Tetrahedron Letters No.17, pp. 1309-1311, 1969. Pergamon Press. Printed in Great Britain.

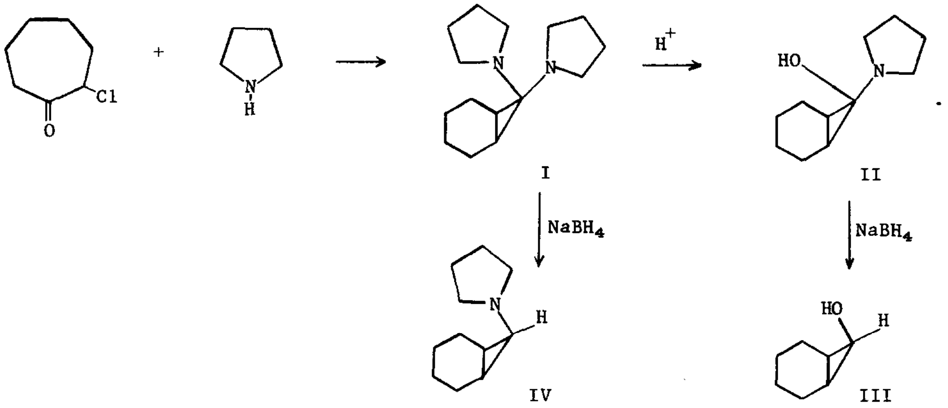
A FACILE SYNTHESIS OF ENDO-7-NORCARANOL

J. Szmuszkovicz, D. J. Duchamp, E. Cerda and C. G. Chidester

The Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

(Received in USA 11 February 1969; received in UK for publication 10 March 1969)

In continuation of our work dealing with the condensation of 2-halo ketones with secondary amines (1), we are now reporting on the reaction of 2-chlorocycloheptanone with pyrrolidine which led to a new and convenient synthesis of endo-7-norcaranol (III).



Condensation of 2-chlorocycloheptanone with 4.5 equivalents of pyrrolidine at reflux temperature afforded 40% yield of 1,1'-(7-norcarylidene)dipyrrolidine (I) (2,3) (mp 45-46°) and 37% of 2-pyrrolidinocycloheptanone (2). This result is analogous to that obtained in the case of 2-chlorocyclohexanone and piperidine (1). However, unlike the case of 6,6-dipiperidinobicyclo[3.1.0]hexane which gave 2-chlorocyclohexanone on treatment with aqueous hydrochloric acid, I afforded 7-(1-pyrrolidinyl)-endo-7-norcaranol (II) (2,3) after similar treatment (4).

The structure of II was confirmed and the stereochemistry assigned on the basis of x-ray analysis which was performed on II hydrochloride, mp 104-106° dec (2). The crystals were found to be monoclinic with crystal data as shown below. The rapid loss of diffracting power of the crystals upon exposure to the atmosphere at room temperature complicated the data

$\underline{a}$ = 6.52 ± 0.02 Å
$\underline{b}$ = 17.16 ± 0.03
$\underline{c}$ = 11.60 ± 0.02
β = 112.9° ± 0.1°
V = 1195 $Å^3$
Space Group $P2_1/c$
Z = 4
ρ calc = 1.21 g/cm^3

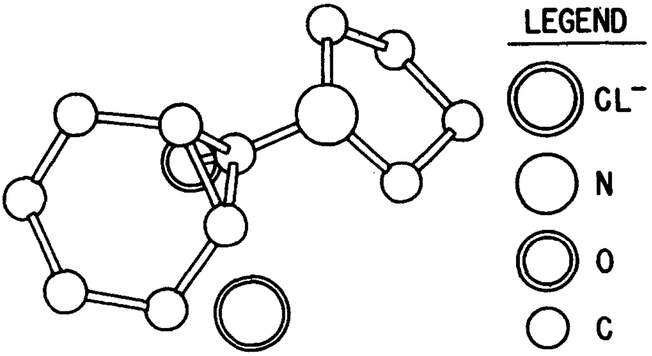
collection process. By use of special techniques, however, a suitable set of x-ray diffraction intensity measurements (1474 reflections) were obtained using the θ-2θ scan technique with CuK_α radiation on an automated diffractometer. These data were corrected for Lorentz and polarization effects, absorption, and crystal deterioration.

Analysis of a three-dimensional Patterson function gave trial positions for the chloride ion and two lighter atoms. A structure-factor and three-dimensional electron density calculation served to locate the remaining eleven light atoms. The atomic positions and thermal parameters then were refined by least-squares. This refinement is proceeding with anisotropic thermal parameters and hydrogen atoms included; the present agreement index R $\left[= \frac{\Sigma[s\,|Fo| - |Fc|\,]}{\Sigma[sFo]} \right]$, is .103. The chemical structure and stereochemistry of II hydrochloride found in this x-ray investigation is shown in Figure. This drawing was made by computer directly from the observed atomic positions in the crystallographic unit cell. Final x-ray results and more details will be published when refinement is complete.

Reduction of II with sodium borohydride gave endo-7-norcaranol (III) (2,5), mp 61-63°; the carbanilate melted at 108-111° (2). The tosylate (6) melted at 79-81° and was identical to an authentic sample (7). The assignment of endo configuration to compound III, the corresponding carbanilate and tosylate is based on nmr spectra (60 mc, $CDCl_3$) which showed a triplet at 201 cps (J=7 cps), 240 cps (J=7 cps) and at 240 cps (J=7 cps) respectively, corresponding to the C_7 hydrogen (5,6).

Treatment of aminal I with sodium borohydride led to the expected (1) endo-1-(7-norcaryl)pyrrolidine (IV) (2) (vpc: 99.5%). The nmr spectrum (60 mc, D_2O) of the hydrochloride (2) (mp 213-215°) showed a triplet for the C_7 hydrogen at 168 cps (J=7.5 cps) (1,6) which supports the endo configuration.

FIG.



Drawing of compound II hydrochloride molecule viewed from a direction normal to the *a* axis and 45° from the *b* axis of the crystallographic unit cell. Hydrogen atoms are not shown.

REFERENCES

1. J. Szmuszkovicz, E. Cerda, M. F. Grostic and J. F. Zieserl, Jr., *Tetrahedron Letters*, 3969 (1967).

2. New compounds described in this communication gave satisfactory elemental analytical data, ultraviolet, infrared and nmr spectra.

3. Molecular weight was obtained by mass spectroscopy.

4. For other cases of aminals and carbinol amines in the cyclopropanone series, see H. H. Wassermann and D. C. Clagett, *J. Am. Chem. Soc.*, **88**, 5368 (1966), and N. J. Turro and W. B. Hammond, *Tetrahedron Letters*, 3085 (1967).

5. The mixture of *endo*- and *exo*-7-norcaranols has been reported by U. Schöllkopf, J. Paust, A. Al-Azrak and H. Schumacher, *Ber.*, **99**, 3391 (1966) and previous references quoted therein.

6. P. von R. Schleyer, G. W. Van Dine, U. Schöllkopf and J. Paust, *J. Am. Chem.* Soc., **88** 2868 (1966).

7. We thank Prof. P. von R. Schleyer for a sample of authentic *endo*-7-norcaranol tosylate.