Improved Synthesis of 2-Substituted-2-Azabicyclo[2.2.2]octanones

Ronald F. Borne, C. Randall Clark, and Richard L. Peden

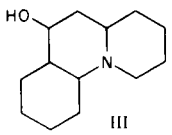
Department of Medicinal Chemistry, School of Pharmacy, University of Mississippi, University, Mississippi 38677

Received January 13, 1973

We are currently involved in studies in which the 2-azabicyclo[2.2.2]octane (isoquinuclidine) ring system is being utilized as a "conformationally rigid" framework for a number of biologically active substances to examine the importance of conformational effects in the interactions of these substances with their biological receptors. Important intermediates in our synthetic approaches are appropiately *N*-substituted 5- and 6-ketones (I and II). These ketones, where R = CH_3, were previous prepared by DeGraw and Kennedy (1) through chromic acid oxi-

I R = CH_3 or $CH_2C_6H_5$ II

dations of the appropriate alcohols. We repeated this procedure but with very poor results--yields of less than 20% were observed. We then explored the dicyclohexylcarbodiimide-DMSO procedure (2) but again with very poor results. A modification of the Oppenauer oxidation using potassium *t*-butoxide was reported by Woodward, *et. al.* (3) to synthesize quininone from quinine. Although it was suggested that this modification appeared to be of particular value in the oxidation of alcohols containing a basic function, few cases appear where this method has been employed. For instance, this method has been successfully used to oxidize dehydropseudocodeine (4) and dihydrothebainol (5). We applied this procedure to 2-benzyl-6-*trans*-hydroxy-2-azabicyclo-[2.2.2]octane and obtained the ketone (previously undescribed) in 77% yield. The oxidation of the 2-methyl-5-*trans*- and 2-methyl-6-*trans*-alcohols also proceeded quite smoothly. Other aminoalcohols have been oxidized by this procedure. Alcohol III gave the corresponding ketone in 60% yield where other oxidative procedures gave maximum yields of 30% (6). We attempted to apply this procedure to simpler alcohols. The oxidations of *N*-methyl-4-hydroxypiperidine and *N*-methyl-3-hydroxypiperidine gave crude products which, on the basis of infrared spectra, were the desired ketones. However, these products resisted all purification attempts.



III

EXPERIMENTAL (7)

2-Benzyl-6-*trans*-hydroxy-2-azabicyclo[2.2.2]octane.

A solution of 30.0 g. (0.13 mole) of 2-benzyl-6-*trans*-hydroxy-2-azabicyclo[2.2.2]octa-3-one (8) in 100 ml. of benzene was added to 100 ml. (0.73 mole) of Red-Al (7). The resulting solution was refluxed for 6 hours, cooled to room temperature, excess hydride destroyed with ethanol and water, and the mixture filtered. The filtrate was dried and evaporated. The residue was distilled to give a clear oil (24.0 g., 80%, b.p. 126-130°/0.07 mm) which solidified on standing. A portion of the solid was recrystallized from *n*-hexane, m.p. 75-76°; ir (film) 3400 cm^{-1} (OH); nmr (deuteriochloroform) δ 1.1-2.2 (broad signals, 4, H-1, H-3, and H-4), 3.75 (s, 2, N-CH_2-Ar), 4.0-4.4 (m, 1, H-6), 7.45 (s, 5, aromatic).

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.42; H, 8.76; N, 6.45. Found: C, 77.33; H, 8.79; N, 6.54.

2-Benzyl-2-azabicyclo[2.2.2]octa-6-one (II, R = $CH_2C_6H_5$).

Benzophenone (29.1 g., 0.16 mole) and potassium *t*-butoxide (8.9 g., 0.08 mole) were combined in 400 ml. of benzene and warmed to 40°. The above alcohol (9.0 g., 0.04 mole) in 60 ml. of benzene was added dropwise. After 30 minutes at 40°, the solution was washed with 3 x 100 ml. portions of water and 5 x 100 ml. portions of 10% hydrochloric acid. The acid extracts were washed with chloroform and made alkaline with potassium carbonate. The basic mixture was extracted with 5 x 100 ml. portions of chloroform. The chloroform extracts were dried and evaporated to yield a yellow liquid. Distillation afforded 7.0 g. (77%, b.p. 113-116°/0.09 mm) of the desired ketone; ir (film) 1740 cm^{-1} (C=O); nmr (deuteriochloroform) δ 1.4-3.4 (broad signals, 10, bicyclic envelope), 3.7 (s, 2, N-CH_2-Ar), 7.5 (s, 5, aromatic). The hydrochloride salt was prepared in the normal manner and recrystallized from ethanol-diethyl ether, m.p. 210-212°.

Anal. Calcd. for $C_{14}H_{18}ClNO$: C, 66.70; H, 7.21; N, 5.56. Found: C, 66.90; H, 7.38; N, 5.45.

Acknowledgement.

The authors gratefully acknowledge financial support of this research by a grant (1 R01 NS09188) from the National Institute

of Neurological Diseases and Stroke and, in part, by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

REFERENCES

(1) J. I. DeGraw and J. G. Kennedy, *J. Heterocyclic Chem.*, 4, 251 (1967).

(2) K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, **87**, 5661, 5670 (1965).

(3) R. B. Woodward, N. L. Wendler, and F. J. Brutschy, *ibid.*, 67, 1425 (1945).

(4) H. Rapoport, R. Naumann, E. R. Bissell, and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

(5) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956).

(6) J. Sam and M. E. Rogers, unpublished results.

(7) Melting points were obtained on a Thomas-Hoover Capillary Melting Point apparatus and are corrected. Ir data were recorded on a Perkin-Elmer 257 spectrophotometer and nmr data on a Jeolco C-60-HL spectrometer. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona. The term Red-Al refers to sodium *bis*-2-methoxyethoxy aluminum hydride and is supplied commercially by Aldrich Chemical Co.

(8) J. W. Huffmann, T. Kamiya, and C. B. S. Rao, *J. Org. Chem.*, **32**, 700 (1967).