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# OXAZOLIDINES via the HOFMANN - LOEFFLER REACTION

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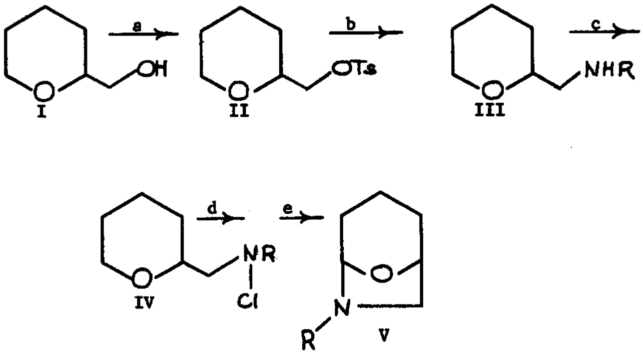
An interest in cyclization reactions, especially those having the possibility of generating the oxazolidine ring system, has caused us to study the Hofmann - Loeffler reaction (1) on substituted 2-amino - methyl tetrahydropyrans. The results reported below constitute the first studies of this reaction wherein cyclization produces an oxazolidine ring.

The overall reaction sequence is shown in Scheme I. Step a , the treatment of commercially available I with p-toluenesulfonyl chloride in pyridine, to yield II, is followed by conversion of II to III by treatment (step b) with the appropriate amine. The conditions of step b vary, depending on the volatility of the amine. The synthesis of

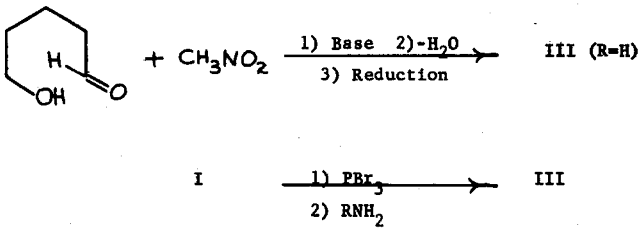
SCHEME I



III (R=H) was accomplished by placing the tosylate in a solution of ammonia in methanol, and heating to 125° in a pressure vessel for one hour. Alternatively for III (R=n-butyl), the tosylate, n-butyl amine and ethanol were refluxed for four hours. The yields of III ranged from 65 - 85%.

The literature relates other syntheses (Scheme II) for the desired III, however, the reaction reported above is more easily carried out and gives higher yields of the product.

SCHEME II

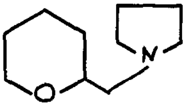


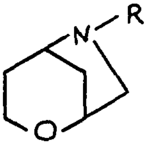
Steps c, d and e of Scheme I constitute the Hofmann - Loeffler reaction. In general, highest yields (Table I) of the 6-aza-8-oxabicyclo-(3.2.1) octanes were obtained by following the procedures of Neale and Walsh (3). Specifically, the amine (III) was dissolved in 2 M sulfuric acid in glacial acetic acid and photolyzed for 6 to 8 hours with pyrex filtered UV light (4). Longer photolysis periods, or the use of unfiltered light, caused considerable, undefined decomposition.

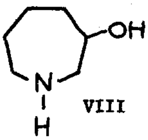
TABLE I

| V (R= ) | | | Percent Yield(2) |
|---|---|---|---|
| H | (waxen solid) | m.p. 73° | 5 |
| $CH_3$ | | b.p. 60°/17mm | 25 |
| $CH_2CH_3$ | | b.p. 33°/2mm | 22 |
| n-butyl | | b.p. 51°/0.5mm | 20 |
| cyclohexyl | | b.p. 100°/0.1mm | 25 |

Mechanistically, an interesting sidelight of the reaction is that the photolysis product of III (R= n-butyl) contains none of the isomer VI (1,5). Also, in no case does there seem to be any material of structure VII (5). The fact that VI and VII do not appear in the product might be attributed to the higher free radical activity ortho to the oxygen atom (6). The major product from each reaction was regenerated III, a not too unusual phenomenon for the Hofmann-Loeffler reaction.


VI


VII


VIII

Briefly, infrared spectral evidence for the formation of the bicycle (V) includes the disappearance of N-H absorption at 3400 cm.$^{-1}$, the shift of C-O absorption from 1075 cm.$^{-1}$ in III to 1025 cm.$^{-1}$ in V (7), and, the introduction of four bands between 800 and 900 cm.$^{-1}$. These latter bands are typical of oxazolidine structures (8). Nuclear magnetic resonance data are now being collected and tentatively corroborate the above assigned structures (9).

Further structural proof for the oxazolidine portion of V (R=H) is the reaction path followed during lithium aluminum hydride reduction. The reduction, with or without added aluminum chloride (10), yields a nitrogen containing oil which demonstrates strong IR absorption at 3400 cm.$^{-1}$, but not at 1600 cm.$^{-1}$. Gas chromatography indicates this reduction product is not III (R=H). The only reasonable alternative, VIII, complies with the experimental data as well as literature suggestions (11).

The author wishes to thank the National Institutes of Health for financial support of this work (12).

## FOOTNOTES

1. For a recent review, see, M. Wolff, Chem. Rev., **63**, 55 (1963).
2. Based on III. Gas chromatography, using both Carbowax 1540 and Silicone SE-30 columns, served as the identification-separation method. All compounds have the correct analysis and demonstrate infrared spectra compatible with the assigned structures. e.g. Anal. cald. for V (R=H), $C_6H_{11}NO$ : C, 63.6; H, 9.75; N, 12.37; mole wt., 113. Found: C, 63.56; H, 9.89; N, 12.19; mole wt., 114. Anal. cald. for V (R=cyclohexyl), $C_{12}H_{21}NO$ : C, 74.0; H, 10.75; N, 7.20. Found : C, 73.73; H, 11.01; N, 6.95.
3. R. Neale and M. Walsh, J. Am. Chem. Soc., **87**, 1255 (1965).
4. The photolysis apparatus consists of a medium pressure mercury lamp of Hanovia design. The photolyzed solutions were one inch from the lamp and thermally insulated by a quartz water jacket.
5. Detection methods included 1), gas chromatography on Carbowax and Silicone columns at 100-150°C, and 2), thin-layer chromatography on Silica Gel G using butanol-acetic acid-water as eluent.
6. Compare, J. Kochi, J. Am. Chem. Soc., **84**, 2122 (1961).
7. Compare the same absorptions for tetrahydrofuran and tetrahydropyran (1070-1140 $cm.^{-1}$) with 8-oxabicyclo(3.2.1)octane (1027 $cm.^{-1}$). A. Cope, J. Am. Chem. Soc., **87**, 3119 (1965).
8. Compare, G. Habermehl, Chem. Ber., **96**, 2029 (1963); M. Senkus, J. Am. Chem. Soc., **67**, 1515 (1945).
9. Nuclear magnetic resonance data are being obtained from Dr. L. Colebrook, University of Rochester, Rochester, New York.
10. E. Eliel and R. Daignault, J. Org. Chem., **30**, 2450 (1965).
11. A comparison is found in the structural proof of the alkaloid samandarine; cf., C. Schopf, et al., Chem. Ber., 2361 (1961).
12. Portions of this paper were presented at the 150th National A.C.S. meeting, Sept., 1965.