Tetrahedron Letters No.1, pp. 97-100, 1970, Pergamon Press. Printed in Great Britain.

THE SYNTHESIS OF 1-AZATWISTANE

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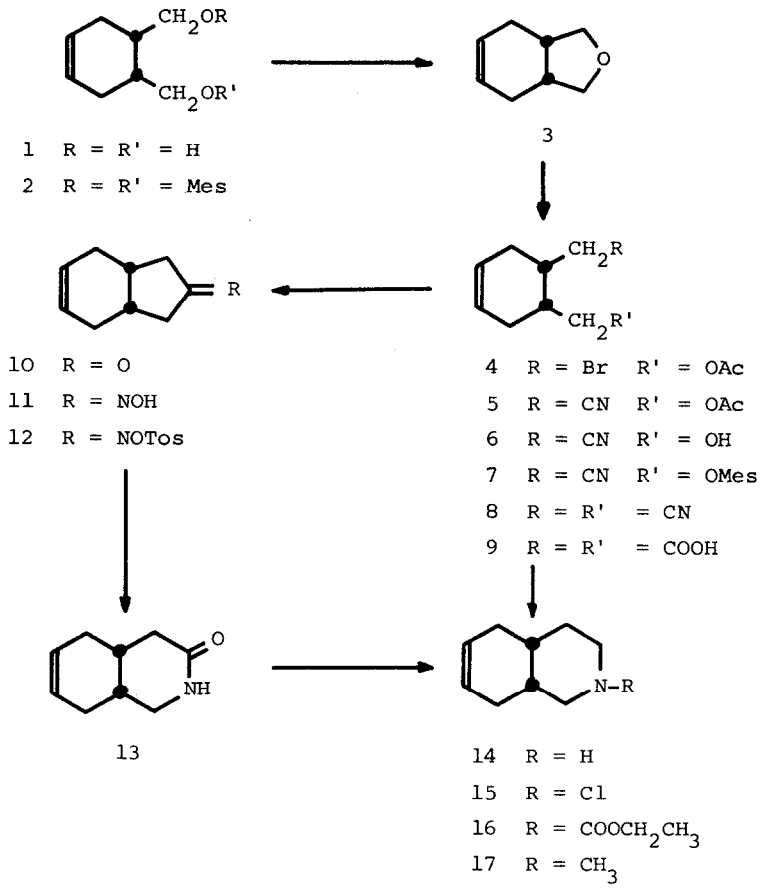
(Received in France 5 December 1969; received in UK for publication 7 December 1969)

In connection with a synthetic project we became interested in the preparation of substituted azatwistanes with a bridgehead nitrogen atom. We decided to use as a bicyclic precursor [1] the cis octahydroisoquinoline 14 [2] which was obtained in the following manner.

Cis-Δ^4-tetrahydrophthalyl alcohol 1 [3,4] was dehydrated in refluxing benzene with p-toluenesulfonic acid to give the ether 3 [4] (80%) [5]. The bromo acetate 4 (b.p. 115°/0.005 mm) was formed in 96% yield by treatment of 3 with acetyl bromide at 100°. Reaction of 4 with sodium cyanide in DMSO to give 5 (b.p. 120-124°/0.001 mm; 91%) followed by hydrolysis with sodium hydroxide in aqueous methanol (to 6: b.p. 123-126°/0.001 mm; 60%) and mesylation produced the nitrile mesylate 7 (m.p. 59-60°; 94.5%). Upon reduction with lithium aluminum hydride/aluminum chloride in ether 7 was cyclized to 14 [6] (b.p. 90.5-91 /14 mm; 92.5%, hydrochloride: m.p. 139-141°).

Alternatively the dimesylate 2 (m.p. 86°) was transformed into the dinitrile 8 (m.p. 46-47°) which was hydrolyzed with aqueous-ethanolic potassium hydroxide to the diacid 9 (m.p. 157-159°). Cyclisation with sodium acetate/acetic anhydride [7] gave the ketone 10 (b.p. 110-115°/12 mm; 66% from 8) which, via the oxime 11 (m.p. 100-105°) and the oxime tosylate 12 (m.p. 95-98°), was rearranged to the lactam 13 (m.p. 131.5-132°; 87% from 10) by treatment with aluminum oxide [8]. Reduction with lithium aluminum hydride in monoglyme/ether gave 14 (67.5%).



1 R = R' = H
2 R = R' = Mes

3

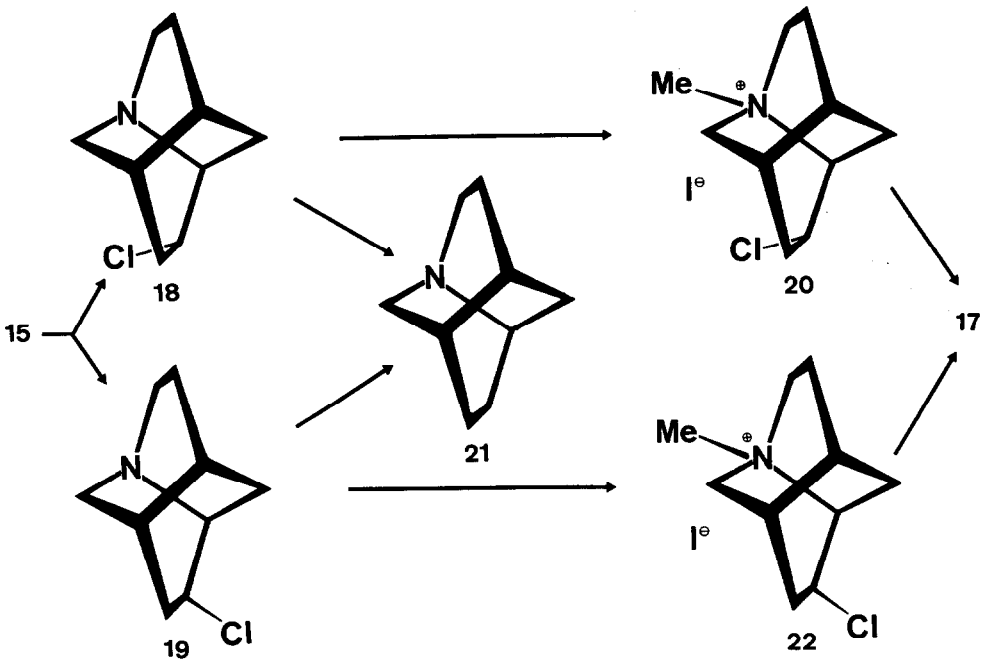
10 R = O
11 R = NOH
12 R = NOTos

4 R = Br R' = OAc
5 R = CN R' = OAc
6 R = CN R' = OH
7 R = CN R' = OMes
8 R = R' = CN
9 R = R' = COOH

13

14 R = H
15 R = Cl
16 R = $COOCH_2CH_3$
17 R = CH_3

The N-chloro compound 15 (b.p. 60°/0.001 mm), obtained from 14 by reaction with N-chlorosuccinimide in ether in quantitative yield, was irradiated in trifluoroacetic acid with a high pressure mercury lamp through a Pyrex filter at room temperature to give a mixture of the two chloro-azatwistanes 18 and 19 in 80% yield (ratio about 4:3). They were separated in benzene solution by addition of p-toluene sulfonic acid sufficient to neutralize the amount of 18 present in the mixture. After removal of the tosylate salt of 18 (m.p. 219-221°; hydrochloride: subl. at 160-170°/750 mm; free base: m.p. 58-60°) the filtrate contained pure 19 (b.p. 50-55°/0.001 mm; tosylate salt: m.p. 178-180°; hydrochloride: subl. at 160-175°/750 mm) [9].



Both chloro-azatwistanes 18 and 19 could be converted into their quaternary methiodides 20 (m.p. 249-250°, dec.) and 22 (m.p. 277°, dec.) respectively which, on reduction with sodium and isopropanol, were smoothly reduced to the cis-N-methyl-octahydroisoquinoline 17 (b.p. 80°/12 mm) in 93 and 90% yields. This compound was identical with material prepared from 14 by carbethoxylation (to 16: b.p. 120°/12 mm) and lithium aluminum hydride reduction.

Reduction of the chloro-azatwistanes 18 and 19 with sodium and isopropanol gave a mixture of the octahydroisoquinoline 14 (isolated as the N-trifluoroacetyl-derivative) and 1-azatwistane 21 (b.p. 80°/12 mm; hydrochloride: subl. at 160-180°/750 mm).

The configurational assignments of the chloro-azatwistanes 18 and 19 were based on characteristic differences in their NMR-spectra and were confirmed by an X-ray crystallographic analysis of the hydrochloride of 19 [10) 11)].

We shall report on the behaviour of the chloro-azatwistanes 18 and 19 under solvolytic conditions in a subsequent communication.

Acknowledgement: It is a special pleasure for the author to acknowledge the numerous stimulating discussions with Prof. R.B. Woodward, Director of the Institute.

REFERENCES AND NOTES

1) Another synthesis of a 1-azatwistane derivative using a [3,3,1]-bicyclic precursor will be reported at a later date.

2) All the new compounds described gave analytical values, NMR and IR spectra in agreement with the structures indicated.

3) J.E. Ladburg and E.E. Turner, J. Chem. Soc. (London) 1954, 3885; W.J. Bailey and J. Rosenberg, J. Amer.Chem. Soc. 77, 73 (1955)

4) E.L. Eliel and C. Pillar, J. Amer.Chem. Soc. 77, 3600 (1955)

5) We are indebted to Dr. J. Hartenstein for these dehydration experiments.

6) Hydrogenation over palladium-charcoal gave cis decahydroisoquinoline (b.p. 80-82°/18 mm; hydrochloride m.p. 180-181°) identical with a sample obtained by hydrogenation of isoquinoline (B. Witkop, J. Amer. Chem. Soc. 70, 2617 (1948) and separation of the cis and trans isomer by preparative VPC.

7) F.C. Uhle, C.M. McEwen, H. Schröter, Ch. Yuan and B.W. Baker, J.Amer. chem. Soc. 82, 1200 (1950); C.A. Grob and O. Weissbach, Helv. Chim. Acta 44, 1736 (1961)

8) J. Cymerman Craig and A.R. Naik, J. Amer. Chem. Soc. 84, 3410 (1962)

9) Both tosylate salts of 18 and 19 are equally insoluble in the medium. The separation is based on the difference in rate of crystallisation rather than solubility.

10) We wish to express our gratitude for this determination to Professor J. Gougoutas and his collaborators at Harvard University, Cambridge, Massachusetts.

11) It is interesting to note that in the reduction of the chloro-azatwistanes to the octahydroisoquinoline 14 the yield of the latter was significantly lower from 18 (35%) than from 19 (56%) in which there is a antiperiplanar arrangement of Cl-C-C-N.