201. *Strychnine and Brucine. Part XLV. Synthetical Experiments. Part III.*

By H. T. Openshaw and Sir Robert Robinson.

The lactam of hexahydrocarbazole-1 : 11-ββ′-dipropionic acid (I) has now been obtained in stereoisomeric forms, one of which has been successfully submitted to the Schmidt reaction.

Attempts to resolve the resulting base (XVIII) have not yet been successful.

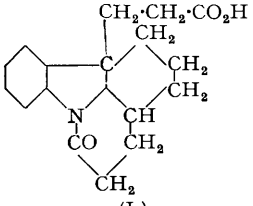
After trials in other directions 4-*carboxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionic acid* (III) has been synthesised from aliphatic intermediates and this has been transformed into a carboxy-derivative of I (II).

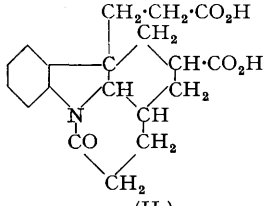
On bromination of the ester of III, followed by elimination of hydrogen bromide and hydrolysis, 6-*carboxy*-3 : 4-*dihydrocoumarin*-8-*β-propionic acid* (IV) was obtained. This acid had already been synthesised in the course of attempts to obtain III from aromatic imtermediates.

The work described in this communication and in Part XLIV was all carried out in 1937—1938 and necessarily set aside during the war; it has now been resumed.

In Part XXXVI (*J.*, 1937, 944) we described the synthesis of the lactam of hexahydrocarbazole-1 : 11-ββ′-dipropionic acid (I) and explained that we hoped to develop the synthesis of a 3-carboxy-derivative (II) of this substance. In order to apply the methods which we had developed for this purpose we required 4-carboxy-*cyclo*hexanone-2 : 6-ββ′-dipropionic acid (III) and the first route tried was by way of 6-*carboxy*-3 : 4-*dihydro-coumarin*-8-β-*propionic acid* (IV). It was hoped that the reduction of the benzene nucleus, hydrolysis, and oxidation would lead to the desired product, but the method failed because catalytic reduction of IV could not be effected.

The acid (IV) was synthesised as follows. *p*-Chlorophenol was condensed with formaldehyde in alkaline solution (G. P. 510,447; *Centr.*, 1931, I, 2115) and the chlorodi(hydroxymethyl)phenol thus obtained gave, on methylation, 4-*chloro*-2 : 6-*di*(*hydroxymethyl*)*anisole* which was oxidised to 4-*chloro*-2 : 6-*diformyl*-*anisole* (V) (cf. Ullmann and Brittner, *Ber.*, 1909, **42**, 2540, for the analogue from *p*-cresol). By condensation with malonic acid in pyridine solution, in the presence of piperidine, this was transformed into 4-*chloroanisole*-2 : 6-ββ′-*diacrylic acid* (VI), which on catalytic reduction yielded *anisole*-2 : 6-ββ′-*dipropionic acid* (VII). An attempt to introduce a carboxyl group into the 4-position of the *ethyl* ester of this compound by means of


(I.)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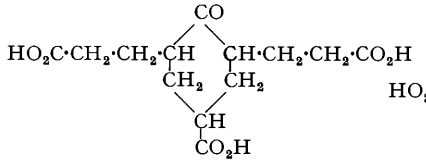
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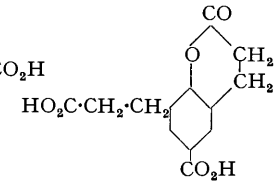
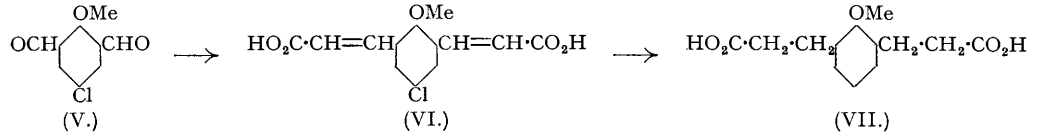
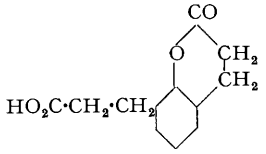

(IV.)

phenylethylcarbamyl chloride and aluminium chloride was unsuccessful. The Friedel–Crafts reaction with acetyl chloride gave a small yield of *ethyl* 4-*acetylanisole*-2 : 6-ββ′-*dipropionate*, characterised by its 2 : 7-*dinitrophenylhydrazone*, but, on account of the poor yield, the oxidation of this compound was not investigated.

On demethylation of the acid (VII) 3 : 4-*dihydrocoumarin*-8-β-*propionic acid* (VIII) was obtained. This substance could not be condensed with formaldehyde in alkaline solution; coupling with benzenediazonium chloride afforded benzeneazodihydrocoumarinpropionic acid, isolated as is *potassium* salt (IX). On reduction with sodium hydrosulphite an amine was obtained, which was converted into the corresponding nitrile by the Sandmeyer method, and thence into the desired acid (IV).

A more convenient method, however, involved the nitration of anisoledipropionic acid (VII); the resulting 4-*nitroanisole*-2 : 6-ββ′-*dipropionic acid* yielded 4-*aminoanisole*-2 : 6-ββ′-*dipropionic acid* on catalytic reduction, and this compound was diazotised and converted into the nitrile (X), which on treatment with hydrobromic acid afforded the acid (IV). The latter was converted into its *dimethyl* ester in the usual manner, but this substance was unaffected by shaking in acetic acid solution with hydrogen and platinic oxide, although ethyl *p*-acetoxybenzoate was readily reduced under the same conditions.


(V.) (VI.) (VII.)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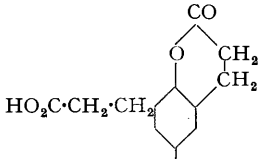
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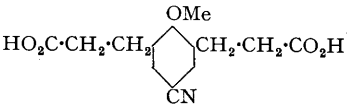
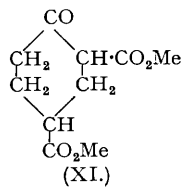

(X.)

A satisfactory synthesis of the keto-tricarboxylic acid (III) was devised on lines similar to those used for the synthesis of *cyclo*hexanonedipropionic acid (Part XXXVI, *loc. cit.*). The preparation of ethyl *cyclo*hexanone-2 : 4-dicarboxylate by the cyclisation of ethyl pentane-1 : 3 : 5-tricarboxylate has been described by Kay and Perkin (*J.*, 1906, **89**, 1647), but the method of preparation of the latter compound from ethyl 3-cyanopentane-1 : 3 : 5-tricarboxylate is inconvenient. In the present work pentane-1 : 3 : 5-tricarboxylic acid has been employed (Bottomley and Perkin, *J.*, 1900, **77**, 299).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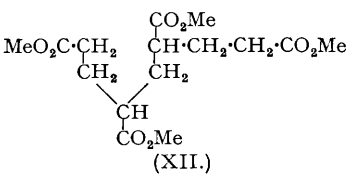
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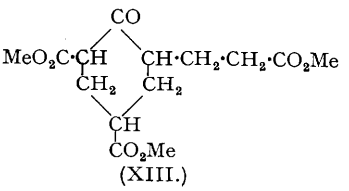
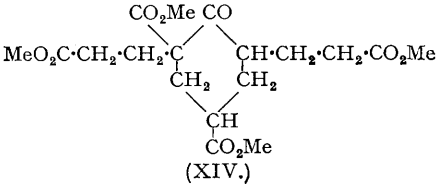

(XIII.)

The *methyl* ester of this acid, on treatment with sodium in benzene, afforded *methyl* cyclo*hexanone*-2 : 4-*dicarboxylate* (XI). When this ester was treated with methyl β-chloropropionate and sodium methoxide in methanolic solution, condensation and ring fission occurred, the product being *methyl heptane*-1 : 3 : 5 : 7-*tetracarboxylate* (XII). Treatment of the benzene solution of this ester with sodium methoxide brought about cyclisation to *methyl* 4 : 6-*dicarbomethoxy*cyclo*hexanone*-2-β-*propionate* (XIII) and the further action of methyl

β-chloropropionate on the sodium derivative of this compound produced *methyl* 4 : 6-*dicarbomethoxy*cyclo*hexanone*-2 : 6-ββ′-*dipropionate* (XIV). The methyl esters were employed on account of their lower boiling points.

When the ester (XIV) was hydrolysed, carbon dioxide was lost and the desired 4-*carboxy*cyclo*hexanone*-2 : 6-ββ′-*dipropionic acid* (III) was obtained.

The *ethyl* ester of III was converted into the methyl ester of the dihydrocoumarin derivative (IV) in the following manner. The substance readily reacted with two molecules of bromine in acetic acid solution, with evolution of hydrogen bromide. The resulting dibromo-ketone (XV) lost hydrogen bromide on heating and was converted into the corresponding phenolic compound (XVI), which was hydrolysed and converted into the methyl ester, identical with the methyl ester of IV.



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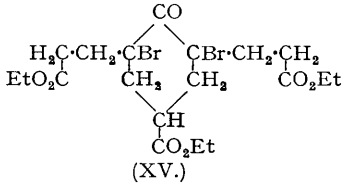

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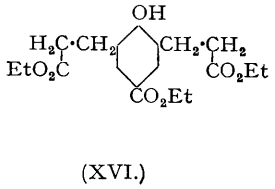
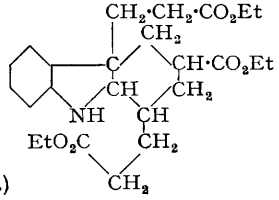


(XVI.)

On treating the phenylhydrazone of the ethyl ester of III with alcoholic hydrogen chloride, reaction occurred with separation of ammonium chloride. The resulting tetrahydrocarbazolenine derivative was reduced by the addition of zinc dust, and a product was thus obtained which exhibited an Otto reaction. It could not be obtained in an analytically pure condition, however, and appeared to be a mixture of the desired ester of II possibly with the ester XVII. Hydrolysis of the ester afforded a small yield of the desired *acid* (II) in a crystalline condition, together with a considerable quantity of amorphous material, which was soluble in strong acid and was probably the acid corresponding to XVII. It underwent atmospheric oxidation in solution, with the production of a red coloration similar to that obtained by the oxidation of strychnidine derivatives.

A crystalline hydrazide could not be obtained by treatment of the ester with hydrazine hydrate. The application of the Schmidt reaction to the acid II has not yet been attempted.



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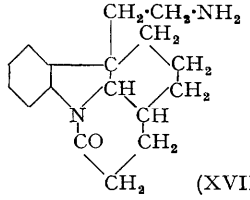
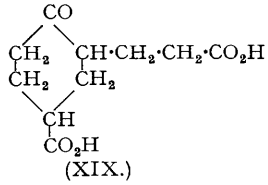


(XVIII.)

As a preliminary we have, however, applied this process to the acid I (Part XXXVI, *loc. cit.*) the method of preparation of which has been modified. In addition to the substance previously isolated (isomeride-A) we have obtained a new substance which is evidently a stereoisomeride (B). This is converted by hydrazoic acid and sulphuric acid into the *lactam-amine*-B (XVIII). The *hydrogen* d-*tartrate* crystallised without resolution.

The N-*dimethyl-base methiodide* was converted into the quaternary *d*-bromocamphorsulphonate, the examination of which will be continued. 4-*Carboxy*cyclo*hexanone*-2-β-*propionic acid* (XIX) has been prepared and converted by the Fischer reaction into the *lactam* of 3-*carboxytetrahydrocarbazole*-1-β-*propionic acid* (XX) and 3-*carboxytetrahydrocarbazolenine*-11-β-*propionic acid* (XXI).



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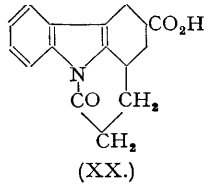

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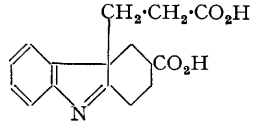

(XXI.)

The reduction of XXI gave a readily oxidisable oil which afforded a stable *acetyl* derivative.

Experimental.

4-*Chloro*-2 : 6-*di*(*hydroxymethyl*)*phenol*.—*p*-Chlorophenol (128 g.) was dissolved in aqueous sodium hydroxide (50 g. in 200 c.c.); formaldehyde (220 c.c. of 40%) was added, and the mixture kept at 30—40°. After 20 hours separation of a sodium salt commenced; after 48 hours it was collected, washed with a little water, and dried. The mother liquor, after being kept for 24 hours, yielded a further quantity of the sodium salt (total 180 g.). Acidification of the final mother liquor afforded some crude chlorodi(hydroxymethyl)phenol, which was purified by crystallisation from alcohol. A sample of sodium salt was dissolved in hot water and treated with dilute acetic acid, when the free chlorodi(hydroxy-

methyl)phenol was precipitated. After crystallisation it had the recorded m. p. 159—161° (*loc. cit.*) and gave an intense blue coloration with alcoholic ferric chloride.

4-*Chloro*-2 : 6-*di*(*hydroxymethyl*)*anisole*.—The crude sodium salt of chlorodi(hydroxymethyl)phenol (135 g.) was dissolved in boiling aqueous sodium hydroxide (12 g. in 500 c.c.), and methyl sulphate (70 c.c.) added at such a rate that the mixture, which was vigorously stirred, maintained itself at the boiling point. After the addition was completed, boiling was continued for 10 minutes, and the mixture was then allowed to cool, with stirring. The product was collected, washed with water, and dissolved in boiling water (1200 c.c.). The solution was decanted from a small amount of brown oil and boiled with norite. The oil was extracted with a further volume (500 c.c.) of boiling water, which was treated with the same norite. The combined filtered solutions, on cooling, deposited the product in long, colourless needles (56 g.), m. p. 127—128°. The *substance* was twice crystallised from water; m. p. 128° (Found: C, 53·2, H, 5·4. $C_9H_{11}O_3Cl$ requires C, 53·5; H, 5·4%).

4-*Chloro*-2 : 6-*diformylanisole* (V).—Recrystallised 4-chloro-2 : 6-di(hydroxymethyl)anisole (53 g.) was dissolved in boiling water (850 c.c.) containing sulphuric acid (40 c.c.), and a solution of potassium dichromate (50 g.) in water (130 c.c.) was gradually added with good shaking. The dialdehyde separated as an oil, which crystallised on cooling and was collected, washed with water, and dried. It retained chromic salts which gave it a green colour, but further purification was unnecessary for the next stage. The *substance* crystallised from acetic acid as colourless, long thin plates, m. p. 113—114°. Recrystallisation from light petroleum (b. p. 60—80°) raised the m. p. to 115—116° (Found: C, 54·1; H, 3·5. $C_9H_7O_3Cl$ requires C, 54·4; H, 3·5%).

4-*Chloroanisole*-2 : 6-*ββ′-diacrylic Acid* (VI).—A mixture of the crude dialdehyde (50 g.), malonic acid (57 g.), pyridine (120 c.c.), and piperidine (2 c.c.) was maintained at 70—90° for 24 hours. It was then heated until the separated solid had redissolved and poured into water (1000 c.c.) and concentrated hydrochloric acid (150 c.c.). The slimy, white precipitate was collected, washed, and dried (60 g.), and crystallised twice from acetic acid (or alcohol). The *acid* was obtained in colourless microscopic needles, m. p. 253—254° (Found: C, 55·7; H, 4·1. $C_{13}H_{11}O_5Cl$ requires C, 55·2; H, 3·9%).

Anisole-2 : 6-*ββ′-dipropionic Acid* (VII).—A solution of the pure diacrylic acid (29 g.) in aqueous potassium hydroxide (19 g. in 140 c.c.) was shaken with hydrogen and palladised strontium carbonate until the required volume of hydrogen (3 mols.) had been absorbed (4—12 hours). The filtered solution was acidified, when the *acid* (21 g.) was precipitated as a colourless oil which rapidly crystallised. It was recrystallised from water or ethyl acetate, forming colourless, flat prisms, m. p. 121—122° (Found: C, 62·1; H, 6·4. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·3%).

Ethyl Anisole-2 : 6-*ββ′-dipropionate*.—The above acid (24·5 g.) was dissolved in a mixture of carbon tetrachloride (100 c.c.), alcohol (20 c.c.), and concentrated sulphuric acid (1 c.c.), and the solution was boiled under the automatic separator (*Org. Synth.*, Coll. Vol. I, 256) until water ceased to separate. The *ester* was isolated in the usual manner, b. p. 175—176°/0·5 mm. (22 g.) (Found: C, 66·0; H, 7·8. $C_{17}H_{24}O_5$ requires C, 66·2; H, 7·8%).

Ethyl 4-*Acetylanisole*-2 : 6-*ββ′-dipropionate*.—A mixture of the above ester (6 g.), acetyl chloride (3 g.), and carbon disulphide (50 c.c.) was treated with aluminium chloride (6 g.) in portions, with cooling in a freezing mixture. After standing at room temperature for 2 hours the mixture was refluxed for 18 hours; hydrogen chloride was slowly evolved. After the product had been decomposed with ice and hydrochloric acid, the resulting oil was isolated by means of ether and distilled. The greater part had b. p. 171—180°/0·3 mm., but a small fraction (0·5 g.) was collected at 220°/0·3 mm.; and on standing this partially solidified. It yielded a 2 : 4-*dinitrophenylhydrazone*, which crystallised from alcohol as orange leaflets, m. p. 128—129° (Found: C, 56·5; H, 5·6. $C_{25}H_{30}O_9N_4$ requires C, 56·6; H, 5·7%).

3 : 4-*Dihydrocoumarin*-8-*β*-*propionic Acid* (VIII).—Anisoledipropionic acid (5 g.) was heated with hydrobromic acid (25 c.c., *d* 1·5) at 140—150° under reflux for 6 hours. On cooling, the clear yellow solution deposited orange crystals (4 g.), and after recrystallising from ethyl acetate, the *acid* was obtained as salmon-pink plates, m. p. 142—143° (Found: C, 65·2; H, 5·2. $C_{13}H_{12}O_4$ requires C, 65·4; H, 5·4%).

Potassium 6-*Benzeneazo*-3 : 4-*dihydrocoumarin*-8-*β*-*propionate* (IX).—The above acid (1·5 g.) was dissolved in aqueous potassium hydroxide (2·3 g. in 12 c.c.) and heated on the steam-bath for a short time to ensure complete hydrolysis of the lactone grouping. The solution was then cooled in a freezing mixture and treated with a diazotised solution of aniline (0·63 g.). On neutralisation of the resulting deep orange solution, an orange crystalline solid separated. After crystallisation from water it had m. p. 187° (Found: C, 52·9; H, 4·8. $C_{18}H_{17}O_5N_2K,H_2O$ requires C, 52·8; H, 4·8%). On acidification of the solution of this *salt*, benzeneazodihydrocoumarinpropionic acid is precipitated as a red gum.

6-*Carboxy*-3 : 4-*dihydrocoumarin*-8-*β*-*propionic Acid* (IV).—The potassium salt of the azo-compound (2·6 g.) was dissolved in hot water (10 c.c.), with the addition of sufficient potassium hydroxide to bring about solution, and was treated with sodium hydrosulphite in small portions until all the colour had disappeared and crystallisation commenced. The mixture was then cooled and the cream-coloured solid collected and dried (1·4 g.).

This substance was then heated with concentrated hydrochloric acid (2 c.c.) for ½ hour, diluted, and diazotised, and the diazo-solution was added to a solution of hydrated copper sulphate (1·5 g.) and potassium cyanide (1·5 g.) in water (10 c.c.). The mixture was kept at the boiling point until evolution of nitrogen had ceased, and was then cooled, filtered from cuprous salts, acidified with hydrochloric acid, and extracted several times with ether. On evaporation of the ether a brown oil remained, and on rubbing with water this crystallised. After recrystallisation from water it formed brown prisms, m. p. 152—154°, which contained nitrogen.

This substance was refluxed with concentrated hydrochloric acid for 6 hours. On cooling and diluting with water, a colourless crystalline solid separated which, after crystallisation from acetic acid, had m. p. 226—227°. It was identified with 6-carboxy-3 : 4-dihydrocoumarin-8-*β*-propionic acid obtained by the method described below.

4-*Nitroanisole*-2 : 6-*ββ′-dipropionic Acid*.—A mixture of anisoledipropionic acid (10 g.) and concentrated nitric acid (10 c.c., *d* 1·4) was gently warmed until a vigorous reaction ensued. The mixture was allowed to boil by the heat of the reaction for 5 minutes; the reaction then slackened, and water (20 c.c.) was added. On cooling, the *nitro*-derivative separated as an almost colourless crystalline solid; it crystallised from water (80 c.c.) in well-formed, very pale yellow needles (7·5 g.), m. p. 181—182° (Found: C, 52·4; H, 5·1. $C_{13}H_{15}O_7N$ requires C, 52·5; H, 5·0%).

4-*Aminoanisole*-2 : 6-*ββ′-dipropionic Acid*.—The nitro-acid (10 g.), dissolved in alcohol (80 c.c.), was shaken with hydrogen in the presence of platinic oxide until the calculated volume of hydrogen had been absorbed. After removal of the catalyst the solution was evaporated to dryness, when a light brown oil remained. This crystallised on scratching, and after recrystallisation from alcohol formed prisms, m. p. 143—145°, which turned brown on standing in air. The *amino-acid hydrochloride* crystallised in minute colourless prisms (7·7 g.), m. p. 250—251°, when a hot solution of the crude product in concentrated hydrochloric acid was allowed to cool; the salt is readily soluble in water (Found: C, 51·6; H, 5·9; N, 4·5. $C_{13}H_{17}O_5N,HCl$ requires C, 51·4; H, 5·9; N, 4·6%).

4-*Cyanoanisole*-2 : 6-*ββ′-dipropionic Acid*.—The foregoing amino-acid hydrochloride (4·6 g.) was dissolved in dilute hydrochloric acid (3 c.c. of concentrated acid and 20 c.c. of water), added to a warm solution of hydrated copper sulphate (4·5 g.) and potassium cyanide (6 g.) in water (30 c.c.), and then boiled gently for 15 minutes. The solution was acidified with hydrochloric acid and filtered hot. The red oil (3·7 g.), deposited on cooling, was isolated by means of ether; it

crystallised in contact with a little acetic acid. Recrystallisation from a small volume of acetic acid afforded colourless prisms of the *nitrile*, m. p. 120—121° (Found : C, 60·8; H, 5·5. $C_{14}H_{15}O_5N$ requires C, 60·7; H, 5·4%).

Methyl 6-*Carbomethoxy*-3 : 4-*dihydrocoumarin*-8-*β-propionate*.—The crude nitrile (3·7 g.) was refluxed for 6 hours with hydrobromic acid (15 c.c., *d* 1·5). On addition of water (10 c.c.) a reddish-brown solid separated (2·7 g.). This crystallised from acetic acid in microscopic leaflets, m. p. 224—226°. Two recrystallisations gave a colourless product, m. p. 228—229° (Found : C, 58·0; H, 5·1. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%). The acid was evidently still impure and was converted into its *methyl* ester. The crude acid (4·3 g.) was refluxed with methanolic hydrogen chloride (20 c.c.) for 6 hours and the product isolated, in the usual manner, as a colourless oil (2·4 g.), b. p. 210—211°/0·8 mm. It solidified on trituration with light petroleum (b. p. 60—80°), and crystallised from ethyl acetate as colourless prisms, m. p. 107° (Found : C, 61·6 ; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%).

Methyl Pentane-1 : 3 : 5-*tricarboxylate* (cf. Bottomley and Perkin, *loc. cit.*).—A mixture of ethyl malonate (414 g.), formalin (140 g. of 37%), and diethylamine (9 g.) was kept for 12 hours and then heated on the steam-bath for 7 hours. On seeding and keeping in the ice-chest, the oil largely crystallised. The solid (212 g.) was collected, washed with 50% alcohol (50 c.c.), thoroughly drained, and dried. A sample crystallised from 70% alcohol as silky needles of the recorded m. p. 53—55°.

The crude ethyl pentanehexacarboxylate (172 g.) was refluxed with concentrated hydrochloric acid (750 c.c.) with slow escape of alcohol. After 15 hours the clear solution was evaporated to dryness under reduced pressure and the residue was decarboxylated by heating at 200° for an hour. Pentanetricarboxylic acid (68 g. or 97%) crystallised on cooling and stirring; a sample was purified by boiling its aqueous solution with norite, filtering, and evaporating to dryness under reduced pressure. It then separated from acetone–chloroform as colourless crystals of the recorded m. p. 113—114°.

A mixture of the crude tricarboxylic acid (68 g.), methanol (70 c.c.), and sulphuric acid (10 c.c.) was heated in an oil-bath until the internal temperature was 100°. Methyl alcohol vapour was then passed through the mixture, the temperature being maintained at 100° (*Org. Synth.*, Vol. X, p. 48). The vapour was led away through a 25 cm. column, and the temperature at the top of this was observed. It rose at first to 75—80° owing to removal of water, and then slowly fell. When it had reached 65—66°, and about 500 c.c. of methanol had distilled, the process was stopped and the *ester* isolated in the usual manner, b. p. 162°/12 mm. (62·5 g., 75%) (Found : C, 53·6; H, 7·3. $C_{11}H_{18}O_6$ requires C, 53·7; H, 7·3%).

Methyl cyclo*Hexanone*-2 : 4-*dicarboxylate* (XI) (cf. Kay and Perkin, *loc. cit.*).—A mixture of methyl pentanetricarboxylate (62·5 g.), powdered sodium (5·9 g.), anhydrous benzene (300 c.c.), and a trace of methanol was refluxed on the steam-bath for 8 hours. It was then cooled and added to ice and dilute hydrochloric acid, the benzene layer was collected, and the aqueous layer was extracted twice with benzene. The combined benzene solutions were washed with dilute aqueous sodium bicarbonate and water, dried, and distilled. The colourless oil (48 g. or 88%), b. p. 145—147°/10 mm., slowly deposited large prisms and after trituration with a little light petroleum the solid had m. p. 40—44° (Found : C, 55·9; H, 6·6. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The *ester* developed an intense violet coloration on treatment with alcoholic ferric chloride.

Methyl Heptane-1 : 3 : 5 : 7-*tetracarboxylate* (XII).—A solution of sodium (8·65 g.) in methanol (180 c.c.) was slowly added to a mixture of methyl *cyclo*hexanonedicarboxylate (80·5 g.), methyl β-chloropropionate (46 g.), methanol (60 c.c.), and sodium iodide (1 g.), with shaking and cooling in ice. The mixture was kept at room temperature for 48 hours, at the end of which time it was neutral to litmus. Most of the alcohol was then distilled, the residue added to ice-water (1000 c.c.), and the *product* isolated by means of ether and distilled. A colourless oil (100·4 g. or 80%) was collected at 168—175°/0·5 mm.; redistilled, b. p. 165°/0·3 mm.; ferric reaction negative (Found : C, 54·6; H, 7·2. $C_{15}H_{24}O_8$ requires C, 54·2; H, 7·2%).

Methyl 4 : 6-*Dicarbomethoxy*cyclo*hexanone*-2-*β-propionate* (XIII).—The foregoing ester (52 g.) was refluxed for 8 hours with a solution of sodium (4·4 g.) in methanol (60 c.c.). After being cooled, the resulting solution was poured into a mixture of ice-water (800 c.c.) and hydrochloric acid (20 c.c.) and the product isolated with ether. On distillation, 42 g. were collected at 173°/0·5 mm. as a colourless oil (Found : C, 55·6; H, 6·8. $C_{14}H_{20}O_7$ requires C, 56·0; H, 6·7%).

Methyl 4 : 6-*Dicarbomethoxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionate* (XIV).—A mixture of powdered sodium (1·7 g.) benzene (20 c.c.), and methanol (3 c.c.) was heated until all the sodium had reacted. It was then cooled and the above keto-ester (22 g.) added. After being heated for 30 minutes, it was again cooled and methyl β-chloropropionate (9·2 g.) was added. After 12 hours the solution was refluxed for 30 minutes, cooled, and mixed with ice-water (50 c.c.). The benzene solution was distilled and 20·2 g. collected at 215—218°/0·5 mm.

It was found more convenient to combine the last two stages into a single process. Powdered sodium (6·95 g.) in benzene (200 c.c.) was treated with methanol (12 c.c.), and, when the reaction had slackened, methyl heptanetetracarboxylate (100·8 g.) was added, and the mixture refluxed for 6 hours. It was then cooled and methyl β-chloropropionate (37·5 g.), dissolved in benzene (50 c.c.), was added. After standing at room temperature overnight the mixture was refluxed for 3 hours, cooled, and the product isolated as before. The desired *ester* (91·4 g.) had b. p. 210—215°/0·35 mm. (Found : C, 55·9; H, 6·8. $C_{18}H_{26}O_9$ requires C, 56·0; H, 6·7%).

4-*Carboxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionic Acid* (III).—The foregoing ester (33·4 g.) was dissolved in concentrated hydrochloric acid (150 c.c.) and refluxed (air condenser) for 2 hours, the alcohol being allowed to escape. The solution was then evaporated to dryness under reduced pressure, when the *tricarboxylic acid* separated as colourless crystals (23·3 g.). A sample was recrystallised from ethyl acetate, when it formed colourless prisms, m. p. 167° (Found : C, 54·4; H, 6·3. $C_{13}H_{18}O_7$ requires C, 54·5; H, 6·3%).

In order to determine whether more than one isomer was present, a sample was fractionally crystallised from ethyl acetate, but all the crops had approximately the same m. p.; the last mother liquor deposited a small amount of amorphous material.

Ethyl 4-*Carbethoxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionate*.—The crude acid obtained above (23 g.) was dissolved in a mixture of alcohol (24 c.c.), carbon tetrachloride (100 c.c.), and sulphuric acid (0·5 c.c.), and the solution was boiled in the usual apparatus until no further separation of water occurred. The isolated product gave 27 g. of the *ester*, b. p. 197—199°/0·3 mm. (Found : C, 61·6; H, 8·1. $C_{19}H_{30}O_7$ requires C, 61·6; H, 8·1%).

Oxidation of Ethyl 4-*Carbethoxy*cyclo*hexanone*-2 : 6-*ββ′-dipropionate*.—The ester (5 g.) was dissolved in acetic acid (15 c.c.), and a solution of bromine (4·4 g.) in acetic acid (22 c.c.) was slowly added, the mixture being kept at 40—50° and well shaken. Hydrogen bromide was evolved and the colour of the bromine was rapidly discharged. The resulting pale yellow liquid was poured into water (300 c.c.), and the precipitated oil was isolated by means of ether. When heated on the steam-bath the product readily lost hydrogen bromide; after 3 hours the decomposition was completed by heating for a short time at 210°/15 mm., and on distillation a viscous oil was collected at 205—214°/0·2 mm.; on redistillation a colourless oil, b. p. 205—209°/0·2 mm., was obtained which partially crystallised on standing to a low-melting solid.

This ester was hydrolysed by refluxing with concentrated hydrochloric acid (20 c.c.) for 4 hours; on cooling and diluting the resulting solution a gummy acid was precipitated, which crystallised on treatment with aqueous acetic acid. This compound (1 g.) was converted into the methyl ester by means of boiling methanolic hydrogen chloride, and the

ester, isolated in the usual manner, had b. p. 205°/0·3 mm. It solidified on cooling and after crystallisation from a little ethyl acetate had m. p. 107°, undepressed on admixture with an authentic specimen of methyl 6-carbomethoxy-3 : 4-dihydrocoumarin-8-β-propionate.

Lactam of 3-*Carboxyhexahydrocarbazole*-1 : 11-*ββ'-dipropionic Acid* (II).—A mixture of ethyl 4-carbethoxy*cyclo*hexanone-2 : 6-*ββ'*-dipropionate (10 g.), phenylhydrazine (2·9 g.), and acetic acid (0·1 c.c.) was heated on the steam-bath for 2 hours in a slow stream of nitrogen; reaction took place with separation of water. The product, an orange-coloured oil, was dissolved in chloroform, washed twice with water, and dried (Na_2SO_4). The chloroform was then removed and the residual oily phenylhydrazone was dissolved in alcohol (30 c.c.). Hydrogen chloride was passed into the solution, which was cooled at first, and then allowed to heat until reaction occurred with separation of ammonium chloride. Passage of hydrogen chloride was continued until the solution was nearly saturated. In order to reduce the tetrahydrocarbazolenine thus produced, zinc dust (10 g.) was added in small portions to the warm mixture, which was finally heated on the steam-bath under reflux for 3—4 hours; almost all of the zinc had then dissolved. After cooling, the resulting nearly colourless solution was poured into water (600 c.c.), and the precipitated oil was taken up in ether, washed twice with dilute hydrochloric acid and then with water, dried (Na_2SO_4), and the ether removed. The residual orange-coloured oil (8 g.) exhibited the Otto reaction; on treatment of a trace of the substance, dissolved in 80% sulphuric acid, with a drop of potassium dichromate solution, a violet coloration was produced, which faded to a rose-red. On distillation, the main fraction was collected at 230—250°/0·3 mm., and distilled again at 225—240°/0·3 mm. as a highly viscous pale yellow oil (Found : C, 68·4; H, 7·8. $C_{23}H_{29}O_5N$ requires C, 69·2; H, 7·3. $C_{25}H_{35}O_6N$ requires C, 67·4; H, 7·9%). (For another sample, b. p. 230°/0·3 mm. : Found : C, 69·75; H, 7·5%.) After distillation, the substance gives an extremely transient colour in the Otto reaction. When the distilled ester was hydrolysed by refluxing with concentrated hydrochloric acid, or with alcoholic potash, only dark-coloured amorphous products were obtained.

In a second experiment, the crude product was not distilled but hydrolysed by heating under reflux with hydrochloric acid (15 c.c.) and water (15 c.c.), until a clear solution was obtained. On cooling and standing for several days a pale brown solid separated from the red solution, and this was collected (1 g.) and washed with dilute hydrochloric acid and with water. After crystallisation from acetic acid it formed colourless microscopic prisms, m. p. 250—257°; a second crystallisation raised the m. p. to 257—258° (Found : C, 66·1; H, 6·6. $C_{19}H_{21}O_5N$ requires C, 66·5; H, 6·1%). When the Otto reaction is applied to this *substance*, a deep blue-violet colour is first produced; this fades in a few seconds through a reddish-purple to a rose-red, which is stable for about a minute and then fades to a light brown. The colour changes are very similar to those given by strychnine, but take place more rapidly.

Lactam of Hexahydrocarbazole-1 : 11-*ββ'-dipropionic Acid. Modification of Method.*—Ethyl *cyclo*hexanonedipropionate (50 g.), phenylhydrazine (18·1 g.), and acetic acid (2 c.c.) were heated together on the steam-bath for 2 hours. The product was taken up in ether, washed several times with water, dried (Na_2SO_4), and the ether evaporated. The orange-coloured oily phenylhydrazone was dissolved in absolute alcohol (100 c.c.) and the solution saturated with hydrogen chloride. Separation of ammonium chloride commenced after a short time, the temperature being allowed to rise to about 60°. After the reaction was completed, the mixture was poured into a large excess of ice-cold aqueous ammonia, and the product isolated by means of ether. After removal of the ether, the oil was dissolved in acetic acid and reduced catalytically. The reduction is usually slow and it is often advantageous to add fresh catalyst (Adams's). Heating to about 30° was also resorted to in some cases.

After the theoretical volume of hydrogen had been taken up, the acetic acid was removed by evaporation under reduced pressure, and the residue boiled with concentrated hydrochloric acid for 1 hour. On adding an equal volume of water and boiling, the product crystallises (37 g. or 74%).

The crude product, a pink or light brown crystalline solid, was crystallised once from acetic acid containing about 20% of water (norite). It then had m. p. approx. 118° and was a mixture of stereoisomers. By continued fractional crystallisation from alcohol and acetic acid it was separated into two substances : A, m. p. 271°, undepressed on admixture with a specimen obtained by the original method (tin reduction), and B, m. p. 232° (Found : C, 72·2, 72·1, 71·8; H, 7·3, 7·0, 7·2; N, 4·7, 4·8. $C_{18}H_{21}O_3N$ requires C, 72·2; H, 7·0; N, 4·7%). The new *isomer* B gives the Otto reaction.

Lactam of 11-β-*Aminoethylhexahydrocarbazole*-1-β-*propionic Acid B.* (XVIII).—The above acid (isomer B, 5 g.) was dissolved in concentrated sulphuric acid (10 c.c.), the solution warmed to 40°, and a chloroform solution of hydrazoic acid (1 equiv.) added slowly with mechanical stirring. Gas evolution ceased after about 2 hours, and the resulting mixture was poured on ice. The chloroform was separated and the solution filtered from a small quantity of unchanged material; on making alkaline with sodium hydroxide, an almost colourless oil (3·4 g.) separated, which was isolated by means of chloroform. A specimen distilled at approx. 220°/0·2 mm. as a very viscous, greenish oil which did not crystallise (Found : C, 75·2; H, 8·6; N, 10·1. $C_{17}H_{22}ON_2$ requires C, 75·5; H, 8·2; N, 10·4%).

The *hydrogen* d-*tartrate* was precipitated as a colourless, crystalline solid when the components were mixed in acetone solution. It was crystallised several times from water, when it was obtained in well-formed prisms, m. p. 201—203° with softening from 175° (Found, in material dried at 100°/15 mm. : C, 57·6; H, 6·8; N, 6·4; loss at 150°, 4·1. $C_{12}H_{22}O_7N_2,H_2O$ requires C, 57·5; H, 6·8; N, 6·4; H_2O, 4·1%). The base recovered from this salt showed no optical activity.

Lactam of 11-β-*Dimethylaminoethylhexahydrocarbazole*-1-β-*propionic Acid B Methiodide.*—The above base, purified through the tartrate, was heated under reflux on the steam-bath, with excess of methyl iodide and sufficient methanol to bring about solution, for 8 hours. The solution was then evaporated to dryness, and the residual gum on treatment with acetone crystallised. It was recrystallised from a small volume of water, when it was obtaind in colourless prisms (Found, in material dried at 100°/15 mm. : C, 52·2; H, 6·9; N, 6·2; I, 27·7; loss at 150°, 4·0. $C_{20}H_{29}ON_2I,H_2O$ requires C, 52·4; H, 6·8; N, 6·1; I, 27·7; H_2O, 3·9%). The quaternary *d*-bromocamphorsulphonate was prepared from the methiodide and silver *d*-bromocamphorsulphonate, which were mixed in equimolecular quantities in aqueous solution. After removal of the silver iodide, the solution was evaporated to dryness. The product crystallised on treatment with ethyl acetate, and was recrystallised from water, when it was obtained in small clusters of colourless prisms, m. p. 265°.

4-*Carboxy*cyclo*hexanone*-2-β-*propionic Acid* (XIX).—Ethyl 4 : 6-dicarbethoxy*cyclo*hexanone-2-β-propionate was hydrolysed by refluxing with concentrated hydrochloric acid for 3 hours; the resulting solution was evaporated to dryness under reduced pressure, when the residue crystallised. It was recrystallised from ethyl acetate; colourless prisms, m. p. 130° (Found : C, 56·4; H, 6·4. $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·5%). The semicarbazone had m. p. 191° (decomp.).

Lactam of 3-*Carboxytetrahydrocarbazole*-1-β-*propionic Acid* (XX).—The above keto-acid (5 g.), phenylhydrazine (2·5 g.), and a little 50% acetic acid were heated together on the steam-bath for 1 hour. Dilute sulphuric acid (50 c.c. of 20%) was then added and the mixture heated to boiling. An almost colourless crystalline solid (0·7 g.) separated, and was collected, washed with dilute acid, and with water, and dried at 100°. It was crystallised from alcohol (25 c.c.) and then formed thin prisms with a greenish tinge, m. p. 257—262°; a second crystallisation raised the m. p. to 270—271° with slight previous sintering (Found : C, 71·6; H, 5·6. $C_{16}H_{15}O_3N$ requires C, 71·4; H, 5·6%).

3-*Carboxytetrahydrocarbazolenine*-11-β-*propionic Acid* (XXI).—The acidic mother liquor from the above preparation was washed twice with ether, made alkaline with ammonia, washed again with ether, and neutralised with acetic acid. The resulting precipitate soon crystallised and was dried at 100° (4·3 g.). It was crystallised first from 50% acetic acid

and then from alcohol and formed almost colourless leaflets, m. p. 222° (decomp.) (Found : C, 66·8; H, 5·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 5·9%).

On shaking with hydrogen and platinic oxide in acetic acid, reduction took place, but the oily product was unstable and rapidly darkened in air. On heating with acetic anhydride, and decomposing with water, a crystalline product was obtained, m. p. 209—210°. This *acetyl* derivative crystallised from ethyl acetate–light petroleum in prismatic needles, m. p. 214—215° (Found : C, 65·1; H, 6·6; N, 4·0. $C_{18}H_{21}O_5N$ requires C, 65·3; H, 6·3; N, 4·2%). The substance is readily soluble in aqueous sodium carbonate and gives a rather fugitive Otto reaction, a bluish-violet coloration. In addition to this substance a small amount of a neutral product was obtained from the acetylation process. This was possibly a cyclic ketone but the amount obtained was insufficient for further study; it gave an Otto reaction.

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