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A GENERAL SYNTHESIS OF MEDIUM-SIZED RING AMINES

Manfred G. Reinecke,[a] Louis R. Kray, and Robert F. Francis

Departments of Chemistry
University of California, Riverside, California, and
Texas Christian University, Fort Worth, Texas, 76129

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Medium-sized, nitrogen containing ring compounds have attracted considerable recent attention because of their unique transannular reactions (1) and because of their relation to a steadily increasing number of alkaloids (2). In connection with studies in these areas we have developed a new synthesis capable of producing a wide variety of complex nine- and ten-membered ring amines in high overall yield from readily available starting materials.

Because of the well known difficulty of forming medium-sized rings by ring closure of acyclic precursors, (3) the present method embodies the principal of peripheral synthesis (4,5) in which the desired nine- or ten-membered ring is present as the external boundary of a readily available (6) 1-azabicycloalkane, I. Addition of a nucleophile H-X to the carbon-nitrogen double bond (7) of the iminum salt II, obtained by mercuric acetate oxidation (8) of I, leads to the tertiary amine III whose quaternary salt IV undergoes an internal elimination to give the medium-sized ring amine

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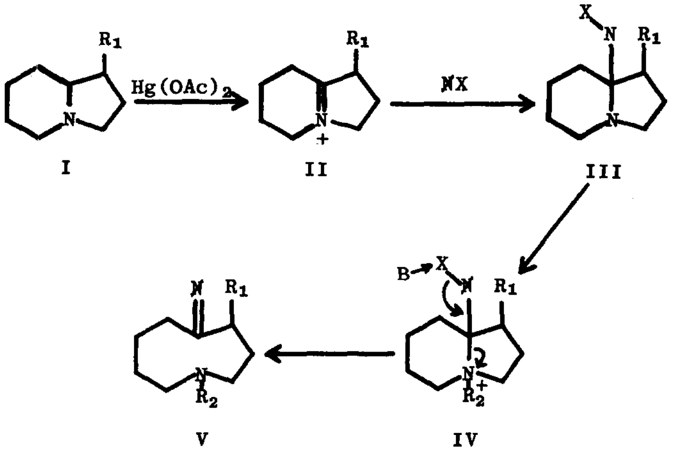
[a] To whom inquiries should be sent at the second address.



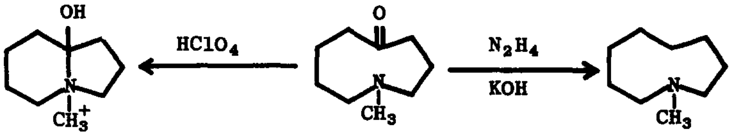
a: $R_1 = H$, $\not{N} = CH\text{-}C_6H_5$, $X = H$, $R_2 = CH_3$

b: $R_1 = C_2H_5$, $\not{N} = CH\text{-}COOC_2H_5$, $X = H$, $R_2 = CH_3$

V. This elimination is induced by the attack of a base, B, on X which in principal may be any group with electrophilic character, but was restricted to hydrogen in the present study. This reaction scheme has been applied successfully to several different 1-azabicycloalkanes and nucleophiles as illustrated by the following examples.

Treatment of $\Delta^{4(9)}$-dehydroindolizidinium perchlorate (9) (IIa) with benzylmagnesium chloride led to a basic oil (IIIa) in 90% yield which formed a picrate (m.p. 167-168.5° d.; Anal. Found: C, 57.05; H, 5.52), 2,4,6-trinitrobenzenesulfonate (m.p. 180-182°; Anal. Found: C, 49.90; H, 4.95) and methiodide (IVa; 90% yield). Reaction of this methiodide (m.p. 300-302°; Anal. Found: C, 54.00; H, 7.06) with sodamide in liquid ammonia gave a colorless oil (Va; 100% yield) whose n.m.r. spectrum indicated the presence of one vinyl proton (singlet, 3.68 τ) and which formed a methiodide (m.p. 169-170.5°; Anal. Found: C, 55.05; H, 7.25) and a 2,4,6-trinitrobenzenesulfonate (m.p. 143-144°; Anal. Found: C, 50.58; H, 5.31).

The structure of this ring-opened product was proven by its oxidation (OsO_4-$NaIO_4$) (10) to benzaldehyde (90%) and an aminoketone, VI, (95%) whose infrared carbonyl absorption (1686 cm^{-1}) disappeared as expected (1a) in the perchlorate salt, VII. Wolff-Kishner reduction of the aminoketone, VI, gave N-methylazacyclononane, VIII, identical in all respects (b.p., v.p.c. retention time, i.r., n.m.r., m.p., and m.m.p. of picrate) with an authentic sample (11).



VII VI VIII

An additional example of the ring-openeing sequence involves the Reformatsky-type reaction of ethyl bromoacetate, zinc and the iminium perchlorate, IIb (m.p. 160-161°; Anal. Found: C, 47.52; H, 7.00; 52% yield) prepared from 1-ethylindolizidine, Ib (12), to produce the tertiary amine, IIIb (b.p. 101-104°/1.0 mm) in 83% yield. Treatment of the methiodide, IVb (m.p. 174-175°; Anal. Found: C, 47.25; H, 7.55; 85% yield), with sodium ethoxide in absolute ethanol led to Vb (b.p. 80-82°/1.0 mm; i.r., 1715 cm^{-1}; n.m.r., one vinyl proton, singlet, 4.36 τ) in 80% yield; 2,4,6-trinitrobenzene sulfonate, m.p. 140-142°; Anal. Found: C, 46.09; H, 5.41.

Investigations of the properties and reactions of the medium-sized ring compounds, V, as well as the scope and application of this general synthetic method are continuing.

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