[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

THE SYNTHESIS OF MORPHAN (2-AZABICYCLO[3.3.1]NONANE)[1]

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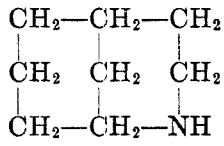
The bicyclic secondary amine morphan (I) is of interest as it constitutes both a portion of the morphine molecule (heavy lines in structure II) and of the strychnine structure in its recently suggested modification (2). It has been synthesized by a sequence of relatively simple transformations.

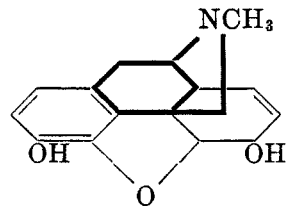
When ethyl *m*-nitrophenylacetate was reduced in *glacial acetic acid*, using Adams' catalyst, six moles of hydrogen were absorbed, and two compounds isolated: ethyl *cis*-(3-aminocyclohexyl)acetate (III) and—due to cyclisation in the course of distillation—the lactam of *cis*-(3-aminocyclohexyl)acetic acid (IV). Also the reduction of 3-nitrophenylacetic acid in glacial acetic acid yields—at any rate, preponderantly (isolated 75%)—the corresponding *cis*-acid, m.p. 269° (dec.). [Cronyn (1) gives m.p. 272–273°].

Protiva and Sorm (3) obtained a (3-aminocyclohexyl)acetic acid (m.p. 230°) which did not yield a lactam and consequently was considered to have the *trans*-configuration. The *cis*-configuration of III follows from the fact that upon prolonged heating and distillation it yields the lactam (IV) as is often the case with esters of δ- and ε-amino acids (4). The *cis*-directing influence of acidic media in such hydrogenation reactions has been observed previously (5, 6).

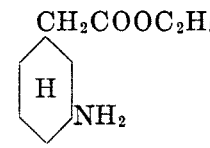
The lactam (IV) is reduced to morphan (I) by means of lithium aluminum hydride in accordance with similar observations of Ruzicka and co-workers (7).



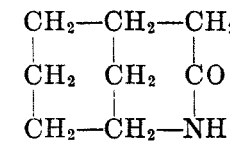
I



II



III



IV

[1] The investigation reported here was ready for publication when the paper by Cronyn (1) was received in Rehovoth. The present paper is believed not only to corroborate Cronyn's results, but also to contain a number of interesting observations which seem to warrant its publication.

EXPERIMENTAL[2]

Ethyl m-nitrophenylacetate. This ester was prepared by the following sequence of reactions: *m*-nitrobenzaldehyde $\xrightarrow[92\%]{Al(OC_3H_7)_3}$ *m*-nitrobenzylalcohol $\xrightarrow[100\%]{\text{HBr in benzene}}$ *m*-nitrobenzyl-bromide (8) $\xrightarrow[60\%]{NaCN}$ *m*-nitrophenylacetonitrile (9, 10) $\xrightarrow[90\%]{20\%\ HCl}$ *m*-nitrophenylacetic acid (9, 11, 12) $\xrightarrow[97\%]{\text{azeotropic esterification}}$ ethyl *m*-nitrophenylacetate (12).

The reduction of other nitroaldehydes to the corresponding nitroalcohols by means of aluminum isopropoxide has been observed before (13–15).

Ethyl 3-aminophenylacetate. A mixture of 2.09 g. of ethyl-*m*-nitrophenylacetate, 0.2 g. of Adams' platinum oxide, and 50 ml. of absolute ethanol was hydrogenated at room temperature and 25 p.s.i. of hydrogen. The reduction was complete in five hours. Only three moles of hydrogen were absorbed. The catalyst was removed and the solvent distilled. Distillation of the residue yielded 1.8 g. of ethyl 3-aminophenylacetate, b.p. 118°/0.1 mm.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8.
Found: C, 67.2; H, 7.3; N, 8.0.

Cronyn (1) reports b.p. 138–140° (3–4 mm.).

Ethyl cis-(3-aminocyclohexyl)acetate (III) *and lactam* (IV). A mixture of 2.09 g. of ethyl *m*-nitrophenylacetate, 0.2 g. of Adams' platinum oxide, and 50 ml. of *glacial acetic acid* was hydrogenated as above at room temperature and 25 p.s.i. of hydrogen. After 2–3 hours, three moles of hydrogen had been absorbed. When the temperature was raised (to 35–40°), the hydrogen uptake continued although somewhat more slowly (four hours), until six moles had been taken up. Treatment as above gave 1.8 g. of an oil, b.p. 132°/37 mm. This was triturated with anhydrous ether and crystallized on prolonged standing in the refrigerator. The ethyl *cis*-(3-aminocyclohexyl)acetate (III) thus obtained melted at 112°.

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6.
Found: C, 64.8; H, 10.1; N, 7.4.

When this reduction was scaled up (4 to 20 times the above quantities), it was impossible to obtain only the ester. Apparently, when larger amounts of ester are distilled (bath temperature of 150°), lactamization partially occurs. A first fraction of the ester (about 10–20%) was followed by the lactam (IV) (20–30%), b.p. 170–190°/37 mm. The compound solidified spontaneously and was recrystallized from anhydrous ether. M.p. 167–168.5°. Cronyn (1) reports m.p. 163.5–165.5°.

Anal. Calc'd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1.
Found: C, 69.4; H, 9.4; N, 10.1.

A higher-boiling fraction (over 200°/37 mm.) was also observed, which according to analysis may consist of diethyl 3-imino-bis(cyclohexylacetate).

Anal. Calc'd for $C_{20}H_{35}NO_4$: N, 4.0. Found: N, 4.25.

When 2.0 g. of ethyl *cis*-(3-aminocyclohexyl)acetate, m.p. 112°, was heated *in vacuo* (bath temperature 140–150°) for 3 hours and then distilled, 1.32 g. of the lactam (IV) was obtained, m.p. 167–168° from anhydrous ether.

Morphan (I). A solution of 3.5 g. of the lactam (IV) in 50 ml. of anhydrous dioxane was added, with stirring, to a boiling suspension of 2 g. (excess) of lithium aluminum hydride in 100 ml. of dioxane. The mixture was refluxed for four hours after the addition was complete. It was then cooled and cautiously decomposed by the addition of excess sodium hydroxide solution, extracted with dioxane, and the extract thoroughly dried with solid potassium hydroxide. Upon distillation, 2.9 g. of an oil was obtained, consisting of unchanged starting material and an amine. It was taken up in 20% hydrochloric acid and the solution thoroughly extracted with ether. The acid phase was then made alkaline and

[2] All melting and boiling points are uncorrected.

the oil which separated (1.6 g.) taken up in ether and converted into the hydrochloride (1.2 g.). It melted at 288° (dec.). Cronyn (1) reports for material which was sublimed, m.p. 300–302° (dec.).

Anal. Calc'd for $C_8H_{16}ClN$: Cl, 22.0. Found: Cl, 22.3 (Volhard titration).

To a cold aqueous solution of the hydrochloride, dilute alkali was added with vigorous stirring. Upon seeding, the oily base was induced to crystallize; it showed m.p. 131–132° and had all properties of a secondary amine. Cronyn (1) reports m.p. 135–137° for material which was sublimed.

cis-(3-Aminocyclohexyl)acetic acid. A mixture of 1.8 g. of *m*-nitrophenylacetic acid, 0.2 g. of Adams' catalyst, and 50 ml. of glacial acetic acid was shaken with hydrogen at 25 p.s.i. and room temperature until six moles of hydrogen had been absorbed. Catalyst and solvent were removed and the oily residue triturated with acetone. Recrystallization from aqueous ethanol gave 1.2 g. of *cis*-(3-aminocyclohexyl)acetic acid, m.p. 269° (dec.). Cronyn (1) reports m.p. 272–273° (dec.).

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.1; H, 9.5; N, 8.9.
Found: C, 61.6; H, 9.5; N, 9.15.

A sample (0.5 g.) of the acid was heated in a sealed tube at 200° for three hours. On trituration with ether, the product gave 0.25 g. of the lactam (IV), m.p. 165°. The melting point was not depressed by admixture of a sample obtained from the ester (III).

SUMMARY

1. Reduction of ethyl *m*-nitrophenylacetate in glacial acetic acid yielded ethyl *cis*-(3-aminocyclohexyl)acetate (III) and—through cyclization in the course of the treatment—the lactam (IV) of *cis*-(3-aminocyclohexyl)acetic acid.

2. Reduction of the lactam (IV) with lithium aluminum hydride yielded morphan, 2-azabicyclo[3.3.1]nonane (I).

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