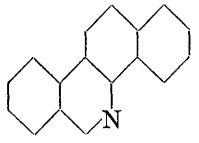
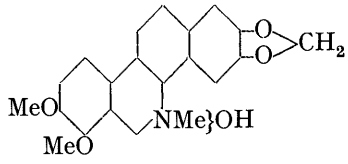
171. *Synthetical Experiments in the Chelidonine–Sanguinarine Group of the Alkaloids. Part I.*

By T. Richardson, Robert Robinson, and E. Seijo.

According to Bruchhausen and Bersch (*Ber.*, 1930, **63**, 2520) and Späth and Kuffner (*Ber.*, 1931, **64**, 370), chelidonine, sanguinarine, and chelerythrine are derivatives of α-naphthaphenanthridine (1 : 2-benzphenanthridine) (I); for example, chelerythrine is represented by the expression (II).

After trial of alternative methods, a general scheme for the synthesis of bases of chelerythrine–sanguinarine type has been worked out and the present communication deals with the preliminaries.

(I.) 



(II.)

With the co-operation of Dr. M. Liguori, we attempted to apply the phenylnaphthylenediamine synthesis of Atkinson and Thorpe (J., 1906, **89**, 1906) to the piperonyl and veratryl series, but without success.

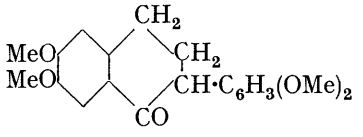
Piperonylacetonitrile, when treated with alcoholic sodium ethoxide, afforded the dimeride, β-*imino*-α-*cyano*-α*γ*-*dipiperonylpropane*, $CH_2O_2{:}C_6H_3{\cdot}CH_2{\cdot}C(:NH){\cdot}CH(CN){\cdot}C_6H_3{:}O_2CH_2$ (III), in about 50% yield and a by-product was probably 6-*amino*-5-*piperonyl*-2 : 4-*dihomopiperonylpyrimidine*. The imine was readily hydrolysed to β-*keto*-α-*cyano*-α*γ*-*dipiperonylpropane*, but neither the imine nor the keto-nitrile could be converted into a naphthalene derivative. These reactions were also examined in the veratryl series.

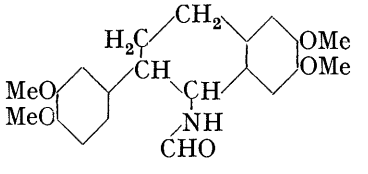
In order to test the applicability of a method similar to Pschorr's phenanthrene synthesis to the phenanthridine group, we reduced the Schiff *base* from 6-nitropiperonal and α-naphthylamine. The diazotisation of the resulting *amine* yielded only a brown tar.

Eventually the following transformations could be effected and a slight modification of them should facilitate the syntheses of chelerythrine and sanguinarine. Condensation of veratraldehyde and acetoveratrone in the usual manner afforded 3 : 4 : 3′ : 4′-*tetramethoxychalkone* and hydrogen cyanide could be added to the double bond with formation of *γ*-*keto*-α-*cyano*-α*γ*-*diveratrylpropane*, $C_6H_3(OMe)_2{\cdot}CH(CN){\cdot}CH_2{\cdot}CO{\cdot}C_6H_3(OMe)_2$ (IV). The nitrile was then hydrolysed by way of the *amide* to the corresponding *keto-acid*, which was reduced by Clemmensen's method to α*γ*-*diveratrylbutyric acid*,

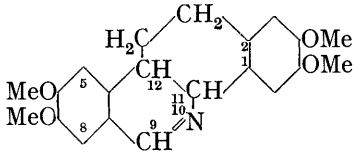
$$C_6H_3(OMe)_2{\cdot}CH(CO_2H){\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_3(OMe)_2$$

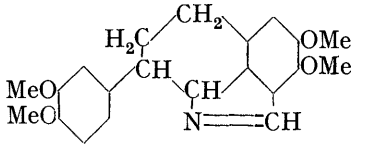
(V). The ring-closure of this substance to a tetralone derivative (VI) was best effected by means of phosphoryl chloride and the substituted *formamide* (VII) could be obtained directly from the ketone by interaction with formamide or by way of the *oxime* and related *amine* in the familiar manner.

(VI.) 



(VII.)

(VIII.) 

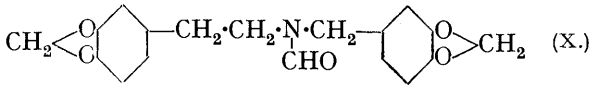


(IX.)

Dehydration of the formamide (VII) by means of phosphoryl chloride yields a base,

$C_{21}H_{23}O_4N$, which might be (VIII) or (IX), but the tetramethoxytetrahydrobenzphenanthridine constitution (VIII) is much the more probable.

A close analogy is provided by the work of Malan and Robinson (J., 1927, 2653), who showed that the action of phosphoryl chloride on formopiperonylmethyl-β-piperonylethylamide (X) gave exclusively a dihydro*iso*quinoline derivative.



(X.)

Some intermediates for a synthesis of chelerythrine along these lines are described.

Experimental.

6-*Nitropiperonylidene-α-naphthylamine*.—A mixture of 6-nitropiperonal (13·6 g.) and α-naphthylamine (10 g.) was heated (bath at 120—130°) for 2½ hours; the mass had then solidified. The product crystallised from benzene in brownish-yellow prisms (19 g.), m. p. 151—153° (Found: C, 67·6; H, 3·8; N, 8·8. $C_{18}H_{12}O_4N_2$ requires C, 67·5; H, 3·8; N, 8·8%), moderately readily soluble in benzene, dioxan, acetic acid or ethyl acetate.

6-*Aminopiperonylidene-α-naphthylamine*.—A solution of nitropiperonylidenenaphthylamine (5 g.) in the minimum quantity of hot dioxan was diluted with twice its volume of alcohol, and a hot solution of crystallised sodium sulphide (7·5 g.) in water (20 c.c.) added. After heating on the steam-bath for about 2 minutes, the mixture was added to water (4 vols.) and cooled to 0°. The yellow crystalline substance, after being washed with water, crystallised from alcohol in long yellow needles (3 g.), m. p. 150—151° (Found: N, 9·6. $C_{18}H_{14}O_2N_2$ requires N, 9·7%). The *base* dissolves in dilute hydrochloric acid to a colourless solution, but all attempts to isolate the products of the decomposition of the related diazonium salt were unsuccessful.

Ethyl α-Cyano-β-veratrylacrylate.—The condensation of veratraldehyde and sodium cyanoacetate was effected under the conditions of Lapworth and McRae's method (J., 1922, **121**, 1699) and the α-cyano-β-veratrylacrylic acid (m. p. 257—259°), obtained in excellent yield, was esterified by means of boiling 4% methyl-alcoholic hydrogen chloride. The ester, which had m. p. 153—155°, has been previously obtained by Piccinini (*Centr.*, 1904, II, 903) by condensation of veratraldehyde and ethyl cyanoacetate and is stated to melt at 156°.

Veratrylsuccinic Acid.—A mixture of ethyl α-cyano-β-veratrylacrylate (6 g.), alcohol (20 c.c.), and potassium cyanide (3·3 g.) was heated on the steam-bath for 10 minutes, then cooled and acidified with hydrochloric acid. An almost colourless, thick oil separated and after several days this crystallised to a mass of white needles, m. p. 93—95° after recrystallisation from methyl alcohol. The crude product was refluxed during 4 hours with 5 times its weight of concentrated hydrochloric acid and the brownish crystals that separated on cooling were collected and recrystallised from aqueous alcohol, affording colourless needles, m. p. 126—128° (Found: C, 53·0; H, 5·9. $C_{12}H_{14}O_6,H_2O$ requires C, 52·9; H, 5·9%). After keeping in a vacuum desiccator over sulphuric acid the anhydrous acid had m. p. 172—174°. An attempt to condense veratrylsuccinic acid with piperonal, with the help of acetic anhydride and sodium acetate, gave a brown tar, from which only some unchanged substance could be isolated. Veratrylsuccinic acid (7 g.) was esterified by refluxing it with alcohol (25 c.c.) and concentrated sulphuric acid (1 c.c.) for 4 hours. The product was isolated by means of ether and had b. p. 232—235°/15 mm. and did not crystallise at — 10°. The methyl ester was prepared in a similar manner and separated from ether–light petroleum in colourless, minute needles, m. p. 64—66°.

Condensation of Methyl Veratrylsuccinate with Piperonal.—A solution of the methyl ester (3·5 g.) and piperonal (1·9 g.) in ether (10 c.c.) was slowly added to a suspension of alcohol-free sodium ethoxide (1·6 g.) in ether (40 c.c.) cooled in a freezing mixture. The liquid quickly became turbid and after keeping in the ice-box for several hours it was shaken with water (100 c.c.), and the separated aqueous layer acidified. A white substance was deposited and this rapidly became yellow. Crystallisation of the condensation product proved to be difficult, but eventually a crystalline powder was obtained from hot ethyl acetate which, recrystallised from boiling alcohol, afforded long, bright yellow needles, m. p. 127—129° (Found: C, 65·0; H, 4·3. $C_{20}H_{16}O_7$ requires C, 65·2; H, 4·4%). This substance appears to be the *anhydride* of the colourless piperonylideneveratrylsuccinic acid; it is insoluble in alkaline solutions in the cold but dissolves on heating. Acidification then affords the colourless acid, which spontaneously changes into the yellow anhydride. The yield of the crystallised anhydride was poor and for this reason this line of attack was abandoned.

3 : 4 : 3′ : 4′-*Tetramethoxychalkone*.—Aqueous sodium hydroxide (100 c.c. of 10%) was added to a solution of veratraldehyde (100 g.) and acetoveratrone (110 g.) in alcohol (1000 c.c.). After keeping at room temperature for 12 hours with occasional shaking, the yellow crystalline precipitate was collected and recrystallised from boiling alcohol, giving elongated, hexagonal, yellow plates (170 g.), m. p. 116—118° (Found : C, 69·4; H, 6·2. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%).

The *chalkone* is easily soluble in boiling ether, alcohol or acetone. When triturated with concentrated hydrochloric acid, it dissolved to a red solution, from which minute, almost black crystals with a metallic lustre quickly separated. This unstable hydrochloride could not be obtained in an analytically pure condition. The action of hydroxylamine on veratrylideneacetoveratrone affords a *substance* which separates from aqueous alcohol in colourless, slender rosettes of needles, m. p. 152—154° (Found : N, 4·2. $C_{19}H_{21}O_5N$ requires N, 4·1%).

The *phenylhydrazone* or related *pyrazoline* could not be prepared in the usual way, but was obtained by adapting the pyridine method of oximation (Cook, Hewett, and Lawrence, J., 1936, 71). Veratrylideneacetoveratrone (1·5 g.), phenylhydrazine hydrochloride (1·5 g.), and pyridine (5 c.c.) were heated together on the steam-bath for 4 hours. The product crystallised from ethyl acetate in almost colourless, thick prisms, m. p. 159—160° (Found : N, 7·1. $C_{25}H_{26}O_4N_2$ requires N, 6·7%).

α-*Keto-αγ-diveratrylpropane*.—Veratrylideneacetoveratrone (5 g.), dissolved in acetic acid (30 c.c.), was hydrogenated under slight pressure with platinum as catalyst. After 345 c.c. of hydrogen had been absorbed (about 1 hour), no further absorption of the gas occurred, and on dilution of the filtered solution with water, a white crystalline solid was precipitated, which was recrystallised twice from ether and formed colourless needles, m. p. 88—90° (Found : C, 69·2; H, 6·4. $C_{19}H_{22}O_5$ requires C, 69·1; H, 6·7%).

An attempt to prepare the cyanohydrin by means of sodium cyanide and hydrochloric acid in alcoholic solution yielded only a minute amount of needles, m. p. 185—188°, which were not identified, the starting material being for the most part recovered unchanged.

γ-*Keto-α-cyano-αγ-diveratrylpropane* (IV).—The addition of hydrogen cyanide to tetramethoxychalkone could not be accomplished by following the method described in " Organic Syntheses " (1930, X, 80) for the similar reaction of benzylideneacetophenone. After 8 hours, only a small amount of the addition product was formed.

A solution of the chalkone (50 g.) and sodium cyanide (20 g.) in methyl alcohol (250 c.c.) was refluxed, and glacial acetic acid gradually added so that the solution remained faintly alkaline to phenolphthalein. After about 10 minutes a white crystalline mass began to separate. The solution was boiled for a further 10 minutes, cooled, and filtered, and the solid washed well with water. The dried addition product crystallised from acetone in colourless plates (45 g.), m. p. 143—144° (Found : C, 67·6; H, 6·0; N, 3·7. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·9; N, 3·9%). The *nitrile* is sparingly soluble in alcohol and ether and easily soluble in hot acetone and acetic acid.

If in the process described above, acetic acid is not added or if boiling is too prolonged, the product is contaminated by another substance consisting of white needles, m. p. 197—199°, probably resulting from the condensation of the nitrile with the unchanged chalkone (cf. Lapworth, J., 1904, **85**, 1358).

The keto-nitrile was recovered unchanged when ring-closure was attempted under the conditions of Hoesch's reaction or with chlorosulphonic acid in chloroform solution. Attempts to protect the carbonyl group by formation of the acetal by means of methyl sulphite (Voss and Blanke, *Annalen*, 1931, **485**, 272) were not successful. The nitrile may be hydrolysed to the acid by boiling concentrated hydrochloric acid, but the product thus obtained is contaminated with an intensely coloured sustance and much material is lost during purification. It is better to proceed by way of the amide.

β-*Veratroyl-α-veratrylpropionamide*.—Concentrated sulphuric acid (10 c.c.) was slowly added to a suspension of the nitrile (10 g.) in glacial acetic acid (100 c.c.). After keeping for 15 minutes at the room temperature, the mixture was poured into ice-water and the white solid was collected and crystallised from alcohol or ethyl acetate; it formed colourless rosettes of needles (9·5 g.), m. p. 160—162° (Found: C, 64·6; H, 6·1; N, 3·8. $C_{20}H_{23}O_6N$ requires C, 64·4; H, 6·2; N, 3·8%).

β-*Veratroyl-α-veratrylpropionic Acid*.—The amide (10 g.) was boiled with aqueous sodium hydroxide (100 c.c. of 7%) and alcohol (50 c.c.) until the evolution of ammonia ceased (5—6 hours). The alkaline solution was diluted with twice its volume of water and kept for ½ hour; when the filtered solution was acidified, the *acid* was precipitated as a white powder, which, crystallised from ethyl acetate–acetic acid, was obtained in pale yellow, slender needles (*ca.* 9 g.), m. p. 193—194° (Found : C, 64·2; H, 5·9. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%).

With phenylhydrazine hydrochloride in pyridine solution this acid furnished pale yellow, stout prisms, m. p. 149—151° (Found: N, 6·6. $C_{26}H_{26}O_5N_2$ requires N, 6·3%). The *derivative* is insoluble in alkaline solutions and is probably the phenylhydrazone anhydride.

αγ-Diveratrylbutyric Acid (V).—The keto-acid (40 g.) was heated with a boiling mixture of toluene (150 c.c.), 5% acetic acid (75 c.c.), concentrated hydrochloric acid (150 c.c.), and amalgamated zinc (100 g.) for 48 hours. Three portions of concentrated hydrochloric acid (50 c.c.) were added at 12-hour intervals. The toluene was separated from the aqueous layer and extracted several times with sodium carbonate solution. Acidification of the extracts gave an oil which rapidly solidified. Crystallised from benzene or aqueous acetic acid, *αγ-diveratrylbutyric acid* was obtained in colourless needles (34 g.), m. p. 118—120° (Found: C, 66·8; H, 6·6. $C_{20}H_{24}O_6$ requires C, 66·7; H, 6·7%), easily soluble in the common organic solvents except light petroleum and slightly soluble in hot water.

Dinitro-derivative. Nitric acid (0·5 c.c., *d* 1·4) was added dropwise to a cooled solution of the acid (1 g.) in acetic acid (5 c.c.). After a few minutes the dark red liquid was poured on ice and the precipitated solid was collected, washed with water, and crystallised twice from boiling ethyl acetate, forming pale yellow, thin needles, m. p. 186—188° (Found: N, 6·3. $C_{20}H_{22}O_{10}N_2$ requires N, 6·2%).

1-*Keto*-6 : 7-*dimethoxy*-2-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VI).—A mixture of *αγ*-diveratrylbutyric acid (5 g.) and phosphoryl chloride (15 c.c.) was boiled for 4 minutes, cooled, and poured on ice. The white solid which separated was extracted with chloroform, and the extract washed with dilute aqueous sodium hydroxide, dried, and evaporated. The residual oil crystallised from alcohol in colourless plates (3·5 g.), m. p. 147—149° (Found: C, 69·9; H, 6·8. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4%).

Oxime. A solution of the ketone (5 g.) and hydroxylamine hydrochloride (5 g.) in pyridine (25 c.c.) was heated at 100° for 5 hours, diluted with water, and extracted with chloroform. The chloroform solution was washed with dilute hydrochloric acid, dried, and evaporated. The *oxime* (4·8 g.) crystallised from alcohol in colourless prisms, m. p. 200—202° (Found: N, 3·8. $C_{20}H_{23}O_5N$ requires N, 3·9%).

1-*Amino*-6 : 7-*dimethoxy*-2-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*.—The oxime (4 g.) was dissolved in propyl alcohol (100 c.c.), and sodium (10 g.) added in two portions. When all the sodium had dissolved, water (100 c.c.) was added, the solution neutralised with acetic acid, and the alcohol distilled in steam; the residual oil, on cooling and shaking, slowly solidified to a mass of white needles. These were collected and extracted twice with cold dilute hydrochloric acid. The insoluble residue (2 g.) was unchanged oxime. The acid solution, on basification, afforded a white, amorphous solid, which was dissolved in a mixture of 2*N*-hydrochloric acid and alcohol (1 : 1), and excess of aqueous ammonia added. After several days, colourless silky needles separated, m. p. 119—121° (Found: C, 69·6; H, 7·5; N, 4·1. $C_{20}H_{25}O_4N$ requires C, 69·9; H, 7·3; N, 4·1%).

1-*Formamido*-6 : 7-*dimethoxy*-2-*veratryl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* (VII).—(a) The above amine (0·5 g.) was dissolved in ether (20 c.c.) and mixed with the calculated amount of anhydrous formic acid; the formate then separated as a white crystalline mass. The ether was removed by filtration, and the formate heated at 150° for 5 minutes. The formyl derivative solidified on cooling and was crystallised from methyl alcohol.

(b) 1-Keto-6 : 7-dimethoxy-2-veratryl-1 : 2 : 3 : 4-tetrahydronaphthalene (4 g.) was mixed with formamide (20 c.c.) and gently heated on a sand-bath for 4 days. The solution was cooled, diluted with water, and extracted with chloroform, the extract washed with water and dried, and the solvent removed. The residual oil readily solidified on trituration with methyl alcohol to yield a white crystalline solid (2·5 g.).

The *formyl* derivative prepared by the two methods described crystallised from methyl alcohol, containing a small amount of chloroform, in very fine, matted needles, m. p. 202—203° (Found: C, 68·1; H, 6·9; N, 3·9. $C_{21}H_{25}O_5N$ requires C, 67·8; H, 6·7; N, 3·9%).

6 : 7 : 4′ : 5′-*Tetramethoxy*-3 : 4 : 11 : 12-*tetrahydro*-1 : 2-*benzphenanthridine* (VIII).—A mixture of the formyl derivative (1 g.), toluene (6 c.c.), and phosphoryl chloride (2 c.c.) was boiled for ¼ hour. The yellow solid which separated was removed, washed with hot toluene, and suspended in hot methyl alcohol (10 c.c.). The alcohol was made alkaline with ammonia, and the white crystalline solid (0·6 g.) which separated on cooling was collected and recrystallised from methyl alcohol–chloroform (4 : 1); it formed colourless prisms, m. p. 230—231° (Found: C, 71·4; H, 6·6. $C_{21}H_{23}O_4N$ requires C, 71·6; H, 6·5%). The reduction and dehydrogenation of this *base* have been accomplished and will be described in a later communication.

Acetopiperone.—Acetopiperone has been previously prepared by oxidising the secondary

alcohol, obtained by interaction of piperonal with methylmagnesium iodide (Klages, *Ber.*, 1903, **36**, 3595; Mameli, *Gazzetta*, 1904, **34**, i, 363), with potassium dichromate or potassium permanganate, but the experimental conditions have not been specified. In our experience potassium permanganate gives the better results.

Potassium permanganate (67 g.) was added in small portions with mechanical stirring to methylpiperonylcarbinol (90 g.), dissolved in acetone (350 c.c.); the temperature was kept at 30—40° by cooling when necessary. Oxidation was complete in about 2 hours. Any small excess of permanganate was destroyed by alcohol. After filtration the manganese precipitate was washed thrice with acetone, and the solvent removed from filtrate and washings. The white crystalline residue consisted of nearly pure acetopiperone (75 g.), m. p. 85°.

Veratrylideneacetopiperone.—Veratraldehyde (15 g.) and acetopiperone (14·5 g.) were condensed together in alcoholic solution by means of sodium hydroxide under the conditions described for the preparation of veratrylideneacetoveratrone (p. 837). The *chalkone* crystallised from alcohol in large, bright yellow prisms, m. p. 133—135° (Found : C, 69·1; H, 5·2. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%). It is less readily soluble than the corresponding tetramethoxy-compound and, though it gives a red coloration with concentrated hydrochloric acid, it does not dissolve to an appreciable extent, nor does it form a characteristic hydrochloride.

γ-Keto-α-cyano-α-veratryl-γ-piperonylpropane.—The addition of hydrogen cyanide to the above chalkone was carried out as described for veratrylideneacetoveratrone (yield, 6 g. from 10 g. of the chalkone); when the mother-liquor was boiled with more sodium cyanide (2 g.) and glacial acetic acid (1 c.c.), a further quantity (3 g.) of the *nitrile* was obtained. It crystallised from acetone in colourless plates, m. p. 144—146° (Found : N, 4·1. $C_{19}H_{17}O_5N$ requires N, 4·1%).

α-Veratryl-β-piperonylpropionamide, prepared like the veratryl analogue, formed colourless plates, m. p. 178—180° (Found : N, 4·1. $C_{19}H_{19}O_6N$ requires N, 3·9%).

β-Imino-α-cyano-αγ-dipiperonylpropane (III).—The following experiments were made by Dr. M. Liguori or in collaboration with him.

A mixture of piperonylacetonitrile (20 g.) and alcoholic sodium ethoxide (1·44 g. of sodium in 30 c.c. of alcohol) was heated for 45 minutes on the steam-bath. The liquid was mixed with water and the oil which then separated was extracted with ether. After removal of the solvent the oily residue was dissolved in alcohol (20 c.c.), ether (30 c.c.) added, and the solution was left to crystallise. After 24 hours the crystals were collected and dried (7·8 g., m. p. 110—111°). The substance separated from alcohol in colourless prisms, m. p. 113—114° (Found : C, 67·3; H, 4·2; N, 8·9. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·4; N, 8·7%).

From the alcohol–ether mother-liquor there slowly separated another compound, which was collected after 15 days and dried (1·5 g., m. p. 164—165°). The alcohol–ether mother-liquor from this was evaporated, and the residue distilled, nearly all at 130—135°/1 mm. (6·5 g.). Recrystallised from alcohol, the product melted at 44—45°, alone or mixed with piperonylacetonitrile.

The compound of m. p. 164—165° crystallised from alcohol–benzene in clusters of prisms, m. p. 170—171° (Found : C, 66·5; H, 4·1; N, 8·4. $C_{27}H_{21}O_6N_3$ requires C, 67·1; H, 4·4; N, 8·7%). This substance is analogous to cyanbenzyline from phenylacetonitrile and is named in the introduction.

When the reaction mixture was heated for 30 minutes only on the steam-bath, the yield (from 20 g. of nitrile) was 9·5 g. of crude β-imino-α-cyano-αγ-dipiperonylpropane, m. p. 109—110°, and 7·5 g. of recovered nitrile.

β-Keto-α-cyano-αγ-dipiperonylpropane.—A mixture of β-imino-α-cyano-αγ-dipiperonylpropane (5 g.), alcohol (50 c.c.), and 2*N*-sulphuric acid (50 c.c.) was heated for ½ hour on the steam-bath. The reaction mixture was poured into water and the product was isolated by means of ether, dissolved in alcohol, and, after partial evaporation of the solvent, left to crystallise for 2 days; it was then collected (4·7 g., m. p. 121—122°). Recrystallised from alcohol, the *keto-nitrile* had m. p. 122—123° (Found : C, 66·7; H, 4·1; N, 4·2. $C_{18}H_{13}O_5N$ requires C, 66·7; H, 4·0; N, 4·3%).

The *oxime*, prepared from the keto-nitrile and a slight excess of hydroxylamine in alcoholic solution, was twice crystallised and had m. p. 150—151° (Found : C, 64·1; H, 4·3; N, 8·1. $C_{18}H_{14}O_5N_2$ requires C, 63·1; H, 4·1; N, 8·3%).

Attempted ring-closure of ketocyanodipiperonylpropane by means of concentrated sulphuric acid, and by chlorosulphonic acid in chloroform solution, gave unsatisfactory results.

Action of Hydrogen Chloride in Acetic Acid Solution on β-Keto-α-cyano-αγ-dipiperonylpropane and β-Imino-α-cyano-αγ-dipiperonylpropane.—A solution of β-keto-α-cyano-αγ-dipiperonylpro-

pane (3 g., m. p. 122—123°) in glacial acetic acid (60 c.c.) was saturated at 0° with hydrogen chloride. The mixture was kept for 3 days in the ice-chest and then concentrated over sodium hydroxide in a vacuum desiccator. The solid residue was sparingly soluble in cold or boiling water, in dilute mineral acids, and in cold aqueous sodium hydroxide. It was soluble in boiling alcohol, benzene, acetic acid and ethyl acetate. After several recrystallisations from alcohol (charcoal) the product was obtained in thin leaflets, m. p. *ca.* 150° with previous sintering (Found : C, 63·3; H, 4·5; N, 4·1. $C_{18}H_{13}O_5N,H_2O$ requires C, 63·3; H, 4·4; N, 4·1%).

A solution of β-amino-α-cyano-αγ-dipiperonylpropane (1 g., m. p. 113—114°) in glacial acetic acid (10 c.c.) was saturated at 0° with dry hydrogen chloride. After 3 days in the ice chest, the clear solution was evaporated in a vacuum over sodium hydroxide. The solid residue after several crystallisations from alcohol (charcoal) was obtained in thin leaflets, m. p. *ca.* 150° with previous sintering (Found : C, 63·2; H, 4·6; N, 4·3%).

A mixture of the two compounds obtained as above from the imino- and the keto-nitrile behaved like either separately on heating.

A solution of the product of m. p. *ca.* 150° in acetic acid, when mixed with sodium acetate and a solution of *p*-nitrobenzenediazonium chloride, gave no noteworthy coloration.

The substance (0·1 g.) was refluxed with aqueous sodium hydroxide (10 c.c. of 10%) for 2 hours. After cooling, the solution was acidified with hydrochloric acid, the crystalline product which separated was extracted with ether, and the solvent evaporated; the residue (0·07 g.), crystallised from benzene in colourless elongated prisms, m. p. 126—127° (Found : C, 60·2; H, 4·7. Calc. for $C_9H_8O_4$: C, 60·0; H, 4·4%). The hydrolytic product is therefore homopiperonylic acid.

β-*Imino-α-cyano-αγ-diveratrylpropane.*—A mixture of veratrylacetonitrile (10 g.) and alcoholic sodium ethoxide (0·65 g. of sodium in 10 c.c. of alcohol) was heated for ½ hour on the steam-bath. The reaction mixture was worked up as in the previous case and gave a product (6 g.), m. p. 128—140°, which was a mixture. The crude product (2 g.) was dissolved in alcohol (20 c.c.) and kept at room temperature. After 2 days the separated crystals were collected (1·2 g. of m. p. 130—132°) and recrystallised from alcohol, being obtained in colourless prisms, m. p. 132—133° (Found : C, 67·7; H, 6·4; N, 7·8, 7·9. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·2; N, 7·9%).

The alcoholic mother-liquors were concentrated and the residue was dissolved in ether (30 c.c.) and kept at room temperature. A crystalline compound that separated was collected after 6 hours (0·5 g., m. p. 165—166°). This substance dissolved in dilute mineral acids and was reprecipitated by the addition of alkali. It dissolved in boiling benzene and alcohol and was sparingly soluble in ether. Recrystallised from alcohol–ether, it was obtained in clusters of flat prisms, m. p. 168—168·5° [Found : C, 67·7; H, 6·5; N, 7·9. $(C_{10}H_{11}O_2N)_3$ requires C, 67·8; H, 6·2; N, 7·9%].

The mother-liquor from the crude product, m. p. 128—140°, was evaporated, and the oily residue distilled. It passed over nearly completely at 150°/1 mm. (1·8 g.). Recrystallised from alcohol, the substance melted at 51—52°, alone or mixed with a specimen of veratrylacetonitrile.

Attempts to improve the yield in the dimerisation of veratrylacetonitrile were unsuccessful. When potassium ethoxide was used, the yield was about 25%, but the results were not consistently obtained. The trimeride (pyrimidine derivative) was obtained as the main product if the heating was prolonged.

6-*Bromoveratrylacetonitrile.*—A solution of bromine (9 g.) in acetic acid (50 c.c.) was added dropwise to veratrylacetonitrile (10 g.), dissolved in glacial acetic acid (30 c.c.). On dilution with water an emulsion was formed, but a crystalline white solid (11·5 g.) soon separated. It crystallised from alcohol in colourless prisms, m. p. 90—92° (Found : Br, 31·3. $C_{10}H_{10}O_2NBr$ requires Br, 31·3%).

Attempts to dimerise this *bromo-nitrile* led to the recovery of some unchanged substance but to no other crystalline product.

Action of Hydrogen Chloride on Veratrylacetonitrile.—A solution of the nitrile (5 g.) in ether (100 c.c.) was saturated at 0° with dry hydrogen chloride, and powdered zinc chloride (5 g.) added. More hydrogen chloride was passed, and the reactants left for 36 hours in the ice-box. The ether was then decanted and the residual solid was decomposed with water, collected, and extracted with boiling alcohol (75 c.c.). The insoluble portion crystallised from boiling acetone in colourless needles, m. p. 213—215°. This substance contained chlorine and gave analytical figures which could not be interpreted (Found : C, 53·0; H, 5·3%).

The alcoholic solution on concentration afforded a small quantity of red needles, m. p. 207—209°. In another experiment dry hydrogen chloride was passed through an ice-cold solution

of the nitrile (5 g.) in ether (100 c.c.) during 4 hours and the solution was kept in the ice-box for 2 days. The crystalline crust was decomposed with water, and on crystallisation of the solid from alcohol a minute amount of colourless prisms, m. p. 140—142°, was obtained and could not be identified.

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