

A FACILE SYNTHESIS OF AN AMINAL OF BICYCLO[3.1.0]HEXAN-
6-ONE AND OF ENDO-6-PIPERIDINOBICYCLO[3.1.0]HEXANE

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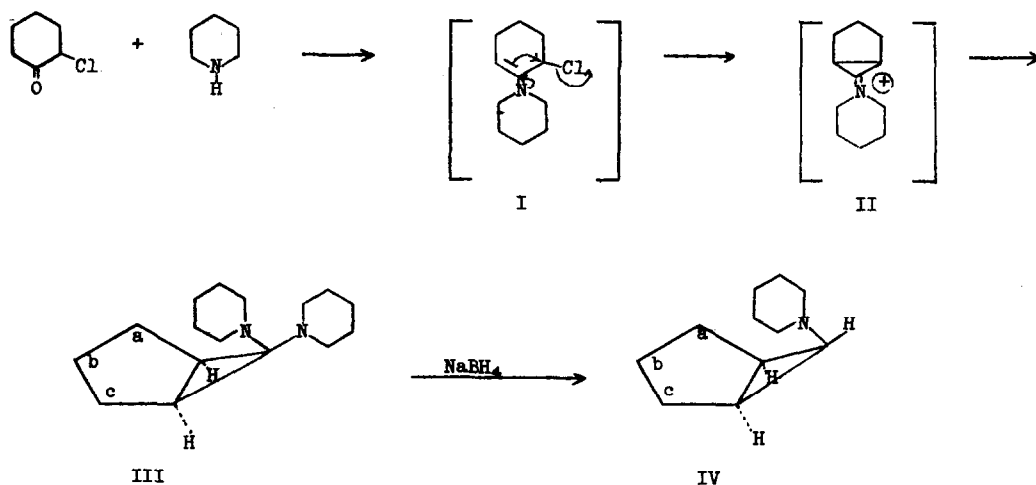
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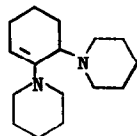
6-Amino substituted bicyclo[3.1.0]hexane derivatives are relatively rare.^{1,2,3,4}

We wish to report preliminary results on the facile two-step synthesis of endo-6-piperidinobicyclo[3.1.0]hexane (IV).

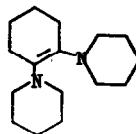
Reaction of 2-chlorocyclohexanone with piperidine afforded 6,6-dipiperidinobicyclo[3.1.0]hexane (III) and 2-piperidinocyclohexanone in 34% and 41% yield,⁵ respectively.⁶ A possible mechanism for the formation of III involves the enamine I and the iminium cation II intermediates, and/or 6-ketobicyclo[3.1.0]hexane. The structure of III⁷ [mp 41-42°; vapor phase chromatography (vpc): 96.4%; mass spectroscopic M.W. 248] was supported by the near infrared spectrum⁸ which showed a band at 1.684 μ (in carbon tetrachloride). The nmr



spectrum⁹ (60 Mc., CDCl_3 solution) showed a band at 102 cps which is compatible with the six abc hydrogens and no band corresponding to a vinyl hydrogen; thus, structures V and VI were



V



VI

excluded from consideration. Hydrogenation of III in presence of either 10% palladium on carbon or 5% rhodium on carbon led to piperidinocyclohexane and piperidine; both were characterized as the corresponding hydrochlorides.¹⁰ Treatment of III with methyl iodide led to N-methyl-piperidinium methiodide.¹⁰

Treatment of III with sodium borohydride afforded endo-6-piperidinobicyclo[3.1.0]hexane (IV)⁷ in 53% yield (bp 88-92° at 14 mm; vpc: 94%; mass spectroscopic M.W. 165; hydrochloride:⁷ mp 212-213°). Compound IV in carbon tetrachloride solution showed a band at 1.690 μ in the near infrared spectrum.⁹ Nmr (60 Mc, CDCl_3 solution) showed a band at 104 cps which is compatible with the six abc hydrogens. Nmr of compound IV hydrochloride (60 Mc, D_2O solution) showed a triplet centered at 179 cps ($J=7$ cps) which corresponds to hydrogen on C_6 . Microhydrogenation in acetic acid in presence of 10% palladium on carbon resulted in the absorption of 1.04 moles of hydrogen. On a larger scale, the hydrogenation led to a mixture which contained cyclohexane,¹⁰ piperidine,¹⁰ and starting material IV.¹⁰

The endo- and exo-6-piperidind[3.1.0]hexanes were synthesized from bicyclo[3.1.0]hex-2-ene-6-endo-carboxaldehyde.¹¹ Oxidation followed by reduction afforded bicyclo[3.1.0]hexane-6-endo-carboxylic acid.¹¹ Curtius degradation^{12,13} gave bicyclo[3.1.0]hexan-6-endo-amine characterized as the hydrochloride:⁷ mp 189° (dec). Nmr (60 Mc, D_2O solution) showed a triplet centered at 168 cps ($J=8$) which corresponds to hydrogen on C_6 . Condensation of the amine with 1,5-diiodopentane in presence of potassium carbonate gave IV, characterized as the hydrochloride which was identical in every respect to the sample prepared starting from 2-chlorocyclohexanone and piperidine.

The above endo acid was converted, via the methyl ester, to the exo-acid.¹¹ Curtius degradation gave bicyclo[3.1.0]hexan-6-exo-amine¹ characterized as the hydrochloride:⁷ mp 221° (dec). Nmr (60 Mc, D_2O solution) showed a triplet centered at 143 cps ($J=1.5$ cps) which corresponds to hydrogen on C_6 . Condensation of the amine with 1,5-diiodopentane as above gave

exo-6-piperidinol[3.1.0]hexane characterized as the hydrochloride: mp 245° (dec). Nmr (60 Mc, D₂O solution) showed a triplet centered at 150 cps (J=1.5 cps) which corresponds to hydrogen on C₆. The free base was identical (by vpc) to the minor component present to the extent of 6% in the reduction product of III with sodium borohydride.

The chemical shift and coupling constant data for the C₆ hydrogen in the four amines reported above confirm the stereochemical assignments.¹⁴ The signal for the C₆ hydrogen in the exo-amines appears 20-30 cps downfield from that in the corresponding endo-amines; the coupling constant in the case of the endo-amines (7-7.5 cps) points to the cis relationship of the hydrogen at C₆ to those at C₁ and C₅, and trans relationship in the case of the exo-amines (1.5-2 cps).

We are studying the extension and implications of the novel reaction described in this communication and will report on them at a later date.

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3. R. Pettit, J. Am. Chem. Soc., 82, 1972 (1960).
4. B. Föhlisch, Ber., 97, 88 (1964).
5. We are optimistic that the yield of III could be improved on further experimentation which would take into account mechanistic considerations.
6. Cf. M. Mousseron, J. Jullien, and Y. Jolchine, Bull. Soc. Chim. France, 757 (1952), who reported only 2-piperidinocyclohexanone from this reaction.
7. New compounds described in this communication gave satisfactory elemental analytical data, ultraviolet, infrared and nmr spectra.
8. Near infrared spectra are very useful for the identification of cyclopropyl systems. Cf. footnote 17 in the reference quoted in footnote 9 of this communication; also, P. G. Gassman and F. V. Zalar, J. Org. Chem., 31, 166 (1966). On the other hand, they should be interpreted with care since some systems devoid of the cyclopropyl moiety also show a band in the 1.68 μ region (private communication from Dr. L. Dorfman), and certain cyclopropane derivatives do not show it [H. E. Simmons, E. P. Blanchard and H. H. Hartzler, J. Org. Chem., 31, 295 (1966)].
9. Cf. comment on p. 979 in the paper by J. Meinwald, A. Lewis and P. G. Gassman, J. Am. Chem. Soc., 84, 977 (1962) concerning the limited use of the nmr in the case of tertiary cyclopropyl protons.

10. Identified by comparison with an authentic sample.
11. J. Meinwald, S. S. Labana and M. S. Chadha, J. Am. Chem. Soc., 85, 582 (1963).
12. The Curtius reaction is known to proceed with retention of configuration. See, for example, Organic Reactions, vol. 3, Wiley, New York, 1946, pp. 340, 270.
13. J. Finkelstein, E. Chiang, F. M. Vane and J. Lee, J. Med. Chem., 9, 319 (1966).
14. P. G. Gassman and F. V. Zalar, Tetrahedron Letters, No. 44, 3251 (1964).
15. The authors thank Mr. L. G. Laurian for laboratory assistance and Mr. G. E. Bronson for the vpc analyses.