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The Electrolytic Reduction of Bicyclic α-Aminoketones. A Method for the Synthesis of Medium Rings Containing Nitrogen. II

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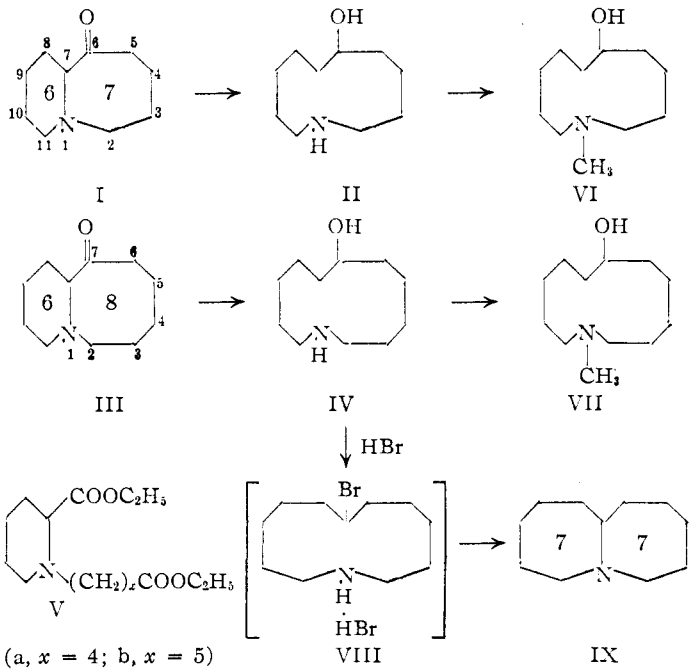
The synthesis of eleven- and twelve-membered ring aminoalcohols has been effected by the general method of electrolytic reduction of bicyclic α-aminoketones, using a lead cathode in 30% sulfuric acid at 60°. Specifically, the electrolytic reduction of 6-keto-1-azabicyclo[5.4.0]hendecane led to the monocyclic product, 6-hydroxyazacyclohendecane. The fact that cleavage of the C_α –N bond had occurred during the reduction was established by N-methylation of the secondary amine product by two independent methods. The similar electrolytic reduction of 7-keto-1-azabicyclo[6.4.0]dodecane produced 7-hydroxyazacyclododecane. The structure of this twelve-membered ring compound was established by N-methylation and by conversion to the symmetrical bicyclic compound, 1-azabicyclo[5.5.0]dodecane.

Our discovery of a new method[2] for the production of medium-size[3] ring compounds containing a nitrogen atom was applied originally[2] to the formation of nine- and ten-membered ring aminoalcohols. This method, the electrolytic reduction of bicyclic α-aminoketones in 30% sulfuric acid at 60° at a lead cathode, has now been employed successfully to make eleven- and twelve-membered ring aminoalcohols.[4] Thus, the electrolytic reduction of 6-keto-1-azabicyclo[5.4.0]hendecane (I) gave 6-hydroxyazacyclohendecane (II), and similar reduction of the higher ring homolog, 7-keto-1-azabicyclo-[6.4.0]dodecane (III), gave 7-hydroxyazacyclododecane (IV).



The immediate precursors of the bicyclic α-aminoketones I and III were the corresponding β-ketoesters (not isolated) formed by Dieckmann ring closure of the aminodiesters, diethyl piperidine-1-δ-valerate-2-carboxylate (Va) and diethyl piperidine-1-ε-caproate-2-carboxylate (Vb), respectively. Compound Va was obtained by condensation of δ-bromovaleronitrile with ethyl 2-piperidinecarboxylate followed by ethanolysis of the ester nitrile. Compound Vb was prepared directly from ethyl 2-piperidinecarboxylate and ethyl ε-bromocaproate. The closure of the seven-membered ring (Va → I) was effected under conditions of high dilution in xylene with potassium *t*-butoxide.[4a] An over-all yield of 79% of 6-keto-1-azabicyclo[5.4.0]hendecane (I) was realized when the aminodiester (Va) was added over a period of 17 hours. The closure of the eight-membered ring (Vb → III) was carried out under similar conditions, and 7-keto-1-azabicyclo[6.4.0]dodecane (III) was obtained in 24% yield when the aminodiester (Vb) was added over a period of 54 hours.

The electrolytic reduction of 6-keto-1-azabicyclo[5.4.0]hendecane (I) at a lead cathode in a catholyte of 30% sulfuric acid at 60°[2] gave a product, $C_{10}H_{21}NO$, isolated in 71% yield. By analogy with the established formation of nine- and ten-membered ring amino alcohols *via* electrolytic reduction,[2] this product was regarded as the eleven-membered ring aminoalcohol II, 6-hydroxyazacyclohendecane, which would result from I by initial Cα–N cleavage followed by reduction of the carbonyl group to a secondary alcohol function. The infrared absorption spectrum of the $C_{10}H_{21}NO$ compound indicated the absence of a carbonyl group and the presence of an hydroxyl (and/or NH) group in the molecule, together with bonding of the latter. In order to establish the structure of the product as monocyclic, it was necessary only to prove the presence of the secondary amine function. Furthermore, since *only* $C_{7(\alpha)}$–N_1 cleavage (rather than C_2–N_1 or C_{11}–N_1 cleavage) in I is consistent with previous observations on the electrolytic reduction of aminoketones,[2,5] a monocyclic product would necessarily possess an eleven-membered ring, as in II. N-Methylation of the reduction product, $C_{10}H_{21}NO$, with formaldehyde–formic acid[6] did yield a new compound, $C_{11}H_{23}NO$, which accord-

(1) Rohm and Haas Company Fellow, 1951–1952.

(2) N. J. Leonard, S. Swann, Jr., and J. Figueras, Jr., THIS JOURNAL, **74**, 4620 (1952).

(3) We are using the classification of H. C. Brown and V. Prelog (see ref. 21 in H. C. Brown, Rosyln S. Fletcher and R. B. Johannesen, *ibid.*, **73**, 212 (1951)) of medium rings as those containing 8 to 12 members.

(4) It has been shown possible to obtain eight-membered ring aminoketones (and thus, certainly, alcohols) *via* the Dieckmann ring closure in dilute solution of the appropriate aminodiester. (See (a) N. J. Leonard and R. C. Sentz, *ibid.*, **74**, 1704 (1952), and also (b) this article.)

(5) N. J. Leonard, S. Swann, Jr., and H. L. Dryden, Jr., *ibid.*, **74**, 2871 (1952).

(6) *Org. Syntheses*, **25**, 89 (1945).

ingly could be assigned structure VI, 1-methyl-6-hydroxyazacyclohendecane, since the infrared absorption spectrum indicated the presence of a methyl group and the retention of the hydroxyl group. Methylation of $C_{10}H_{21}NO$ (II) with an equimolar amount of methyl iodide in the presence of potassium bicarbonate gave the same product (VI), as evidenced by absorption spectra and the identity of the picrates of the compounds obtained by the two methylation procedures. Direct evidence for the position of the hydroxyl group in II and VI was not obtained, but in view of the previous work in these laboratories,[5] there was no reason to expect that the original carbonyl group and the final hydroxyl group would occupy different relative positions.

The electrolytic reduction of 7-keto-1-azabicyclo[6.4.0]dodecane (III) gave a single isolable product, $C_{11}H_{23}NO$, in 42% yield of the purified material. On the basis of analogy with the reduction products of the ring homologs of III, elemental analysis of the base and its picrate, and infrared spectral data, which indicated the absence of the carbonyl group and the presence of OH and/or NH, together with a definite bonded structure, the reduction product was regarded as the twelve-membered ring amino-alcohol IV, 7-hydroxyazacyclododecane. It is of interest to note that IV is the only member of the series of azacycloalkanols thus far obtained[2,4b] which is a solid (m.p. 127–128°). Scale molecular models show the strong possibility of intramolecular N–H–O bonding, which would result in a beautifully symmetrical conformation. Proof that IV is the structure of the reduction product was not fully attained by the methylation sequence. The action of formaldehyde–formic acid on the reduction product $C_{11}H_{23}NO$ gave a base which did not have the exact composition required for 1-methyl-7-hydroxyazacyclododecane (VII), $C_{12}H_{25}NO$, although a picrate was obtained which had the correct analysis for this derivative of VII. The infrared spectrum of the base showed the retention of the hydroxyl group and the introduction of a methyl group; however, the spectrum also indicated the presence of a carbonyl-containing impurity. An alternative structure proof for IV was followed which indicated both the presence of the secondary amine function and the location of the hydroxyl at C-7. Compound IV was converted by treatment with 48% hydrobromic acid to the bromoamine hydrobromide VIII, which was not isolated but was treated directly with sodium hydroxide to effect internal alkylation. The base thus obtained was characterized as 1-azabicyclo[5.5.0]dodecane (IX) by melting point and infrared comparison of the picrate with an authentic sample of 1-azabicyclo-[5.5.0]dodecane picrate.[7]

Experimental[8]

Ethyl Piperidine-1-δ-valeronitrile-2-carboxylate.—Alkylation[2] of ethyl 2-piperidinecarboxylate with δ-bromovaleronitrile in the presence of anhydrous potassium carbonate gave ethyl piperidine-1-δ-valeronitrile-2-carboxylate, b.p. 99° (0.05 mm.), $n^{20}D$ 1.4688, d^{20}_4 1.0141, yield 67%.

Anal. Calcd. for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.76; *MR*D, 65.40. Found: C, 65.40; H, 9.40; N, 12.16; *MR*D, 65.45.

Diethyl Piperidine-1-δ-valerate-2-carboxylate (Va).—A solution of 16 g. (0.07 mole) of ethyl piperidine-1-δ-valeronitrile-2-carboxylate in 50 ml. of absolute ethanol was cooled in an ice-bath and saturated with dry hydrogen chloride. The solution was boiled under reflux for one hour, 1.2 ml. of water was added, and heating was continued one-half hour. The solution was concentrated *in vacuo*, cooled in an ice-bath, and made alkaline with 40% aqueous sodium hydroxide. The alkaline solution was extracted with ether. The ether extracts were dried, the ether was removed, and the residue was distilled, b.p. 89–90° (0.03 mm.), $n^{20}D$ 1.4603, d^{20}_4 1.0176, yield 13 g. (68%).

Anal. Calcd. for $C_{15}H_{27}NO_4$: C, 63.13; H, 9.54; N, 4.91; *MR*D, 76.54. Found: C, 63.04; H, 9.52; N, 4.94; *MR*D, 76.84.

Diethyl Piperidine-1-ε-caproate-2-carboxylate (Vb).—Condensation of ethyl ε-bromocaproate with ethyl 2-piperidinecarboxylate in the presence of potassium carbonate gave a colorless liquid, b.p. 102–104° (0.04 mm.), $n^{20}D$ 1.4602, d^{20}_4 1.0098, yield 43%.

Anal. Calcd. for $C_{16}H_{29}NO_4$: C, 64.18; H, 9.76; N, 4.68; *MR*D, 81.16. Found: C, 64.32; H, 9.76; N, 4.62; *MR*D, 81.24.

6-Keto-1-azabicyclo[5.4.0]hendecane (I).—The Dieckmann ring closure of diethyl piperidine-1-δ-valerate-2-carboxylate (Va) was carried out according to directions of Leonard and Sentz,[4a] followed by hydrolysis and decarboxylation. The diester was added over a period of 17 hours. From 19.8 g. (0.07 mole) of the aminodiester was obtained 8.5 g. (79%) of the desired bicyclic aminoketone as a colorless liquid, b.p. 124–125° (21 mm.), $n^{20}D$ 1.4925.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 74.39; H, 10.05; N, 8.44.

The infrared absorption spectrum, as determined on the pure liquid, showed a strong band at 1705 cm.$^{-1}$, indicative of the ketone carbonyl.

The picrate, formed in dry ether, crystallized from 95% ethanol as fine yellow needles, m.p. 193–193.5°.

Anal. Calcd. for $C_{16}H_{20}N_4O_8$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.67; H, 5.23; N, 13.97.

The picrolonate, formed in dry ether, crystallized from 95% ethanol as fine yellow needles, m.p. 188°.

Anal. Calcd. for $C_{20}H_{25}N_5O_6$: C, 55.67; H, 5.84; N, 16.23. Found: C, 55.77; H, 5.83; N, 16.50.

7-Keto-1-azabicyclo[6.4.0]dodecane (III).—The Dieckmann ring closure of Vb was effected under the conditions which were successful in the first example of the closure of an eight-membered ring.[4a] From 21 g. (0.07 mole) of diethyl piperidine-1-ε-caproate-2-carboxylate, added to potassium *t*-butoxide in refluxing xylene over a period of 54 hours, after hydrolysis and decarboxylation, 3 g. (24%) of the aminoketone was obtained as a colorless liquid, b.p. 146–147° (21 mm.), $n^{20}D$ 1.4992.

Anal. Calcd. for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 73.02; H, 10.43; N, 7.97.

The infrared spectrum had a strong absorption peak at 1700 cm.$^{-1}$ indicative of the ketone carbonyl.

The picrate, formed in dry ether, crystallized from aqueous methanol as clusters of yellow needles, m.p. 156.5–157°.

Anal. Calcd. for $C_{17}H_{22}N_4O_8$: C, 49.75; H, 5.41; N, 13.65. Found: C, 49.83; H, 5.12; N, 13.52.

The picrolonate, formed in dry ether, was obtained from ethanol–ether as clusters of orange needles, m.p. 167.5–168.5°.

Anal. Calcd. for $C_{21}H_{27}N_5O_6$: C, 56.62; H, 6.11; N, 15.72. Found: C, 56.47; H, 6.03; N, 15.86.

Electrolytic Reductions.—The lead cathode (of 99.95% purity or better) was cast in a graphite mold initially at a temperature of 25°. The cathode was originally anodized in perchloric acid prior to use. In this work and in previous experiments in this series, the cathode was prepared prior

(7) N. J. Leonard and W. E. Goode, THIS JOURNAL, **72**, 5404 (1950).

(8) All melting points are corrected. We are indebted to Miss Helen Miklas for the determination of the infrared spectra and for her assistance in their interpretation, and to Mrs. Jean Fortney, Mrs. Katherine Pih, Mrs. Esther Fett, Mr. Joseph Nemeth and Miss Emily Davis for the microanalyses.

to use by the modified Tafel procedure.[9] The apparatus and the reduction procedure employed have been described by Swann.[9] The electrolytic reductions were carried out at the lead cathode at 60° in a catholyte of 30% sulfuric acid, as with the bicyclic α-aminoketones possessing six–five- and six–six-membered fused rings.[2] The isolation procedure followed was also that used previously.

Electrolytic Reduction of 6-Keto-1-azabicyclo[5.4.0]hendecane.—From 5.5 g. (0.033 mole) of 6-keto-1-azabicyclo-[5.4.0]hendecane in 100 ml. of 30% sulfuric acid was obtained 4.0 g. (71%) of a single product, b.p. 162° (21 mm.), $n^{20}D$ 1.5010, with an elemental composition consistent for 6-hydroxyazacyclohendecane (II).

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.96; H, 12.35; N, 8.37.

The infrared spectrum had a strong absorption peak at 3310 cm.$^{-1}$ (OH and/or NH), but no absorption in the carbonyl region.

The picrate, formed in ether, crystallized from 95% ethanol as fine yellow needles, m.p. 184.5°.

Anal. Calcd. for $C_{16}H_{24}N_4O_8$: C, 47.99; H, 6.04; N, 14.00. Found: C, 48.21; H, 6.23; N, 14.22.

1-Methyl-6-hydroxyazacyclohendecane (VI).—N-Methylation of the $C_{10}H_{21}NO$ reduction product was carried out first by the use of formaldehyde and formic acid.[2,6] From 1.5 g. of 6-hydroxyazacyclohendecane was obtained 0.95 g. (59%) of a colorless liquid, b.p. 147–148° (20 mm.), $n^{20}D$ 1.4980, which had a composition correct for 1-methyl-6-hydroxyazacyclohendecane.

Anal. Calcd. for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.24; H, 12.26; N, 7.85.

The infrared absorption spectrum of the liquid indicated the presence of an hydroxyl function (peak at 3320 cm.$^{-1}$). A new peak, not present in the spectrum of the $C_{10}H_{21}NO$ compound (II), appeared at 1352 cm.$^{-1}$ and was taken as indicative of the N-methyl group (II had a "shoulder" at 1377, VI, at 1365 cm.$^{-1}$). A new band at 2750 cm.$^{-1}$ was also observed for VI. The presence of trace amounts of impurities possibly containing a carbonyl function (1720 cm.$^{-1}$) and unsaturation (1602 cm.$^{-1}$) was evident in the spectrum. Hydrogenation over platinum oxide catalyst at 30° and 1 atm. for 22 hours failed to remove the impurity. It should be noted that the parent substance (II), as first obtained and prior to methylation, had no absorption in the 1600–1800 cm.$^{-1}$ region. However, compound II was allowed to stand in the laboratory for more than a week before any methylation reaction was attempted, so that the final impurities in VI could well have a source other than side-reactions during the N-methylation.

The picrate, formed in ether–benzene, crystallized from ethyl acetate–cyclohexane as yellow needles, m.p. 154.5–155°.

Anal. Calcd. for $C_{17}H_{26}N_4O_8$: C, 49.26; H, 6.33; N, 13.52. Found: C, 49.50; H, 6.28; N, 13.74.

The methylation of II was carried out using methyl iodide and potassium bicarbonate as a check on the formaldehyde–formic acid procedure. A mixture of 0.3 g. (1.8 millimoles) of 6-hydroxyazacyclohendecane, 0.27 g. (1.9 millimoles) of methyl iodide and 0.35 g. (3.5 millimoles) of potassium bicarbonate with 40 ml. of benzene was heated on a steam-bath for 3 hours. After cooling, the mixture was made basic with 40% sodium hydroxide. The benzene layer was separated and washed with 40% aqueous sodium hydroxide. The aqueous layer and the washings were combined, saturated with potassium carbonate, and extracted with ether. The combined ethereal and benzene extracts were dried and the solvents were removed. The residual colorless liquid, b.p. 160° (28 mm.), had an infrared spectrum identical with that of the compound obtained by the use of formaldehyde–formic acid, except that the extraneous absorption at 1720 and 1602 cm.$^{-1}$ was only slightly evident. The picrate was formed and recrystallized as described in the preceding section. The fine yellow needles, m.p 154–154.5°, did not depress the melting point of the picrate of the product obtained by methylation with formaldehyde–formic acid.

Electrolytic Reduction of 7-Keto-1-azabicyclo[6.4.0]dodecane.—From 3.0 g. (1.7 millimoles) of 7-keto-1-azabicyclo[6.4.0]dodecane in 100 ml. of 30% sulfuric acid was obtained 1.3 g. (42%) of pure product, m.p. 127–128° (colorless needles from ether), with an elemental composition consistent for 7-hydroxyazacyclododecane (IV).

Anal. Calcd. for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56; mol. wt., 185.3. Found: C, 71.01; H, 12.69; N, 7.50; mol. wt. (Rast camphor), 186.

The infrared spectrum, as obtained for a Nujol mull, had a strong absorption peak at 3260 cm.$^{-1}$ (OH and/or NH). There was no absorption in the carbonyl region of the spectrum.

The picrate, formed in ether, crystallized from 95% ethanol as fine yellow needles, m.p. 209°.

Anal. Calcd. for $C_{17}H_{26}N_4O_8$: C, 49.26; H, 6.33; N, 13.52. Found; C, 49.48; H, 6.41; N, 13.58.

1-Methyl-7-hydroxyazacyclododecane (VII).—The N-methylation procedure followed was the formaldehyde–formic acid method used for II. The product obtained from IV, b.p. 85° (0.08 mm.), $n^{20}D$ 1.4891, yield 56%, did not have the exact composition required for 1-methyl-7-hydroxyazacyclododecane. The infrared spectrum of the liquid showed the presence of a methyl group (peaks at 1347 and 2750 cm.$^{-1}$ which were not present for IV; a "shoulder" was present in the spectrum of each: 1380 for IV and 1370 cm.$^{-1}$ for VII), the retention of the hydroxyl group (peak at 3300 cm.$^{-1}$), and apparently a carbonyl-containing inpurity (peak at 1723 cm.$^{-1}$). The nature of the carbonyl compound was not investigated.

The picrate, formed in ether–benzene, crystallized from ethyl acetate–cyclohexane as yellow needles, m.p. 190.5–191°, with an analysis correct for the picrate of VII.

Anal. Calcd. for $C_{18}H_{28}N_4O_8$: C, 50.46; H, 6.59; N, 13.08. Found: C, 50.66; H, 6.53; N, 12.87.

1-Azabicyclo[5.5.0]dodecane (IX).—7-Hydroxy-1-azacyclododecane was treated with three equivalents of hydrogen bromide (as 48% hydrobromic acid) for 4 hours on a steam-bath. The solution was cooled and made basic with 40% sodium hydroxide. The mixture was allowed to stand overnight and then extracted with ether. The ethereal solution was dried and a solution of picric acid in benzene was added. Three picrates were separated. One was probably that of the starting material, 7-hydroxyazacyclododecane picrate, another was low-melting (86–90°) and present in minor amount, while the main portion, m.p. 138–141°, crystallized as small plates from absolute ethanol, m.p. 141–143°. Mixtures of this picrate with an authentic sample[7] of 1-azabicyclo[5.5.0]dodecane picrate (plates from ethanol, m.p. 141–142°) were not depressed in melting point. The infrared spectra of the two picrate samples were identical, as determined in Nujol mull.

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(9) S. Swann, Jr., "Electrolytic Reductions," in A. Weissberger, editor, "Technique of Organic Reactions," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1948.