum ether yielded 36 g (75%) of the hydroxylamine: mp 135–136°; nmr ($CDCl_3$) δ 1.14 (d, 3, J = 6 Hz, C_3 CH_3), 2.89 (s, 3, NCH_3), 4.87 (broad s, 1, OH), 5.46 (s, 1, C_5 H); uv max 265 mμ (ϵ 10,800), inflection 300 (2300).

Anal. Calcd for $C_{17}H_{19}ClN_2O$: C, 67.43; H, 6.32; N, 9.25. Found: C, 67.44; H, 6.41; N, 9.42.

3-Benzyl-7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1d**).—3-Benzyl-7-chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide (**9d**) (39 g, 0.1 mol) was added to a suspension of 20 g (0.5 mol) of lithium aluminum hydride in 500 ml of ether. The mixture was

refluxed for 2 hr. Regular work-up followed by crystallization from methylene chloride–hexane gave 30.6 g (81%) of product with mp 140–143°: nmr ($CDCl_3$) δ 2.83 (s, 3, NCH_3), 4.97 (s, 1, OH), 5.47 (s, 1, C_5 H).

Anal. Calcd for $C_{23}H_{23}ClN_2O$: C, 72.91; H, 6.12; N, 7.39. Found: C, 72.90; H, 6.11; N, 7.59.

6-Chloro-1,2,3,4-tetrahydroquinoxaline (3a).[7] **1.**—A mixture of 2.75 g (0.01 mol) of 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1a**),[2] 40 ml of methylene chloride, and 2 ml (0.028 mol) of thionyl chloride was allowed to stand at room temperature for 1 hr. Water (100 ml) and 100 ml of hexane were added. The two phases were well agitated for 10 min. The aqueous layer was separated and washed with ether. The organic phase was extracted twice with 1 *N* hydrochloric acid. The aqueous layer was combined with the acid extracts which were then made alkaline with sodium hydroxide and extracted with benzene. The extracts were dried over sodium sulfate and evaporated to give 2.1 g of residue which was chromatographed on 60 g of silica gel with solvent mixtures (v/v) of methylene chloride–ethyl acetate (1:1) followed by ethyl acetate–ethanol (9:1).

Thin layer chromatographically pure fractions eluted with the first solvent system were combined and evaporated. Crystallization from methylene chloride–hexane yielded 0.24 g (14%) of 6-chloro-1,2,3,4-tetrahydroquinoxaline, mp 112–114°.[7]

The pure fractions eluted with ethyl acetate–ethanol were also combined and evaporated. The crystalline residue was recrystallized from methylene chloride–hexane to give 0.9 g (35%) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (**2a**), mp 170–172°.[3]

2.—Phosphorus oxychloride (3.3 ml or 0.03 mol) was added to an ice-cooled solution of 2.75 g of 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1a**) in 80 ml of methylene chloride. The mixture was stirred for 3 hr at room temperature and worked up as above. The solid residue obtained was recrystallized twice from benzene–hexane to yield 0.9 g (53%) of 6-chloro-1,2,3,4-tetrahydroquinoxaline. A small amount of **2a** was present in the mother liquors as determined by thin layer chromatography.

6-Chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (3b). **1.**—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1 ml (0.014 mol) of thionyl chloride, and 30 ml of methylene chloride was stirred at room temperature for 15 min. The dark purple reaction mixture was worked up as described above. The base obtained as a yellow oil (1.4 g) was short path distilled under high vacuum to yield 1.15 g (63%) of distillate which solidified. Recrystallization from ether–petroleum ether gave the pure product: mp 51–53°; nmr ($CDCl_3$) δ 2.80 (broad s, 3, NCH_3), 3.0–4.0 (m, 5, NH, C_2 H, C_3 H): uv max 227–228 mμ (ε 33,300), 268–273 (5700), 320–324 (5250).

Anal. Calcd for $C_9H_{11}ClN_2$: C, 59.20; H, 6.07; N, 15.34. Found: C, 59.13; H, 6.14; N, 15.44.

The benzaldehyde present in the original organic layer was isolated and identified as the 2,4-dinitrophenylhydrazone derivative.

2.—Phosphorus oxychloride (20 ml, 0.22 mol) was added to a solution of 29 g (0.1 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**) in 300 ml of methylene chloride cooled to −20°. The temperature was allowed to reach 10° within 30 min. After addition of 300 ml of ether and 300 ml of water, the mixture was stirred vigorously for 15 min. Extraction, short-path distillation under high vacuum, and crystallization from ether–petroleum ether yielded 8.2 g (45%) of **3b**. The benzoyl derivative of **3b**, mp 128–130°, was also prepared and analyzed.

Anal. Calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 67.15; H, 5.24; N, 9.68.

6-Chloro-1,3-dimethyl-1,2,3,4-tetrahydroquinoxaline (3c).—A solution of 9 g (0.03 mol) of 7-chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1c**) in 100 ml of methylene chloride was cooled to −20°. Phosphorus oxychloride (6 ml, 0.065 mol) was added and the temperature was allowed to rise to 20° within 1.5 hr. The usual hydrolytic work-up followed by short-path distillation of the bases yielded 2.8 g (47%) of a light yellow oil which was crystallized from petroleum ether to give the pure product: mp 35–37°; nmr ($CDCl_3$) δ 1.13 (d, 3, J = 6.5 Hz, C_3 CH_3), 2.80 (broad s, 3, NCH_3), 6.2–6.8 (m, 3, aromatic H); uv max 226–227 mμ (ε 33,250), 272–273 (5800), 320–322 (5370).

Anal. Calcd for $C_{10}H_{13}ClN_2$: C, 61.07; H, 6.66; N, 14.24. Found: C, 61.05; H, 6.66; N, 14.35.

The *p*-chlorobenzoyl derivative (mp 124–128°) obtained under Schotten–Baumann conditions was crystallized from methanol: nmr ($CDCl_3$) δ 1.18 (d, 3, J = 6.5 Hz, C_3 CH_3), 2.98 (s, 3, NCH_3), 4.9 (m, 1, C_3 H); uv max 224–225 mμ (ε 27,200), 254–257 (16,000), 338–342 (4400); ir ($CHCl_3$) 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{16}Cl_2N_2O$: C, 60.91; H, 4.81; N, 8.36. Found: C, 61.12; H, 4.78; N, 8.46.

3-Benzyl-6-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (3d).—A mixture of 15 g (0.04 mol) of 3-benzyl-7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1d**), 30 ml of phosphorus oxychloride, and 100 ml of chloroform was refluxed for 20 min. The solvent and excess reagent were evaporated under reduced pressure and the residue was distributed between methanol–1 *N* hydrochloric acid (1:1) and ether–hexane (1:1) v/v. The aqueous phase was separated, made alkaline with sodium hydroxide, and extracted with ether. The combined extracts were dried and evaporated. The residue (9.8 g) was chromatographed over 200 g of silica gel with benzene. Homogeneous fractions were combined and evaporated. Crystallization of the residue from ether–hexane yielded 4.6 g (42%) of product with mp 67–69°: nmr ($CDCl_3$) δ 2.5–4.0 (m, 6, NH, C_2 H, C_3 H, $CH_2C_6H_5$), 2.8 (s, 3, NCH_3), 6.25–6.7 (m, 3, C_5H, C_7H, C_8H), 7.7–5 (m, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.45; H, 6.28; N, 10.27. Found: C, 70.50; H, 6.48; N, 10.37.

The monohydrochloride (mp 135–145° dec) was prepared and recrystallized from 2-propanol–methylene chloride.

Anal. Calcd for $C_{16}H_{17}ClN_2$.HCl: C, 62.14; H, 5.82; N, 9.06. Found: C, 62.25; H, 6.12; N, 9.06.

4-Benzyl-6-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (4b).—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1 ml (0.014 mol) of thionyl chloride, and 40 ml of methylene chloride was stirred at room temperature for 15 min. The solvent was removed under reduced pressure and the dark purple residue was dissolved in 40 ml of dry tetrahydrofuran. This solution was added to a suspension of 1 g of lithium aluminum hydride in 40 ml of tetrahydrofuran whereupon immediate decolorization was observed. The reaction mixture was hydrolyzed by addition of 5 ml of water. The inorganic material was filtered and washed with ether. The filtrate was dried and evaporated to leave 2.7 g of residue which was chromatographed on 60 g of silica gel with benzene, followed by benzene–ether (1:1, v/v). Evaporation of the fractions eluted with benzene and crystallization of the residue from methylene chloride–hexane yielded 1.33 g (49%) of product: mp 122–124°; nmr ($CDCl_3$) δ 2.78 (s, 3, NCH_3), 3–3.5 (m, 4, C_2 H, C_3 H), 4.37 (s, 2, $NCH_2C_6H_5$), 6.25–6.7 (m, 3, C_5 H, C_7 H, C_8 H), 7.21 (s, 5, C_6H_5).

Anal. Calcd for $C_{16}H_{17}ClN_2$: C, 70.44; H, 6.28; N, 10.26. Found: C, 70.16; H, 6.27; N, 10.23.

The fractions eluted with benzene–ether (1:1) left 0.2 g of oily 5-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline (**3b**).

Compound **4b** was also prepared by heating 6-chloro-1-methyl-1,2,3,4-tetrahydroquinoxaline with benzyl chloride.

1-Acetyl-4-acetoxy-7-chloro-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (5).—A mixture of 8.25 g (0.03 mol) of 7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1a**), 100 ml of methylene chloride, 15 ml of acetic anhydride, and 20 ml of pyridine was allowed to stand at room temperature for 3 hr. The reaction mixture was washed twice with water, dried over sodium sulfate, and evaporated. The residue was crystallized from ether–hexane to give 7.3 g (68%) of product: mp 134–136°; ir ($CHCl_3$) 1750 (OC=O), 1645 cm^{-1} (NC=O); uv max 237–238 mμ (ε 8820), inflection 280 (530).

Anal. Calcd for $C_{19}H_{19}ClN_2O_3$: C, 63.60; H, 5.34; N, 7.81. Found: C, 63.62; H, 5.45; N, 7.78.

1-Acetyl-7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (6).[2]—A solution of 7.2 g (0.02 mol) of the diacetate **5** in 100 ml of warm methanol was treated with 40 ml of 1 *N* sodium hydroxide and the mixture was stirred for 15 min at 40–50°. The crystals which precipitated upon the addition of ice were collected, washed with water, and dissolved in methylene chloride. The solution was dried and evaporated. Crystallization of the residue from ethyl acetate–hexane yielded 4.9 g (77%) of the known **6**, mp 160–162°.

(7) J. C. Cavagnol and F. Y. Wiselogle, *J. Amer. Chem. Soc.*, **69**, 795 (1947).

1-Acetyl-7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (7).[2]—A mixture of 3.2 g (0.01 mol) of 1-acetyl-7-chloro-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine, 60 ml of methylene chloride, and 4 ml of (0.044 mol) of phosphorus oxychloride was stirred at room temperature for 3 hr. The usual hydrolytic work-up left 2.7 g of residue which was chromatographed on 90 g of silica gel with ethyl acetate. Crystallization of the evaporated clean fractions from ethyl acetate–hexane yielded 1.4 g (47%) of product, mp 164–166° (some starting material was eluated first).

6-Chloro-1-methyl-4-phenylcarbamoyl-1,2,3,4-tetrahydroquinoxaline (8).—A mixture of 2.9 g (0.01 mol) of 7-chloro-4-hydroxy-1-methyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1b**), 1.5 g (0.0125 mol) of phenyl isocyanate, and 40 ml of toluene was refluxed for 24 hr. The crystals which separated from the cooled reaction mixture were collected by filtration and recrystallized twice from ethyl acetate–ethanol to yield 1.2 g (40%) of **8**: mp 190–192°; nmr (DMSO-*d*) δ 2.89 (s, 3, NCH_3), 3.1–4 (m, 4, C_2 H, C_3 H), 8.85 (s, 1, NH); uv max 227–228 mμ (ϵ 24,300), 244–246 (20,800), 273–274 (17,900); ir (KBr) 3250 (NH), 1640 cm^{-1} (NC=O).

Anal. Calcd for $C_{16}H_{16}ClN_3O$: C, 63.68; H, 5.34; N, 13.92. Found: C, 63.48; H, 5.39; N, 14.01.

The original filtrate was extracted three times with 1 *N* hydrochloric acid. The combined extracts were made alkaline with ammonia and extracted with benzene. The dried and evaporated extracts left a yellow oil which was chromatographed on 40 g of silica gel with ethyl acetate. The known 7-chloro-2,3-dihydro-1-methyl-5-phenyl-1*H*-1,4-benzodiazepine (0.18 g, 6.6%) was obtained, melting point and mixture melting point with an authentic sample,[3] 97–99°.

7-Chloro-2,3-dihydro-1,3-dimethyl-5-phenyl-1*H*-1,4-benzodiazepine (2c).—A mixture of 5 g (0.0165 mol) of 7-chloro-1,3-dimethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine (**1c**), 2.5 g (0.045 mol) of potassium hydroxide, and 50 ml of ethanol was refluxed for 24 hr. The solvent was removed under reduced pressure and the residue was distributed between benzene and water. The organic layer was dried over sodium sulfate and evaporated. Crystallization of the residue from methylene chloride–petroleum ether gave 3.1 g (66%) of product, mp 102–104°.

Anal. Calcd for $C_{17}H_{17}ClN_2$: C, 71.70; H, 6.02. Found: C, 71.90; H, 6.24.

By the same procedure the known compounds **2a**[3] and **2b**[3] were obtained from **1a**[2] and **1b** in 93 and 72% yield, respectively.

Registry No.—**1b**, 28121-71-3; **1c**, 28199-16-8; **1d**, 28199-17-9; **2c**, 28199-18-0; **3b**, 28199-19-1; **3b** benzoyl, 28199-20-4; **3c**, 28199-21-5; **3c** *p*-chlorobenzoyl, 28199-22-6; **3d**, 28199-23-7; **3d** HCl, 28199-24-8; **4b**, 28199-25-9; **5**, 28199-26-0; **6**, 1803-97-0; **7**, 1803-95-8; **8**, 28199-28-2; **9c**, 28199-29-3; **9d**, 28199-30-6.

Acknowledgment.—We wish to thank the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. F. Scheidl for the microanalyses, Dr. T. Williams for the nmr spectra, Dr. Toome for the uv spectra, and Mr. S. Traiman for the ir spectra.

Pyrimidines. XI. The Conversion of 5-Hydroxyuracils into 6-Alkyluracils *via* Claisen Rearrangements[1]

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Received October 2, 1970

Approaches to the synthesis of 6-carbon-substituted pyrimidine nucleosides from 5-hydroxypyrimidine nucleosides have been investigated using N-alkylated 5-hydroxyuracils as model compounds. 5-Allyl ethers of hydroxyuracils readily undergo Claisen rearrangement at ~120° to give the 6-allyl-5-hydroxyuracils in very high yield. These rearrangements proceed by a normal intramolecular Claisen mechanism. Under more drastic conditions (207°), 5-allylamino-1,3-dimethyluracil undergoes an amino-Claisen rearrangement to 6-allyl-5-amino-1,3-dimethyluracil. 5-Benzyloxy-1,3-dimethyluracil undergoes a different type of rearrangement at 207° to give 6-benzyl-1,3-dimethyl-5-hydroxyuracil. Direct electrophilic attack at C-6 of 5-hydroxyuracils is demonstrated with the hydroxymethylation of 1-methyl-5-hydroxyuracil. Two methods for removal of a pyrimidine 5-hydroxyl group are given. Thus hydrogenolysis of the 5-tetrazolyl ether of 1,3-dimethyl-6-propyl-5-hydroxyuracil and treatment of 1,3-dimethyl-5-mesyloxy-6-propyldihydrouracil with 1,5-diazobicyclo[5.4.0]-undecene-5 (DBU) both afford 1,3-dimethyl-6-propyluracil. The synthesis of 5-allyloxyuridine and subsequent Claisen rearrangement to give 6-allyl-5-hydroxyuridine is described.

Orotidylic acid (the 5′-phosphate ester of 6-carboxyuridine) plays an important role in the biosynthesis of the nucleotide components of ribonucleic acid. Synthetic pyrimidine nucleosides bearing a carbon substituent at C-6 are of interest because of their structural similarity to orotidylic acid, and it is possible that compounds of this class may interfere with nucleic acid metabolism. However, 6-carbon-substituted nucleosides are not easily prepared and the first examples of synthetic compounds of this type were described only recently.[2,3] These compounds, the 6-methyl and 5,6-dimethyl analogs of uridine and cytidine, were prepared in low yield by use of conventional procedures involving the initial condensation of suitable 6-methylcytosines with halogeno sugars.

An alternative approach to the synthesis of 6-substituted nucleosides, namely substitution of C-6 of a *preformed* nucleoside, is shown in Scheme I, which illustrates two possible methods for converting a 5-hydroxyuracil A into a 6-carbon substituted uracil C. One route involves the rearrangement of suitable 5-hydroxyuracil ethers B to give the isomeric 6-substituted 5-hydroxyuracils D. The other route involves the formation of compounds D by direct attack of a carbon electrophile at C-6 of A. Removal of the 5-hydroxyl group of D would then effect an overall synthesis of C from A. We have now investigated these general approaches and the results obtained using N-alkylated 5-hydroxyuracils as models form the subject of this paper.

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478), and by a Postdoctoral Fellowship (to A. T.) from the Westchester Division of the American Cancer Society.

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