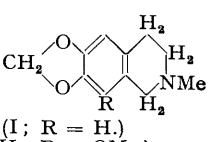
429. *Reduction of Cotarnine and Certain Derivatives thereof.*

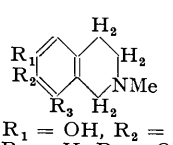
By David B. Clayson.

Reduction of hydrocotarnine with sodium and *iso*amyl alcohol in xylene gives hydrohydrastinine, whereas with sodium and liquid ammonia 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III) is produced. Cotarnine with sodium and liquid ammonia, to which ammonium chloride or sodium hydroxide has been added, gives (III) or 1 : 6-dihydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline, respectively. Some 2 : 2-dimethyltetrahydro*iso*quinolinium iodides were reduced by sodium and liquid ammonia to the corrresponding dimethyl-2-*o*-tolylethylamines.

The production of hydrohydrastinine (I) from hydrocotarnine (II) was first carried out by Pyman and Remfry (*J.*, 1912, 1595) who also obtained small quantities of the related phenolic bases (III), (IV), (V), and (VI). Reduction by sodium and alcohol was also applied by Kondo and Nagasato (*J. Pharm. Soc. Japan*, 1924, **507**, 326) to cotarnine itself with the formation of hydrocotarnine, hydrohydrastinine, and 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinoline (III). The use of inert solvents in reductions of this nature has been shown to lead to increased yields of the final product (Rowe, *J. Soc. Chem. Ind.*, 1920, **39**, 241T).



(I; R = H.)
(II; R = OMe.)



(III; R_1 = OH, R_2 = H, R_3 = OMe.)
(IV; R_1 = H, R_2 = OH, R_3 = OMe.)
(V; R_1 = R_3 = H, R_2 = OH.)
(VI; R_1 = OH, R_2 = R_3 = H.)

The hydrocotarnine used in the present work was obtained by catalytic reduction of cotarnine hydrochloride with hydrogen and Adams's catalyst, which was found to be more convenient than those previously described (Pyman and Remfry, *loc. cit.*; Beckett and Wright, *J.*, 1875, **28**, 577; Bandow and Wolffenstein, *Ber.*, 1898, **31**, 1577).

The results of various reductions of hydrocotarnine by sodium, an alcohol, and an inert

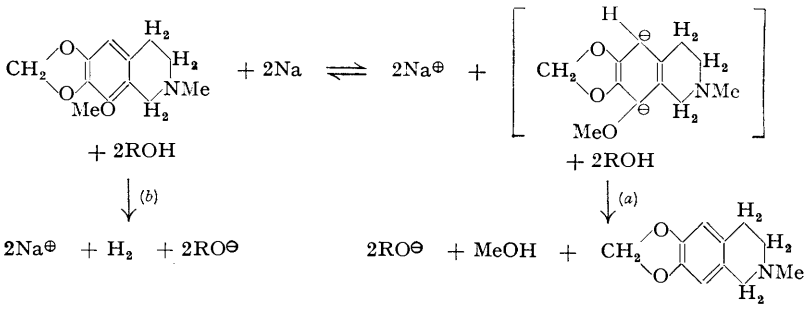
solvent are summarised in the table. The nature of the solvent and of the alcohol, as well as the quantity of sodium used, were all of critical importance to the final yield, the best results being obtained with *iso*amyl alcohol, xylene, and six atoms of sodium for each molecule of hydrocotarnine. In experiments on a larger scale the yields were increased to 60% owing to the lessening of mechanical losses.

Reduction of hydrocotarnine (5 *g.*) *to* (I) *by sodium, alcohol, and an inert solvent.*

Alcohol.	Solvent.	Sodium, g.	Yield, %.
Ethyl	Xylene	1·63	0
,,	,,	1·63	0
,,	Toluene	4·0	0
*iso*Amyl	Tetralin	4·0	12
,,	Xylene	4·0	32
,,	,,	2·0	mixture [1]
,,	,,	3·0	50
,,	Toluene	3·0	40 [2]
*iso*Propyl	Xylene	3·0	mixture [1]
,,	,,	3·8	45

[1] Mixture of hydrocotarnine and hydrohydrastinine; losses during fractional crystallisation of the hydrobromides prevent quantitative results being obtained.
[2] Two experiments.

The order of efficiency of the alcohols used (*iso*amyl > *iso*propyl ⋙ ethyl alcohol) is consistent with Birch's hypothesis (*J.*, 1945, 809), first applied to reductions by sodium in liquid ammonia and later extended to all reductions by sodium and an alcohol (Birch, *Nature*, 1946, **158**, 585). Decreasing the proton availability in the alcohol favours the reaction between the alcohol and the anion (*a*) relative to the proton and sodium reaction (*b*) :



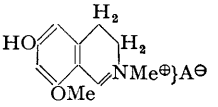
Birch (*Nature*, *loc. cit.*) considers that the liquid ammonia in reductions with sodium and liquid ammonia acts only as a solvent. In the present case the reaction takes a different course when carried out in this medium. Treatment of hydrocotarnine with sodium and liquid ammonia gives a practically quantitative yield of 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III) by fission of the methylenedioxy-group. Under similar conditions hydrohydrastinine yields a mixture of 6- (V) and 7-hydroxy-2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinoline (VI).

In the presence of ammonium chloride, cotarnine hydrochloride is reduced by sodium and liquid ammonia to 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (III); if however, sodium hydroxide or ethoxide is previously added to the solution the cotarnine hydrochloride is reduced in the main to 1 : 6-dihydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinoline characterised as the iodide, bromide, and picrate (VII) and also obtained from (III) and iodine in ethanol.

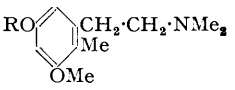
6 : 8-Dimethoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline was prepared from the tetrahydro-base (III) and diazomethane. One molecular proportion of methyl iodide and the base, with or without alkali, gave only 6-hydroxy-8-methoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium iodide. Prolonged methylation with excess of methyl iodide, potassium carbonate, and acetone gave 6 : 8-dimethoxy-1 : 2 : 3 : 4-tetrahydro-2 : 2-dimethyl*iso*quinolinium iodide.

Dr. A. J. Birch (private communication) reported that he had split benzyltrimethylammonium iodides to trimethylamine and toluene derivatives by means of sodium and liquid ammonia. During the present investigation this observation was extended to a number of 2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium iodides : 2-*o*-tolylethyldimethylamines were

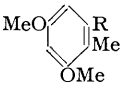
produced in the four examples studied. Thus the reduction follows the course of the catalytic reduction of these compounds (Emde and Kull, *Arch. Pharm.*, 1936, **274**, 173) instead of that of the Emde degradation with sodium amalgam (Emde, *Annalen*, 1912, **391**, 88) which leads to 2-vinylbenzyldimethylamines.



(VII.)



(VIII; R = H.)
(IX; R = Me.)



(X; R = Et.)
(XI; R = CH:CH$_2$.)

Hydrocotarnine methiodide or 6-hydroxy-8-methoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro-*iso*quinolinium iodide was reduced by sodium, alcohol, and liquid ammonia to dimethyl-2-(5′-hydroxy-3′-methoxy-2′-methylphenyl)ethylamine (VIII). In these cases the free phenolic group in the product protects the benzene ring from reduction by the sodium and alcohol (Birch, *J.*, 1944, 430). As the products from the fission of the 2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium iodide and 6 : 8-dimethoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydroisoquinolinium iodide, namely, dimethyl-2-*o*-tolylethylamine and dimethyl-2-(3′ : 5′-dimethoxy-2′-methylphenyl)ethylamine (IX), contain no protecting group it was necessary to omit the alcohol with a consequent diminution of the yield caused by the formation of high-boiling products. Trimethyl-2-(3′ : 5′-dimethoxy-2′-methylphenyl)ethylammonium iodide was split by sodium and liquid ammonia to 4 : 6-dimethoxy-2-ethyltoluene (X), but treatment with alkali gave 3 : 5-dimethoxy-2-methylstyrene (XI). According to Emde and Kull (*loc. cit.*) catalytic reduction is without effect on trimethylphenylethylammonium salts.

It is possible that the reductive splitting of these dimethyltetrahydro*iso*quinolinium salts may be of value in preparing definitely orientated *o*-ethyltoluene derivatives, etc.

Experimental.

Hydrocotarnine.—Cotarnine hydrochloride (30 g.) in water (40 c.c.) was reduced at room temperature/2 atmospheres by hydrogen and Adams's catalyst (50 mg.). The theoretical amount (3·1 l.) of hydrogen was taken up in 60—90 minutes. Hydrocotarnine hydrochloride was often precipitated towards the end of the reduction. Water (50 c.c.) was added, the solution filtered from the catalyst, and the base precipitated by aqueous ammonia. Two extractions with ether (70 c.c. each), and evaporation of the dried (Na_2SO_4) solution gave hydrocotarnine (95%), m. p. 55—56°, b. p. 182—183°/15 mm.

Hydrohydrastinine.—Hydrocotarnine (25 g.) and sodium (15 g.) in xylene (400 c.c.) in a three-necked flask fitted with stirrer, dropping funnel, and reflux condenser were heated on the sand-bath. The sodium in the boiling solution was finely dispersed by vigorous stirring and *iso*amyl alcohol (50 c.c.) run in. Stirring was continued for 20 minutes after the first vigorous reaction had abated, the solution was cooled, and the acid-soluble portion extracted with 10% hydrochloric acid (250 c.c.). The extract was basified and the non-phenolic bases extracted with ether (3 × 400 c.c.). The ether was evaporated off and the hydrohydrastinine separated from the hydrocotarnine by fractional crystallisation of the hydrobromides (Pyman and Remfry, *loc. cit.*). Hydrohydrastinine hydrobromide (m. p. 276—278°) was decomposed by aqueous potassium carbonate, the base extracted with ether and dried, and the solvent evaporated. Hydrohydrastinine (12·5 g., 60%), obtained as an oil, crystallised when kept; m. p. 61°.

6-*Hydroxy*-8-*methoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—(a) *From hydrocotarnine.* Hydrocotarnine (50 g.) was melted and dissolved in ether (50 c.c.). The solution was added to liquid ammonia (1·7 l.) containing ammonium chloride (30 g.) in a large Dewar flask. Sodium (20 g.) was added cautiously with mechanical stirring until a permanent blue colour was obtained. The ammonia was allowed to evaporate, water (400 c.c.) added, and the sodium salt of the phenolic base decomposed by a stream of carbon dioxide. After being set aside overnight, the crude 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (96%), m. p. 193—195°, was collected and recrystallised from ethyl acetate; m. p. 201—203°. The hydriodide had m. p. 223—224°.

(b) *From cotarnine hydrochloride.* Cotarnine hydrochloride (5 g.) and ammonium chloride (5 g.) in liquid ammonia (100 c.c.) were stirred by hand, and sodium (2·7 g.) was added in small pieces until a permanent blue colour was obtained. Evaporation of the ammonia, addition of water (40 c.c.), extraction of the non-phenolic products with ether, and saturation of the solution with ammonium acetate gave 6-hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (50%), m. p. 180—185°. Recrystallisation from ethyl acetate gave a product having m. p. and mixed m. p. 202—203°.

6 : 8-*Dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline.—6-Hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (2 g.) in absolute methanol (20 c.c.) was treated with diazomethane [from methylnitrosourea (10 g.) in ether (50 c.c.)] and set aside for 48 hours. The resulting solution was evaporated to dryness and partitioned between ether (40 c.c.) and 10% aqueous sodium hydroxide (20 c.c.). The ethereal extract was dried (Na_2SO_4); 6 : 8-*dimethoxy*-2-*methyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinoline, purified by distillation, had b. p. 93°/0·1 mm. (Found : C, 69·1; H, 8·2. $C_{12}H_{17}O_2N$ requires C, 69·5; H, 8·2%). The *picrate* forms rectangular orange prisms, m. p. 164°, from ethanol (Found : C, 49·5; H, 4·8. $C_{18}H_{20}O_9N_4$ requires C, 49·8; H, 4·6%).

6-*Hydroxy*-8-*methoxy*-2-*methyl*-3 : 4-*dihydro*isoquinolinium *Iodide*.—(*a*) Liquid ammonia (100 c.c.) was made " alkaline " by the addition of ethanol (8 c.c.), sodium (1 g.), and a few drops of water. When the sodium had reacted, cotarnine hydrochloride (10 g.) and then sodium (2·7 g.) were added slowly with hand-stirring. The ammonia was allowed to evaporate and the resultant solid dissolved in sodium hydroxide solution (60 c.c.). The sodium salt was decomposed by saturating the solution with ammonium acetate, and the product was extracted with ether (6 g., 79%). The viscous oil, left on the evaporation of the solvent, could not be induced to crystallise. The oil (3 g.) in 15% hydrochloric acid (10 c.c.) was mixed with sodium iodide (4 g.) in water (5 c.c.), giving 6-*hydroxy*-8-*methoxy*-2-*methyl*-3 : 4-dihydro*iso*quinolinium iodide as colourless needles which lost water at 125° and, after two recrystallisations from water, had m. p. 206° (Found : C, 41·4; H, 4·4; N, 4·3. $C_{11}H_{14}O_2NI$ requires C, 41·4; H, 4·4; N, 4·4%). The *hydrobromide* recrystallises from ethanol in colourless needles as the hemihydrate, m. p. 222—224° (Found : C, 46·9; H, 5·0; N, 5·2. $C_{11}H_{14}O_2NBr,\frac{1}{2}H_2O$ requires C, 47·0; H, 5·3; N, 5·0%). The *picrate* was precipitated from hot ethanolic solutions and crystallised from glacial acetic acid as needles, m. p. 226—228° (Found : C, 49·1, 49·1; H, 4·0, 3·9. $C_{17}H_{14}O_9N_4$ requires C, 48·6; H, 3·8%).

(*b*) 6-Hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (1 g.) and potassium acetate (0·6 g.) in ethanol (10 c.c.) were boiled under reflux with iodine (1·4 g.) in ethanol (15 c.c.) until the iodine colour had largely disappeared. When the mixture was cooled in the ice-chest, 6-hydroxy-8-methoxy-2-methyl-3 : 4-dihydro*iso*quinolinium iodide (1·2 g.), m. p. 200—201°, was obtained; after one recrystallisation from water it had m. p. and mixed m. p. 202—204°.

6 : 8-*Dimethoxy*-2 : 2-*dimethyl*-1 : 2 : 3 : 4-*tetrahydro*isoquinolinium *Iodide*.—6-Hydroxy-8-methoxy-2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline (5 g.) in acetone (100 c.c.) was heated under reflux with methyl iodide (5 g.) and potassium carbonate (10 g.) for 12 hours. The solvent was removed, the residue was extracted twice with boiling ethanol (100, 20 c.c.), and the combined extracts were reduced to a quarter of their original volume. Cooling and adding ether precipitated the *dimethoxy-iodide* as an oil which solidified when kept. This was pure enough for the next reaction. Recrystallisation from glacial acetic acid gave white needles, m. p. 206—207° (Found : C, 44·4; H, 5·7; N, 3·5. $C_{13}H_{20}O_2NI$ requires C, 45·0; H, 5·7; N, 4·0%). The derived *picrate* crystallised from ethanol in yellow needles, m. p. 151° (Found : C, 50·9; H, 4·8; N, 12·1. $C_{19}H_{22}O_9N_4$ requires C, 50·7; H, 4·9; N, 12·4%).

Dimethyl-2-(3′ : 5′-*dimethoxy*-2′-*methylphenyl*)*ethylamine*.—To the preceding methiodide (6 g.) in liquid ammonia (80 c.c.) was added sodium (1 g.) in small pieces with stirring until a permanent blue colour was obtained. The ammonia was evaporated off and water added (30 c.c.) with gentle warming to remove the last traces of ammonia. The cooled solution was extracted twice with ether (25 c.c.), and the *product* (1·2 g.) purified twice by distillation; b. p. 104°/0·3 mm. (Found : C, 69·6; H, 9·4; N, 6·7. $C_{13}H_{21}O_2N$ requires C, 70·0; H, 9·4; N, 6·3%). The colourless liquid gave a *picrate* crystallising from glacial acetic acid in long yellow prisms, m. p. 177—179° (Found : C, 50·6; H, 5·2. $C_{19}H_{24}O_9N_4$ requires C, 50·4; H, 5·3%). To the base (1·2 g.) in ethanol (15 c.c.) was added methyl iodide (2 g.) and the whole boiled under reflux for 1 hour. The *methiodide* (1·8 g.) crystallised out when the mixture cooled, and, recrystallised from glacial acetic acid, had m. p. 242—243° (Found : C, 46·4; H, 6·7; N, 3·5. $C_{14}H_{24}O_2NI$ requires C, 46·0; H, 6·6; N, 3·8%).

3 : 5-*Dimethoxy*-2-*methylstyrene*.—The above methiodide (1 g.) was heated under reflux for 4 hours with 10% sodium hydroxide solution (20 c.c.). Trimethylamine was evolved. The cooled solution was extracted with ether. 3 : 5-*Dimethoxy*-2-*methylstyrene*, purified by distillation, had b. p. 95°/0·7 mm. (Found : C, 73·8; H, 7·9. $C_{11}H_{14}O_2$ requires C, 74·2; H, 8·0%). A large amount of polymer was formed.

4 : 6-*Dimethoxy*-2-*ethyltoluene*.—The methiodide (1·8 g.) in liquid ammonia (100 c.c.) was treated with sodium until a permanent blue colour was obtained. The ammonia was evaporated and the residue partitioned between water (30 c.c.) and ether (20 c.c.). The oily *compound* left on evaporation of the ether was purified by distillation; it had b. p. 75°/0·4 mm. (Found : C, 73·0; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%).

Dimethyl-2-(5′-*hydroxy*-3′-*methoxy*-2′-*methylphenyl*)*ethylamine*.—Hydrocotarnine methiodide (or 6-hydroxy-8-methoxy-2 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinolinium methiodide) (8 g.) in liquid ammonia (100 c.c.) containing ethanol (5 c.c.) was treated with sodium until a permanent blue colour was obtained. The ammonia was evaporated and the residue taken up in water (30 c.c.). The sodium salt of the phenolic base was decomposed by carbon dioxide, and the product (3·5 g.) collected and dried. The *base*, which is soluble in ethanol and chloroform, was recrystallised from toluene; m. p. 168—169° (Found : C, 68·8; H, 9·2. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·1%). The *methiodide* crystallises from glacial acetic acid in glistening white plates, m. p. 197—198° (Found : C, 43·7; H, 6·5; N, 4·0. $C_{13}H_{22}O_2NI$ requires C, 44·4; H, 6·3; N, 4·0%). The *methopicrate* crystallises from ethanol or glacial acetic acid in orange needles, m. p. 215—216° (Found : C, 50·5; H, 5·2. $C_{19}H_{24}O_9N_4$ requires C, 50·5; H, 5·3%).

Dimethyl-2-o-*tolylethylamine*.—2 : 2-Dimethyltetrahydro*iso*quinolinium iodide (2·5 g.) was treated with sodium and liquid ammonia in the usual way. The *product* (1 g.) was extracted from the residue left by the evaporation of the ammonia with ether and was purified by distillation; b. p. 223—224°; it gave an aurichloride, m. p. 138°, methiodide, m. p. 250° and picrate, m. p. 136—137° (cf. Emde and Kull, *loc. cit.*, who cite base, b. p. 223—224°, aurichloride, m. p. 138°, methiodide, m. p. 250°, and picrate, m. p. 126—127°).

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