Synthesis of 1-Substituted-3-bromopyrrolidines

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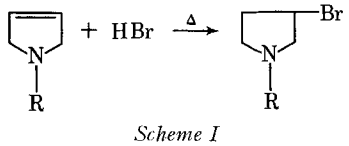
Considerable interest has been shown in 3-substituted pyrrolidines because of their physiological activity on the central nervous system. The preparation of several 1-substituted-3-bromopyrrolidines is described. In addition, a unique technique of halopyrrolidine synthesis, virtually eliminating self-quaternization, is presented.

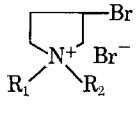
INTEREST in 1-alkyl-3-halopyrrolidines has been stimulated by their usefulness as intermediates for the preparation of central nervous system stimulants, antispasmodics, ganglionic stimulants, anticholinergics, and parasympathetic depressants (1–5). Many theoretical routes to 1-alkyl-3-halopyrrolidines are possible; however, most are quite costly and involve several steps. Preparation of 1-alkyl-3-halopyrrolidines by hydrohalogenation of 1-alkyl-Δ^3-pyrrolines offers an inexpensive and direct approach to this type of compound. Extensive information regarding the addition of hydrogen halides to straight chain olefins is present in the literature (6–8). Some work has been reported using cyclic olefins (9, 10); however, no reference was found disclosing the addition of hydrogen halides to Δ^3-pyrrolines.

1-Alkyl-Δ^3-pyrrolines were prepared by cyclization of *cis*-1,4-dichlorobutene-2 with the appropriate primary amines (11, 12). Low reaction temperature conditions favorable for hydrobrominating butene-1 (8) and pentene-1 (6) were not successful with the 1-substituted-Δ^3-pyrrolines in aqueous or nonaqueous media. Successful hydrobromination was achieved using 60% aqueous HBr at 120–125°. No reaction was obtained with the commercially available 48% HBr at the same conditions. Although hydrobromination of 1-substituted-Δ^3-pyrrolines obviously does not occur with the facility of the olefin systems, here too, the rate of HBr addition was found to far exceed hydrochlorination under the necessary temperature conditions. (Scheme I.)



Scheme I

The 1-substituted-3-bromopyrrolidines were subsequently converted to their amine and quaternary salts. (I–VI.)



R_1	R_2
I, H	CH_3
II, CH_3	CH_3
III, H	C_2H_5
IV, CH_3	C_2H_5
V, H	$C_6H_5CH_2$—
VI, CH_3	$C_6H_5CH_2$—

Received March 22, 1967, from the S. B. Penick Research Laboratory, Orange, N J 07050

Accepted for publication May 19, 1967.

The authors thank J. Swidinsky for synthesizing the substituted pyrrolines and Mr. Russo and his staff, S. B. Penick and Company Control Laboratory, for the analyses reported in this paper.

The preparation of the above pyrrolidine salts, with the exception of V, afforded no difficulty. Some dissociation of the pyrroline salt occurs during the hydrobromination reaction as shown by the resultant formation of a mixture of 1-ethyl-3-chloropyrrolidine and 1-ethyl-3-bromopyrrolidine when starting with 1-ethyl-Δ^3-pyrroline hydrochloride. Self-quaternization occurs to a significant degree also during the hydrobromination reaction, especially with I, forming presumably 1-alkyl-1-(1′-alkyl-3′-pyrrolidyl)-3-bromopyrrolidinium bromides. The authors have found that by first forming the quaternary salt of the 1-substituted-Δ^3-pyrrolines, self-quaternization during the hydrobromination reaction is minimized. For example, hydrobromination of 1-methyl-Δ^3-pyrroline methobromide produced 57% of II and a 32% recovery of the starting quaternary, whereas hydrobromination of 1-methyl-Δ^3-pyrroline gave only 22% of I and a 10% recovery of the starting amine.

EXPERIMENTAL

The hydrobromination reaction was conducted in a 500-ml. pressure bottle mounted on a Parr shaker apparatus equipped for heating. Since bromopyrrolidines tend to self-quaternize even under refrigeration, the products were converted immediately after isolation to their amine or quaternary salts with hydrogen bromide or methyl bromide. Benzene was used as the reaction medium and afforded a quantitative recovery of the respective pyrrolidine salts.

1-Methyl-3-bromopyrrolidine—A solution of 16.39 Gm. (0.1 mole) of 1-methyl-Δ^3-pyrroline hydrobromide in 67.5 Gm. (0.5 mole) of 60% HBr was heated at 120–125° for 24 hr. After cooling to 25°, the reaction mixture was adjusted to pH 11 by the addition of 25% NaOH (100 Gm.). The oil layer was extracted with benzene (2 × 25 ml.), washed with water (10 ml.), and azeotroped dry at atmospheric pressure while charcoaling for 15 min. Filtration of the charcoal resulted in a light yellow benzene solution which was analyzed by vapor phase chromatography; yield 3.6 Gm. of 1-methyl-3-bromopyrrolidine (22% of theory). This benzene solution was carefully gassed with dry hydrogen bromide to pH 7. The amine salt was filtered and recrystallized from acetone to yield I, m.p. 92–93°.

Anal.—Calcd. for $C_5H_{11}Br_2N$: N, 5.72; Br^-, 32.6; Br, 65.2. Found: N, 5.79; Br^-, 33.4; Br, 64.6.

1-Ethyl-3-bromopyrrolidine—This compound was prepared as described above in 60% of theory yield and was converted to III, m.p. 89–90°.

Anal.—Calcd. for $C_6H_{13}Br_2N$: N, 5.4; Br^-, 30.9; Br, 61.8. Found: N, 5.5; Br^-, 31.8; Br, 62.1.

1-Benzyl-3-bromopyrrolidine—This substance was prepared in the same manner in 52% of theory yield and converted by the addition of methyl bromide gas to VI, m.p. 134–135°.

Anal.—Calcd. for $C_{12}H_{17}Br_2N$: N, 4.2; Br^-, 23.9; Br, 47.8. Found: N, 4.9; Br^-, 24.8; Br, 48.9.

1-Methyl-Δ^3-pyrroline Methobromide—A solution of 8.3 Gm. (0.1 mole) of 1-methyl-Δ^3-pyrroline in 100 ml. of methyl ethyl ketone was treated with 9.5 Gm. of methyl bromide gas. The resulting solid was filtered to yield 17.79 Gm., 100% of theory, 1-methyl-Δ^3-pyrroline methobromide, m.p. 303–304°.

Anal.—Calcd. for $C_6H_{12}BrN$: N, 7.88; Br^-, 44.9; Br, 44.9. Found: N, 8.58; Br^-, 45.37; Br, 45.40.

1-Methyl-3-bromopyrrolidine Methobromide (II)—A solution of 17.79 Gm. (0.1 mole) of 1-methyl-Δ^3-pyrroline methobromide in 67.5 Gm. of 60% HBr was reacted as described above. The excess hydrobromic acid was distilled and the residue crystallized from 2 B ethyl alcohol (90 ml.) to yield 57% of theory II, m.p. 190–191°.

Anal.—Calcd. for $C_6H_{13}Br_2N$: N, 5.4; Br^-, 30.9; Br, 61.8. Found: N, 5.3; Br^-, 32.1; Br, 62.9.

1-Ethyl-3-bromopyrrolidine Methobromide (IV)—This compound, similarly prepared from 1-ethyl-Δ^3-pyrroline methobromide, m.p. 265–266°, was extremely hygroscopic and required rapid crystallization from a mixture of methyl ethyl ketone (50 ml.) and 2 B ethyl alcohol (10 ml.), m.p. 134–135°.

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Communications

Synthesis of the *Veratrum* Alkaloid Verazine from Tomatid-5-en-3β-ol

Sir:

Recently, several new minor alkaloids have been isolated from *Veratrum album* subsp. *lobelianum* (Bernh.) Suessenguth (1). In a preceding communication (2) we described the structural elucidation of one of these new alkaloids, verazine, which according to chemical transformations and physical measurements possesses the structure 25*S*-22,26-epimino-cholesta-5,22(*N*)-dien-3β-ol (I). In this paper the establishment of this structure by a nine-step synthesis of compound I starting from the spirosolane alkaloid tomatid-5-en-3β-ol (II) (3) is reported.

Reduction of II with sodium borohydride in methanol afforded (22*S*:25*S*)-22,26-epimino-cholest-5-ene-3β,16β-diol (III), m.p. 165–167°, 189–191°, and $[\alpha]_D$ −69.1°[1] in 70% yield. Acetylation of III with acetic anhydride/pyridine at 20° for 14 hr. gave nearly quantitatively the amorphous *O,O,N*-triacetate (IV) with $[\alpha]_D$ −10.3°. Hydrolysis of this compound by refluxing with 5% potassium hydroxide in methanol for 2 hr. furnished (22*S*:25*S*)-22,26-acetylepimino-cholest-5-ene-3β, 16β-diol (V), m.p. 248–250°, $[\alpha]_D$ −35° (yield 81%). The *N*-acetyl-diol (V) through partial oxidation with 1 equivalent chromium trioxide in acetic acid–sodium acetate yields 80% (22*S*:25*S*)-22,26-acetylepimino-3β-hydroxy-cholest-5-en-16-one (VI), m.p. 213–215°, $[\alpha]_D$ −121.1°. Treatment of this ketone (VI) with ethanedithiol–hydrochloric acid followed by desulfurization of the obtained thioketal (VII) with Raney nickel in ethanol gave (22*S*:25*S*)-22,26-acetylepimino-cholest-5-en-3β-ol (VIII), m.p. 256–258°, and $[\alpha]_D$ −19.4° (74%).

[1] Melting points are corrected. All rotations in chloroform (c = 0.5). The infrared and molecular mass spectra of all new compounds described in this communication are in agreement with the proposed structure. The authors are indebted to Dr. R. Tummler, Dresden, for the molecular mass spectra.