2-Phenyl-4*H*-3,1-benzoxazin-4-one (**2a**) was synthesized independently according to the procedure described by Bogert, *et al.*,[15] mp 124° (lit.[15] mp 124.5°).

2-(4′-Bromophenyl)-4*H*-3,1-benzoxazin-4-one (**2b**) was synthesized by a modification of Bogert's[15] procedure with *p*-bromobenzoyl chloride, mp 185–189° (lit.[16] mp 183–184°).

The cyclohexane, chloroform, benzene, and acetone were spectroscopic grade. They were further dried over magnesium sulfate and distilled through a 30-cm column. Only the middle cuts were used. The cyclohexene, toluene, and methylisopropyl ketone were reagent grade and were purified as described above. The 95% ethanol was made from absolute ethanol and distilled water. The acetic acid was reagent grade.

Typical Irradiation Experiments. With Rayonet 2537-and 3500-Å Lamps.—**1a** or **1b** (0.5 g) was dissolved in 650 ml of solvent, placed in a quartz reaction vessel fitted with a magnetic stirrer, and irradiated for an extended period of time.

With Hanovia 450-W Medium-Pressure Immersion Lamp (No Filter).—One gram of **1a** or **1b** was dissolved in 750 ml of solvent, placed in a water-cooled reaction chamber, and irradiated for 1–3 hr. The benzoxazinone (**2a** or **2b**) was separated from the unreacted starting material by sublimation (95°, 0.1 mm, 30 hr).

Quantum Yields.—For quantum-yield determinations light from a Bausch and Lomb high-intensity monochromator equipped with an Osram HBO-200W super-pressure mercury source was employed. The monochromator settings were at 254, 265, 295, 302, 305, and 350 $m\mu$ and the exit slits were set at 4 mm. Under these conditions the maximum band width was 29.6 $m\mu$. The light passed directly into a standard glass-stoppered 10 × 10 mm silica cuvette which served as the reaction vessel. The cell was held 5.5 cm from the exit port of the monochromator in a metal compartment maintained at constant temperature by flowing water. Light incident on the reaction solution was determined by irradiating samples of actinometer solution both before and after irradiation of the reaction solution. The extent of reaction was determined by the decrease in absorbance at 442 $m\mu$ with **1a** and 450 $m\mu$ with **2a**, and the period of irradiation was such that the reaction proceeded less than 10% to completion. Calculations of quantum yields were performed with the procedure described by Calvert and Pitts.[17]

Spin Orbit Coupling.—Irradiation of a 10^{-4} *M* solution of **1b** in cyclohexane showed a decreased rate of reaction from that of the nonbrominated material, **1a** (see Table I).[6] In order to determine the nature of this rate retardation as a spin orbit effect,[5] a cyclohexane solution of 13 ml of 1.08×10^{-4} *M* **1a** and 1 ml of ethyl bromide was irradiated in reference to a sample of 10^{-4} *M* **1a** in cyclohexane without ethyl bromide. An observed rate decrease in the former solution seemed to establish the intermolecular spin orbit effect.[4]

Registry No.—**1a**, 1969-74-0; **2a**, 1022-46-4.

Acknowledgment.—One of us (D. R. E.) wishes to express his indebtedness to Professor O. L. Chapman for many helpful discussions.

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A Facile Synthesis of New Heterocycles from Glutaraldehyde

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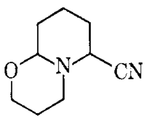
Received June 8, 1970

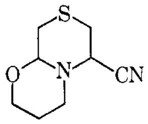
The reaction of glutaraldehyde dicyanohydrin with 3-aminopropanol to give the reduced pyrido[2,1-*b*][1,3]-oxazine (**1**) has been reported.[1] The apparent resemblance of this reaction to the remarkable Robinson–Schöpf synthesis[2] of pseudopelletierine from methylamine, acetone dicarboxylic acid, and glutaraldehyde suggested the following extensions.



1

The reported procedure has been simplified and the yields improved by the use of a phosphate buffer and by the generation of the cyanohydrin *in situ* rather than in a separate step.[3] Thus an 80% yield of **1** is obtained when potassium cyanide (1.5 mol), glutaraldehyde (1.0 mol), and 3-aminopropanol (1.07 mol) are stirred in a phosphate buffer at pH 4 for 4 hr compared with 67% after 20 hr from the pure dicyanohydrin.[1] The reaction is pH sensitive and proceeds best between pH 3 and 7, only resinous products being formed at high pH. This pH dependence has also been reported for the synthesis of pseudopelletierine[4] and suggests that both reactions share a Mannich-like mechanism.

The following heterocycles were prepared by this simplified procedure.



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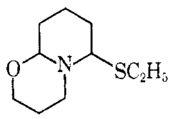

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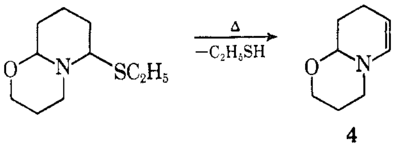
Compound **2**, a new ring system, was prepared in 45% overall yield from thiodiacetaldehyde diethylacetal.[5] Replacement of potassium cyanide in the synthesis by ethanethiol gave the product **3** in 88% yield. Although this product is thermally unstable and fails to give crystalline products with hydrochloric, perchloric, or picric acids, a concentrate with the proper ir spectrum was obtained. The ir spectrum of the distillation product showed a band at 1630 cm^{-1} which indicated that the enamine **4** had been formed. All attempts to characterize this labile enamine failed. Attempts to prepare more stable products by using diethyl malonate or ethyl cyanoacetate with glutaraldehyde and 3-aminopropanol in aqueous alcoholic solution instead of cyanide led only to intractable gums. As expected, amines (ammonia, benzylamine) and succinimide failed to give the corresponding bicyclic 1,1-diamine derivatives. An unusual 1,1-diamine, **5**, was, however, prepared by sub-



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[1] H. E. Johnson, U. S. Patent 3,375,249 (1968), to Union Carbide Corporation.

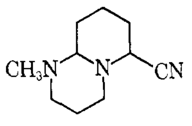
[2] Sir R. Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917); C. Schöpf and G. Lehmann, *Justus Liebigs Ann. Chem.*, **518**, 1 (1935); C. Schöpf, *Angew. Chem.*, **50**, 779, 797 (1937); L. A. Paquette and J. W. Heimaster, *J. Amer. Chem. Soc.*, **88**, 763 (1966).

[3] H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 1298 (1962).

[4] A. C. Cope, H. L. Dryden, C. G. Overberger, and A. A. D'Addieco, *J. Amer. Chem. Soc.*, **73**, 3416 (1951).

[5] C. L. Zirkle, F. R. Gerns, A. M. Parloff, and A. Burger, *J. Org. Chem.*, **26**, 395 (1961).

stituting *N*-methylpropane-1,3-diamine for 3-aminopropanol in the synthesis of **1**. The diamine was sufficiently stable in neutral or basic, aqueous solution to be readily isolated but no crystalline salts could be prepared.



5

These reactions are further examples of intramolecular Mannich reactions some of which have been described by Leonard[6] and elegantly exploited by Wenkert[7] in the synthesis of alkaloids. The successive generation of two imine (or iminium) groups by reaction of a primary amine with a dialdehyde in the presence of a nucleophile appears to provide a versatile synthetic tool which has yet to be widely used. Tricyclic products[8] have already been reported from this type of reaction and Lichtenthaler reports[9] an analogous reaction of glutaraldehyde, nitromethane, and benzylamine to give a cyclohexane derivative.

Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a Varian HA-100 nmr spectrometer.

6-Cyano-3,4,7,8,9,9a-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]-oxazine (1).—A solution of potassium cyanide (24.45 g, 0.375 mol) in water (150 ml) was brought to pH 7 by the addition of 17 ml of 85% phosphoric acid. A 50% aqueous solution of glutaraldehyde (50 g, 0.25 mol) was added at 20° causing some turbidity. 3-Aminopropanol (20 g, 0.267 mol) was then added dropwise. During the addition, the temperature rose to 38° and was accompanied by a temporary rise in pH to 8 followed by a decrease to pH 7. After standing for 4 hr, the pale yellow solution was extracted with five 25-ml portions of methylene chloride. The combined extracts were dried (Na_2SO_4), concentrated, and distilled, giving 32.4 g (78%) of the product **1**: bp 128–130° (0.5 mm); ir (film) 2941, 2857, 2739 (CH), 2222 ($C\equiv N$), 1265, 1258, 1142, 1123, 1092, 1069, 1061 (OCN);[10] nmr ($CDCl_3$) δ 1.3–2.2 (m, 9), 2.6–3.25 (m, 2), 3.4–4.1 ppm (m, 4). Treatment of **1** with anhydrous hydrogen chloride in ether and recrystallization from ether gave the hydrochloride: mp 145–146°; ir (KBr) 2958, 2915, 2739 (CH), 2500 (broad, NH, obscuring $C\equiv N$), 1298, 1156, 1096, 1070 cm^{-1} (COC).[10]

Anal. Calcd for $C_9H_{15}N_2OCl$: C, 53.33; H, 7.46; N, 13.82. Found: C, 53.15; H, 7.52; N, 14.02.

6-Ethylthio-3,4,7,8,9,9a-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]-oxazine (3).—A 50% aqueous solution of glutaraldehyde (255 g, 1.3 mol) was added with stirring to a mixture of ethanethiol (78.9 g, 1.27 mol), methanol (90 ml), and water (300 ml) at 0°. 3-Aminopropanol (90 g, 1.2 mol) was added dropwise with stirring during which time the temperature rose to 32° and the mixture became heterogeneous and bright yellow. After stirring overnight, the mixture was basified (NaOH) and extracted with six 100-ml portions of methylene chloride. The dried (Na_2SO_4) extract was filtered through activated charcoal and concentrated to give a clear orange oil (211.9 g, 88% based on 3-aminopropanol), ir (film) 2941, 2857, 2732 (CH), 1312, 1273, 1149, 1126, 1098 cm^{-1} (COC).[10]

Anal. Calcd for $C_{10}H_{19}NOS$: C, 59.67; H, 9.52; N, 6.96. Found: C, 60.00; H, 9.43; N, 6.68.

Attempted distillation of the product from a Woods metal bath at 155° gave a small amount of yellow liquid (crude **4**): bp 62–66° (1.75 mm); ir (film) 1630 ($C{=}C$), 1200–1100 cm^{-1} (COC).[10]

6-Cyano-1-methyl-1,2,3,4,7,8,9,9a-octahydro-6*H*-pyrido[1,2-*a*]-pyrimidine (5).—The pH of a solution of potassium cyanide (24.45 g, 0.375 mol) in water (150 ml) was brought to 7 by the addition of 17 ml of 85% phosphoric acid. A 50% aqueous solution of glutaraldehyde (50 g, 0.25 mol) was added, followed by the dropwise addition of 24.2 g (0.275 mol) of *N*-methyl-1,3-propanediamine. The diamine caused an exothermic reaction to 55° and an increase in pH which was controlled by dropwise addition of 85% phosphoric acid.

After the addition was complete, the heterogeneous mixture was allowed to stand for 4 hr, basified with 40% sodium hydroxide solution, and extracted with three 100-ml portions of ether. The dried (Na_2SO_4) extracts were concentrated and distilled giving 10 g of **5** (20.2%): bp 136–137° (2.5 mm); ir (film) 2941, 2857, 2793, 2710, 2577 (CH), 2222 cm^{-1} ($C\equiv N$).

Anal. Calcd for $C_{10}H_{17}N_3$: C, 66.99; H, 9.57; N, 23.44. Found: C, 66.99; H, 9.39; N, 23.17.

A further 5.1 g, bp 137–143° (2.5 mm), of material with a virtually identical ir spectrum was collected bringing the total yield to 30.5%.

6-Cyano-3,4,6,7,9,9a-hexahydro-2*H*-1,4-thiazino[3,4-*b*][1,3]-oxazine (2).—Thiodiacetaldehyde tetraethylacetal[5] (50 g, 0.188 mol) was stirred with 250 ml of water containing 5 ml of concentrated hydrochloric acid at 55°. The mixture became homogeneous in 10 min and was stirred for a further 50 min. After cooling to 0°, a solution of 18.8 g (0.29 mol) of potassium cyanide in 50 ml of water at 0° was added, the pH being kept below 7.5 by concurrent addition of cold 50% aqueous phosphoric acid (30 ml). A flocculent white precipitate remained suspended in the mixture. 3-Aminopropanol (14.1 g, 0.188 mol) dissolved in 25 ml of water was then added, the pH again being maintained between 6.5 and 8 by the addition of 50% aqueous phosphoric acid (10 ml required). The temperature was allowed to rise to 25° during the addition and the precipitate virtually dissolved leaving a pale yellow solution. The mixture was allowed to stand overnight and was then basified and extracted with three 75-ml portions of methylene chloride. The dried ($MgSO_4$) extract was concentrated to give 21.4 g of a yellow oil which crystallized on standing. Recrystallization from ethanol gave 15.6 g (45%) of crude product, mp 116–119°, which on further recrystallization gave pure **2**, mp 126–127°. The mother liquors smelled strongly of hydrogen cyanide: ir (KBr) 2980, 2898, 2857, 2777, 2739, 2666 (CH), 2257 ($C\equiv N$), 1282, 1257, 1234, 1219, 1206, 1183, 1145, 1111, 1003, 1070 cm^{-1} (COC);[10] nmr ($CDCl_3$) δ 1.6 (m, 1), 2.1 (m, 1), 2.6–3.3 (m, 6), 3.6 (m, 1), 4.1 (m, 3).

Anal. Calcd for $C_8H_{12}N_2OS$: C, 52.16; H, 6.57; N, 15.21. Found: C, 52.00; H, 6.53; N, 14.99.

Registry No.—**1**, 19791-32-3; **1** hydrochloride, 26693-23-2; **2**, 15311-74-7; **3**, 26731-49-7; **4**, 26693-20-9; **5**, 26693-21-0.

Acknowledgments.—The author wishes to thank the following: Professors H. O. House and H. H. Wasserman for helpful discussions; Mr. C. B. Strow and Mr. H. L. Joyce and their colleagues for the nmr and ir spectra.

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Ring Strain Effects on Aromatic Reactivity. A Molecular Orbital Treatment

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Received June 29, 1970

The first theoretical discussion of the reduced reactivity of the α position of strained benzocycloalkenes was advanced by Mills and Nixon[1] over 40 years ago.

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