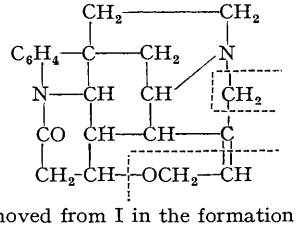
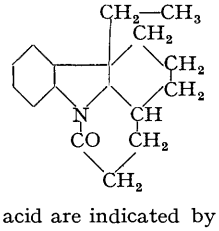
200. *Strychnine and Brucine. Part XLIV. Synthetical Experiments. Part II.*

By H. L. Holmes, H. T. Openshaw, and Sir Robert Robinson.

Starting with the Leuchs degradation of strychnine (I) * further operations, possibly by way of cuninecarboxylic acid (cf. Part XLIII), might result in the production of the lactam (II). This substance has accordingly been synthesised by methods entirely analogous to those already developed for the preparation of a carboxy-derivative of II (Part XXXVI, Openshaw and Robinson, *J.*, 1937, 941).

(I.)



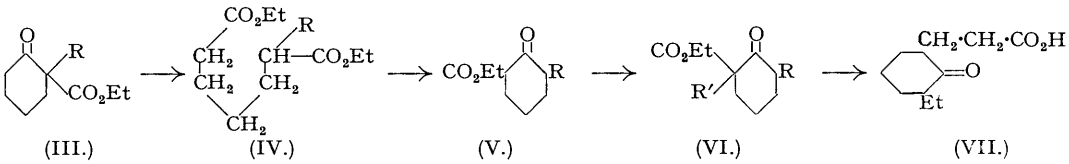


(II.)

The groups removed from I in the formation of cuninecarboxylic acid are indicated by the dotted lines in the formula.

* The older formula for strychnine is retained because it was the working hypothesis in this investigation.

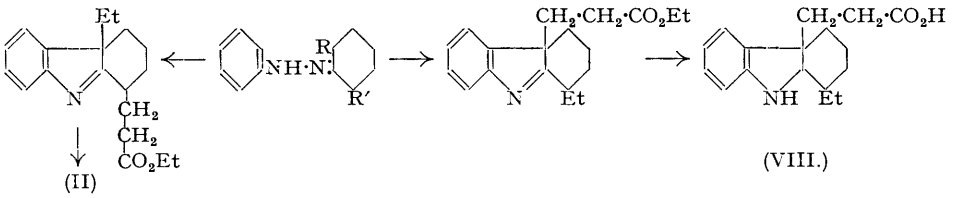
2-*Ethyl*cyclo*hexanone*-6-β-*propionic acid* (VII) has been obtained in accordance with the scheme below, in which R is Et and R′ is $CH_2{\cdot}CH_2{\cdot}CO_2Et$, or alternatively R is $CH_2{\cdot}CH_2{\cdot}CO_2Et$ and R′ is Et.



(III.) (IV.) (V.) (VI.) (VII.)

The transformation of III to V was in part direct under the influence of alcoholic sodium ethoxide (cf. Part XXXVI, *loc. cit.*); the intermediate product (IV) was, however, also isolated, and converted into V by means of sodium.

The *ethyl* ester of VII was condensed with phenylhydrazine and then changed by the action of alcoholic hydrogen chloride into a mixture of indolenines, which were not separated and purified but catalytically hydrogenated. It was then possible to isolate the *lactam* of 11-*ethylhexahydrocarbazole*-1-β-*propionic acid* (II) and 1-*ethylhexahydrocarbazole*-11-β-*propionic acid* (VIII).



(II) (VIII.)

Experimental.

Ethyl 6-*Ethyl*cyclo*hexanone*-2-*carboxylate*.—A mixture of ethyl 2-ethyl*cyclo*hexanone-2-carboxylate (98 g.; cf. F. E. King, Barltrop, and Walley, *J.*, 1945, 279) and alcoholic sodium ethoxide (11·5 g. of sodium in 140 c.c.) was refluxed for 8 hours. After cooling, dilution with water, and acidification, the oil was collected by means of ether. Distillation afforded (1), 40 g., b. p. 122—125°/9 mm., and (2) 60·6 g., b. p. 135—141°/9 mm. On redistillation (1) had b. p. 122—123°/9 mm. and gave an intense violet coloration with ferric chloride in alcoholic solution; (2) had b. p. 137—138°/9 mm. ($n_D^{20°}$ 1·4682) (Found: C, 64·2; H, 9·7. $C_{13}H_{24}O_4$ requires C, 63·9; H, 9·8%).

This *ethyl* α-*ethylpimelate* (20 g.) in benzene (300 c.c.) was refluxed with granulated sodium (3 g.) for 6 hours. The isolated product had b. p. 122—123°/9 mm. ($n_D^{20°}$ 1·4690) and gave an intense ferric reaction (Found: C, 66·3; H, 9·2. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%). In addition to 16·0 g. of this *ethyl ethyl*cyclo*hexanonecarboxylate*, identical with the product obtained directly, there were isolated 4·0 g. of unchanged ester, b. p. 137—138°/9 mm.

Hydrolysis of ethyl α-ethylpimelate by means of aqueous alcoholic potassium hydroxide and acidification furnished α-ethylpimelic acid which crystallised from benzene–light petroleum (b. p. 40—60°) in prisms, m. p. 41—43°.

Ethyl 6-*Carbethoxy*-2-*ethyl*cyclo*hexanone*-6-β-*propionate*.—Ethyl 6-ethyl*cyclo*hexanone-2-carboxylate (12·0 g.) was converted into a gelatinous sodio-derivative by means of granulated sodium (1·4 g.) in boiling benzene (60 c.c.) during 2 hours. Ethyl β-chloropropionate (9·0 g.) was added to the cooled mixture which was then refluxed for 5 hours. The isolated product gave (1) b. p. 175°/10 mm., 1·8 g., (2) b. p. 183—188°/10 mm., 12·1 g., and a small amount of oil of higher b. p. The main fraction, on redistillation, had b. p. 184—185°/10 mm.; $n_D^{20°}$ 1·4582 (Found: C, 64·7; H, 8·6. $C_{16}H_{26}O_5$ requires C, 64·4; H, 8·7%).

The ethyl α-ethylpimelate, obtained as already described, may conveniently be employed. A solution of the ester (64·0 g.) in benzene (300 c.c.) was refluxed with granulated sodium (6·1 g.) until the metal disappeared. Ethyl β-chloropropionate (40·0 g.) was introduced and refluxing continued for 6 hours. The yield was 60·2 g., b. p. 182—184°/9 mm., and a few g. of unchanged ester were recovered.

Ethyl 6-*Carbethoxy*-6-*ethyl*cyclo*hexanone*-2-β-*propionate*.—Ethyl 6-carbethoxy*cyclo*hexanone-2-β-propionate (13·5 g.) (Openshaw and Robinson *loc. cit.*) was refluxed with benzene (40 c.c.) and granulated sodium (1·15 g.) until the metal disappeared. Ethyl iodide (6·0 g.) was added and refluxing continued for 3 hours. The product (14·9 g.), isolated in the customary manner, had b. p. 185—187°/10—11 mm. ($n_D^{20°}$ 1·4662) (Found: C, 64·2; H, 8·2. $C_{16}H_{26}O_5$ requires C, 64·4; H, 8·1%). On hydrolysis with boiling concentrated hydrochloric acid for 20 hours, 8·0 g. of this *ester* afforded 4·1 g. of ethyl*cyclo*hexanonepropionic acid. This crystallised from light petroleum (b. p. 60—80°) in colourless plates, m. p. 80—80·4°, alone or mixed with the acid obtained as described below. The ethyl ester had b. p. 149—150°/10 mm.; $n_D^{20°}$ 1·4599.

2-*Ethyl*cyclo*hexanone*-6-β-*propionic Acid* (VII).—Ethyl 6-carbethoxy-2-ethyl*cyclo*hexanone-6-β-propionate (100 g.) was refluxed for 24 hours with hydrochloric acid (760 c.c.; *d* 1·17), allowing alcohol to escape at 3-hourly intervals. On cooling, the acid separated in white, glistening plates and a little more was obtained by concentration of the solution (yield, 55 g., m. p. 74—78°). The *acid* crystallised from light petroleum (b. p. 60—80°) in glistening plates, m. p. 80—80·4° (Found: C, 66·7, 66·6; H, 9·3, 9·2. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·2%) (Equiv., N/100-NaOH, 194·5. Theory, 198). The sodium salt is rather sparingly soluble and crystallises from water.

The *ethyl* ester was prepared by slow distillation of a mixture of the acid (18·5 g.) with ethanol (11 c.c.), carbon tetrachloride (35 c.c.), and 8 drops of sulphuric acid. The isolated product (14·0 g.) had b. p. 157°/15 mm., 149—150°/9—10 mm.; $n_D^{20°}$ 1·4600 (Found: C, 69·3; H, 9·7. $C_{13}H_{22}O_3$ requires C, 69·1; H, 9·8%).

Lactam of 11-*Ethylhexahydrocarbazole*-1-β-*propionic Acid* (II).—A mixture of ethyl 2-ethyl*cyclo*hexanone-6-β-propionate (11·5 g.), phenylhydrazine (5·9 g.), and 4 drops of acetic acid was heated on the steam-bath for 2 hours. After addition of ether (200 c.c.), the solution was twice washed with water, dried (Na_2SO_4), and the solvent removed. The reddish coloured oily residue was taken up in alcohol (80 c.c.) and saturated with hydrogen chloride below 40°. Ammonium chloride soon separated and, when no more appeared to be formed, water was added and enough ammonia to give an alkaline reaction.

The oil was extracted with chloroform (3 × 150 c.c.), and the solution washed with water, shaken with norite, dried, filtered, and evaporated (residue, 14·0 g.).

This mixture of indolenines was dissolved in acetic acid (100 c.c.), platinic oxide (0·1 g.) added, and the solution shaken under hydrogen at 17°/753 mm.; 1060 c.c. were absorbed (theory, 1100 c.c.). The filtered solution was concentrated, added to water (1000 c.c.), and extracted with chloroform. The washed and dried extract was evaporated and the brown oily residue was refluxed for 3 hours with hydrochloric acid (30 c.c., *d* 1·17) and water (10 c.c.). The suspended oil was dissolved in chloroform (aqueous solution *A*, see below) and the solution was washed with water, dried, and distilled. After removal of the solvent, a viscous brown oil was obtained, b. p. 181—185°/0·32 mm. (4·9 g.). This set to a hard yellow resin but the *lactam* crystallised from methanol in feathery needles and then from ethyl acetate in elongated prisms, m. p. 106·8—107·5° (Found : C, 80·0, 80·0; H, 8·2, 8·2; N, 5·3, 5·4. $C_{17}H_{21}ON$ requires C, 80·0; H, 8·3; N, 5·5%). The Otto reaction was an intense purple coloration fading to brown.

1-*Ethylhexahydrocarbazole*-11-*β-propionic Acid* (VIII).—The aqueous acid solution (*A*, see above) was concentrated and cooled; dark brown crystals (1·82 g.) then separated. This material was recrystallised four times from dilute hydrochloric acid (charcoal) and obtained as colourless plates that softened at 265°, m. p. 271° (Found : C, 66·1; H, 7·9, N, 4·5, 4·4. $C_{17}H_{24}O_2NCl$ requires C, 65·9; H, 7·8; N, 4·5%). This *hydrochloride* exhibited no Otto reaction.

The free *amino-acid* was isolated by addition of ammonia to the aqueous suspension of the salt until solution occurred and then, on making just acid with acetic acid, the substance crystallised. It separated from aqueous alcohol as glistening plates, m. p. 156—157° (Found : C, 74·8; H, 8·4; N, 5·1. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·5; N, 5·1%).

11-*Ethyl*-1 : 9-*trimethylenehexahydrocarbazole*.—The above lactam (13·8 g.) in 60% sulphuric acid (200 c.c.) was reduced at a lead cathode in the usual apparatus (cf. *J.*, 1927, 1600). A current of 4·6 amps. (*ca.* 0·05 amp./cm.^{2}) was passed for 24 hours and the temperature was not allowed to rise above 20°.

The filtered solution was basified and the oily product collected by means of chloroform and distilled; b. p. 189°/16 mm. (9·1 g.). The base crystallised from methanol in glistening plates, m. p. 51·2° (Found : C, 84·3, 84·6, 84·6; H, 9·6; N, 5·8%). A weakly acid solution shows the strychnidine reaction, a red coloration on the addition of ferric chloride. With Ehrlich's reagent under the usual conditions it develops a blue coloration.

This is not, however, an indole reaction but is due to condensation in the *p*-position to nitrogen in the benzene nucleus. A similar reaction is exhibited by 1-alkyltetrahydroquinolines and by strychnidine.

A reagent was prepared by dissolving *p*-dimethylaminobenzaldehyde (1·2 g.) in alcohol (30 c.c.), hydrochloric acid (50 c.c., *d* 1·17), and water (50 c.c.). A mixture of the sample (8—10 mg.), alcohol (4 c.c.), and the reagent (1·5 c.c.) was heated on the steam-bath for 2 minutes.

No colour was developed with strychnine, dihydrostrychnine, methylstrychnine, ethoxymethyldihydro*neo*strychnine, dihydrostrychnidine-B, *iso*strychnine, dihydro*iso*strychnine, *iso*dihydrostrychnine, hexahydrostrychnine, methoxymethyltetrahydrostrychnidine, methoxymethyltetrahydrostrychnidine-B, brucine, dihydrobrucine, brucidine, β-colubridine, 9-methyltetrahydrocarbazole, and 9-methylhexahydrocarbazole.

A blue coloration developed with strychnidine, strychnidine methochloride, dihydro*iso*strychnidine, α-colubridine (intense greenish-blue), the base $C_{22}H_{30}N_2$ (Part XXV, p. 577), and the *des*-base-A from dihydrostrychnidine-A, m. p. 143°.

*neo*Strychnidine gave a pale greenish-blue, the base-*θ*, m. p. 192° (Part XXV, p. 579), gave a pale green, and methoxymethyldihydro*neo*strychnidine gave a pale blue coloration; tetrahydrostrychnine gave a bright greenish-yellow coloration. We are obliged to Professor Wilson Baker for making the above comparisons.

α-Colubridine gives an intense crimson coloration with ferric chloride (bluer than with strychnidine) whereas β-colubridine gives an orange-red, much weaker, coloration. Similarly strychnidine and α-colubridine develop orange-yellow to orange-red colorations when heated with various aldehydes (anisaldehyde, furfuraldehyde, veratraldehyde, vanillin) and hydrochloric acid, but β-colubridine does not exhibit these reactions.

After condensation with formaldehyde in acid solution the ferric reaction of α-colubridine is an intense bluish-violet coloration; that of β-colubridine remains unchanged by the preliminary treatment and hence the base does not condense with formaldehyde. The tests on the colubridines were carried out with solutions prepared by reducing the colubrines with amalgamated zinc and boiling concentrated hydrochloric acid. They are in harmony with the view that the reactions depend on condensations in the *p*-position to nitrogen in the benzene nucleus, and with the accepted constitutions of the colubrines.

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