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COMMUNICATIONS

Novel Behavior of *N*-Methyl-3-benzoyl-3-hydroxypiperidine under Conditions of Von Braun Demethylation

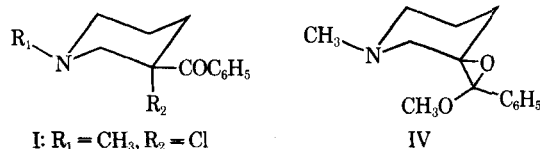
Keyphrases □ *N*-Methyl-3-benzoyl-3-hydroxypiperidine—novel behavior, Von Braun demethylation □ *N*-Methylethanolamines, tertiary—Von Braun demethylation, novel reaction with cyanogen bromide □ Von Braun demethylation—novel reaction of tertiary *N*-methylethanolamines with cyanogen bromide

Sir:

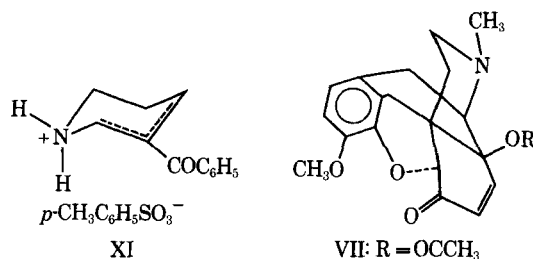
The Von Braun demethylation (1, 2) effected by treatment of tertiary *N*-methylethanolamines with CNBr has been successful with Compounds I-IV (2) but has failed in the conversion of V to VI (2). The unusual behavior of similarly constituted tertiary *N*-methylethanolamines (3-5) is borne out, if only in a negative sense, by the work of others (6, 7) who described the demethylation of 14-acetoxycodeinone (VII) and 14-acetyoxydihydrocodeinone (VIII) but not of the 14-hydroxy analogs (IX and X) from which they were prepared. The nature of the impediment by the hydroxyl group is suggested by studies of other investigators (8-10) on alkyl cyanates, by previous studies in these laboratories on epoxy ether (IV) formation from I (13-15) and on the chemistry of the hydroxyl group in V, IX, and X (3-5), and by the character of the reaction mixture and products obtained by treatment of V with CNBr.

Under the usual reaction conditions, V (8 g.) afforded a benzene-insoluble, water-soluble plastic mass. The IR spectrum exhibited bands at 2218 (CN) and 1675 cm^{-1} (C=O, ketone) as well as a band at 3470 cm^{-1} , characteristic of but weaker than the expected absorption for the OH group of V. The acid-washed, benzene-soluble fraction of the reaction mixture (<1 g.) exhibited bands at 2218 (CN) and 1680 cm^{-1} (C=O, ketone) but no band in the 3500- cm^{-1} region. This oil exhibited a positive Beilstein test for halogen. Follow-

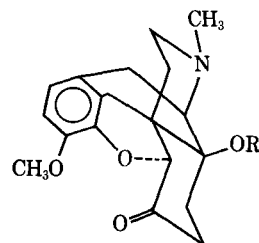
ing hydrolysis in concentrated HCl, water and excess acid were removed *in vacuo*. The residue was dissolved in water. The solution was washed with chloroform, alkalinized with sodium carbonate, and extracted again with chloroform. Evaporation of the extract afforded



- I: $R_1 = \text{CH}_3, R_2 = \text{Cl}$
 II: $R_1 = \text{CH}_3, R_2 = \text{O}_2\text{CCH}_3$
 III: $R_1 = \text{CH}_3, R_2 = \text{OCH}_3$
 V: $R_1 = \text{CH}_3, R_2 = \text{OH}$
 VI: $R_1 = \text{CN}, R_2 = \text{OH}$
 XII: $R_1 = \text{H}, R_2 = \text{OH}$
 XIII: $R_1 = \text{CH}_3, R_2 = \text{OCN}$
 XIV: $R_1 = \text{CH}_3, R_2 = \text{Br}$
 XV: $R_1 = \text{CN}, R_2 = \text{OCN}$
 XVI: $R_1 = \text{CN}, R_2 = \text{Br}$
 XVII: $R_1 = \text{H}, R_2 = \text{Br}$



- VII: $R = \text{OCCH}_3$
 IX: $R = \text{H}$



- VIII: $R = \text{OCCH}_3$
 X: $R = \text{H}$

<0.5 g. of oil, which was dissolved in 20 ml. of ethanol and treated with a solution of 1.0 g. of *p*-toluenesulfonic acid in 10 ml. of ethanol. The resulting salt (<70 mg.) was either 4,5,6,1- or 1,2,5,6-tetrahydro-3-benzoyl-piperidinium *p*-toluenesulfonate (XI), m.p. 105–106°; IR (mineral oil) 1685 cm.⁻¹ (C=O, $\alpha,\beta,\alpha',\beta'$ -unsaturated ketone) and no band in the 3500-cm.⁻¹ region.

Anal.—Calc. for C₁₉H₂₁NO₄S: C, 63.49; H, 5.89; N, 3.90; S, 8.92. Found: C, 63.9; H, 6.62; N, 3.72; S, 8.82.

While acid may conceivably have been present in trace amounts in the benzene fraction of the reaction mixture, formation of XI from VI by acid catalysis is contrary to all chemical precedent and to all experience with Compounds V, VI, and XII (2, 3, 11–15). This, as well as the fact that the neutral, benzene-soluble oil contains bromine which must be organically bound, clearly requires functionalization of the C₃—OH group of V. Thus, in the presence of CNBr, formation of alkyl cyanate (XIII) must occur. Subsequent considerations clearly implicate this as the first step. Formation of the α -bromo ketone (XIV) from the α -cyanato ketone (XIII) is consistent with both the chemistry of alkyl cyanates (8–10) and the well-known conversion of I to V under *quasi*-Favorskii conditions. The latter reaction is now known to proceed (with retention of configuration) through internally assisted ion pairs (3, 11–15). There is no precedent to support participation of the corresponding cyanamide moiety of XV in cyanate–bromide exchange. In fact, quite the reverse is true (13, 15). This tends to rule out XV as a precursor to XVI and suggests that cyanate formation is the first step.

Predilection of CNBr for the hydroxyl group rather than the amine group in V is explicable on the basis of the following facts. The carbonyl (benzoyl) group has an acid-strengthening effect on the hydroxyl group (3, 4). The hydroxyl group, undoubtedly as a function of its (axial) stereochemistry, is totally hydrogen bonded; as a result, the nitrogen bears significant positive character (3, 4, *cf.*, 5). This rationale augurs well for the absence of measurable quantities of VI in the benzene-soluble fraction and requires that XIV is the precursor of XVI, the principal component of the benzene-soluble fraction. While olefin might have been generated at the levels of XIII–XVI, it may also have been formed from XVII during the workup.

In view of the fact that only one characterizable compound could be isolated from the reaction mixture, and in view of the interesting chemical and stereochemical aspects of this reaction, further investigations are now in progress using optically pure V.

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Efficient Deoxygenation of Water by Gas Permeation

Keyphrases Oxygen levels in water—technique for reduction, gas permeation Deoxygenation of water—by gas permeation Gas permeation—utilized for reducing oxygen levels in water Water—deoxygenation by gas permeation

Sir:

The oxidative processes which drug moieties undergo involve dissolved molecular oxygen, which is assumed to be a free radical propagated route (1, 2). Schou (3) noted that dissolved oxygen levels must reach a critical concentration before the chain reactions are initiated. In a consideration of the kinetic implications of oxidative degradation, it would appear worthwhile to investigate the possibility of developing a simple, rapid, and economical procedure to deoxygenate water used in the preparation of liquid pharmaceutical systems. Therefore, we recently made preliminary studies in the deoxygenation of solvent water utilizing a gas permeator¹ equipped with dacron fibers.

The operation of gas permeators is based on the principle of selective separation using the membrane walls of hollow fibers. The selectivity of the membrane permits removal of a particular component in the system, depending upon the type of fiber employed; the separation follows Fick's law of diffusion. The selection of the proper membrane fiber is based on solubility considerations, because the component to be removed should be more soluble than the water in the membrane.

Cole and Genetelli (4) recently demonstrated that laboratory models of gas permeators are efficient and prac-

¹ Permasep, DuPont.