25. *The Synthesis of Long-chain Aliphatic Acids from Acetylenic Compounds. Part II. The Synthesis of a Geometrical Isomer of Pellitorine.*

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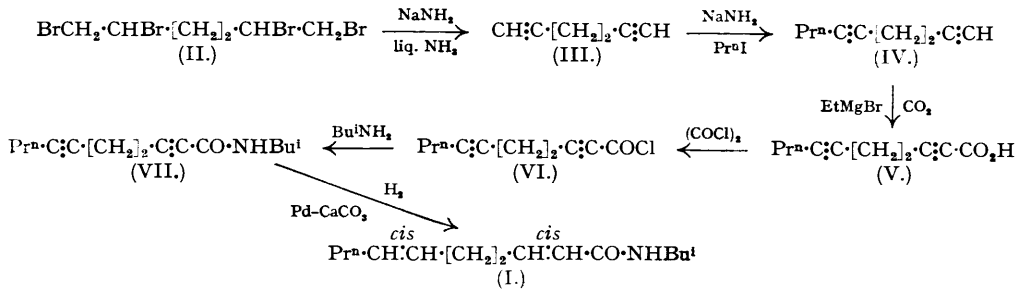
A geometrical isomer of the insecticide pellitorine (I; configuration about the double bonds unknown) has been synthesised by one of the methods used for the preparation of the herculin isomer described in the preceding paper. An improved preparation of dipropargyl (III) is given. The differential monoalkylation of (III), followed by carboxylation, yielded the diacetylenic acid (V), which was converted into the *N-iso*butyl-amide (VII). Partial hydrogenation of this gave *N-iso*butylnona-1(*cis*) : 5(*cis*)-diene-1-carboxyamide (*cis-cis*-pellitorine) (I), which however was not identical with the natural insecticide.

The root of the North African plant *Anacyclus pyrethrum* DC. has been used medicinally to stimulate the activity of the salivary glands and for the alleviation of bronchitis. The powdered root when chewed causes a persistent tingling sensation and partial insensibility of the tongue, accompanied by profuse salivation. The active principle, pellitorine, has been examined by various workers (Bucheim, *Arch. Exp. Path. Pharm.*, 1876, **5**, 455; Dunstan and Garnett, *J.*, 1895, **67**, 100; Schneegans, *Pharm. Ztg.*, 1896, **41**, 668). It was first obtained in the pure state by Gulland and Hopton (*J.*, 1930, 6), who showed it to be an *N-iso*butylnonadienecarboxyamide. The exact location of the double bonds in pellitorine has recently been established by Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366), who showed it to be the *N-iso*butylnona-1 : 5-diene-1-carboxyamide (I; configuration about the double bonds unknown). The American author also found this material (a lower homologue of herculin; cf. preceding paper) to possess insecticidal properties.

The synthesis of the *cis-cis*-isomer (I) has been accomplished by one of the methods employed for the preparation of the herculin isomer described in the previous paper. The starting material, dipropargyl (hexa-1 : 5-diyne) (III), had previously been obtained in rather poor yield (*ca.* 35%) by the dehydrobromination of 1 : 2 : 5 : 6-tetrabromohexane (II) with alcoholic



potassium hydroxide (*inter al.*, Griner, *Ann. Chim.*, 1892, **26**, 347; Lespieau, *ibid.*, 1912, **27**, 152). Heating the tetrabromide with sodamide in light petroleum gave only very small yields of the hydrocarbon (Bourguel, *ibid.*, 1925, **3**, 233). It has been shown that sodamide in liquid ammonia is an efficient and mild dehydrobrominating agent (Vaughn, Vogt, and Nieuwland, *J. Amer. Chem. Soc.*, 1934, **56**, 2120), and when the tetrabromide (II) (obtained by the addition of bromine to diallyl) was treated with an excess of this reagent, the diacetylene (III) could be isolated in 56% yield.

When (III) reacted first with 1·1 moles of sodamide in liquid ammonia and then with propyl iodide, the required monoalkylation product, *nona*-1 : 5-*diyne* (IV), was formed in 44% yield. The Grignard complex of (IV) was carbonated with solid carbon dioxide at atmospheric pressure, whereupon the diacetylenic *acid* (V), a crystalline solid, m. p. 87°, was formed. Although the yield obtained in this manner was very poor (*ca.* 8%), it could be increased to 63% by carrying out the reaction under pressure in an autoclave. The acid (V) was converted into the acid chloride (VI) by treatment with oxalyl chloride, excess of *iso*butylamine then giving the crystalline diacetylenic N-iso*butyl-amide* (VII). When this absorbed two moles of hydrogen in the presence of a palladium–calcium carbonate catalyst, the N-iso*butylnona*-1(cis) : 5(cis)-*diene*-1-*carboxyamide* (cis-cis-*pellitorine*) (I) was obtained as a homogeneous liquid. (The reasons for assigning the *cis*-configuration to ethylenic compounds obtained by the catalytic partial hydrogenation of acetylenes has already been given in the previous paper.)

It has been found that the second method used for the synthesis of the herculin isomer could not be applied in this case, as compounds of the type $RC{:}C{\cdot}CH_2{\cdot}CH_2X$ and $R{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH_2X$ (where X = halogen) on treatment with sodium acetylide in liquid ammonia mainly underwent dehydrohalogenation rather than normal condensation (Sondheimer, forthcoming communication).

The pellitorine isomer (I) obtained by the method described proved to be a somewhat viscous liquid, which could not be induced to crystallise, whereas natural pellitorine is a crystalline solid, m. p. 72° (Gulland and Hopton, *loc. cit.*; Jacobson, *loc. cit.*). Moreover, although (I) had a very bitter taste, it exhibited none of the physiological properties of pellitorine described above.

That (I) differed from pellitorine solely in its geometrical configuration was confirmed by complete hydrogenation to the crystalline *N-iso*butylnonane-1-carboxyamide, and by potassium permanganate oxidation, whereby the three fragments (butyric, succinic, and *N-iso*butyloxamic acid) were isolated in yields very similar to those obtained by Jacobson (*loc. cit.*) for the natural pellitorine.

It is interesting to note the close structural similarity between the acid moiety (VIII) of pellitorine and the violet perfume, nona-2 : 6-dien-1-al (IX). Two methods for the synthesis of the latter have been developed (Ruzicka and Schinz, *Helv. Chim. Acta*, 1934, **17**, 1602; Hunsdiecker, *Chem. Ber.*, 1947, **80**, 137), and application of either of these methods should give

(VIII.) $Pr^n{\cdot}CH{:}CH{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}CO_2H$ $\qquad$ $Et{\cdot}CH{:}CH{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}CHO$ (IX.)

the acid (VIII) in both the 1(*trans*) : 5(*trans*)- and the 1(*trans*) : 5(*cis*)-configurations. By analogy with the natural nonadienal (IX) and nonadienol (Takei *et al.*, *Bull. Agric. Chem. Soc. Japan*, 1938, **14**, 64; *Chem. Zentr.*, 1938, II, 3696; Ruzicka, Schinz, and Susz, *Helv. Chim. Acta*, 1944, **27**, 1561; Sondheimer, forthcoming publication), and with other αβ-unsaturated acids (cf. English, Bonner, and Haagen-Smit, *J. Amer. Chem. Soc.*, 1939, **61**, 3434; Lauer and Gensler, *ibid.*, 1945, **67**, 1171) the latter configuration is most probably the one present in natural pellitorine. The synthesis of this 1(*trans*) : 5(*cis*)-pellitorine by the methods indicated is now in progress in these laboratories.

Experimental.

Dipropargyl (*Hexa*-1 : 5-*diyne*) (III).—1 : 2 : 5 : 6-Tetrabromohexane was prepared in 95% yield by the gradual addition of the theoretical amount of bromine to a well-cooled solution of diallyl (hexa-1 : 5-diene) in ether, followed by removal of solvent under reduced pressure.

A suspension of sodamide in liquid ammonia (4 l.) was prepared from sodium (322 g., 14 moles), the ferric nitrate catalyst described by Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) being used to catalyse the transformation. Tetrabromohexane (704 g., 1·75 moles) in dry ether (1·6 l.) was added dropwise during 2 hours to the cooled (alcohol–carbon dioxide) and stirred suspension, which was then stirred for another 3 hours. The reaction mixture was set aside overnight without cooling, whereby most of the ammonia evaporated. (It was found advisable to allow the ammonia to evaporate before decomposing the sodio-complex, in order to minimise losses of the volatile product.) Ether, ice, and water were added to the residue, the aqueous layer was washed with ether, and the combined organic extracts were washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water, and then dried. The solvent (*ca.* 2·5 l.) was removed through a Dufton column; distillation of the residue through the same column gave dipropargyl (76·9 g., 56%) as a colourless liquid, b. p. 87·5—88·5°/758 mm., n_D^{23} 1·4380—1·4382 (Griner, *Ann. Chim.*, 1892, [6], **26**, 347, gives b. p. 85—86°). There remained a small (*ca.* 10 g.) non-volatile brown residue.

Nona-1 : 5-*diyne* (IV).—Dipropargyl (14·6 g.) in dry ether (25 c.c.) was added during 15 minutes to a cooled (alcohol–carbon dioxide) and stirred suspension of sodamide in liquid ammonia (200 c.c.), prepared from sodium (4·7 g.) by the catalytic procedure. After 1 hour's stirring, propyl iodide (40 g.) in ether (40 c.c.) was added dropwise during 30 minutes, and the cooled mixture was then stirred for a further 6 hours. Ammonium chloride (*ca.* 15 g.) was introduced, the ammonia was evaporated on the steam-bath, and the product was isolated with ether. Distillation then gave *nona*-1 : 5-*diyne* (9·9 g., 44%) as a mobile pleasant-smelling liquid, b. p. 62°/19 mm., n_D^{21} 1·4562—1·4565 (Found: C, 89·65; H, 10·2. C_9H_{12} requires C, 89·9; H, 10·1%).

Nona-1 : 5-*diyne*-1-*carboxylic Acid* (V).—Nona-1 : 5-diyne (4·8 g.) in dry ether (10 c.c.) was added during 5 minutes to a stirred solution of ethylmagnesium bromide (from magnesium, 1·3 g.) in ether (80 c.c.) in an atmosphere of nitrogen. The solution was heated under reflux for 90 minutes and then cooled in ice. It was poured on to a large excess of solid carbon dioxide in a stainless-steel autoclave, which was then sealed and allowed to attain room temperature. After 14 hours the autoclave was opened, and the solid complex decomposed with dilute sulphuric acid. More ether was added, and the ethereal layer was washed with water and sodium hydrogen carbonate solution. The latter extract was washed with ether, acidified, and again shaken with ether. This last ether extract was dried and evaporated, yielding a residue which on cooling completely solidified. Crystallisation from light petroleum (b. p. 60—80°) gave *nona*-1 : 5-*diyne*-1-*carboxylic acid* (4·15 g., 63%) as plates, m. p. 85—86° raised to 87° by further crystallisation (Found: C, 73·45; H, 7·5. $C_{10}H_{12}O_2$ requires C, 73·15; H, 7·35%).

The experiment was also carried out similarly, except that the carboxylation with solid carbon

dioxide was at atmospheric pressure (cf. Part I, preceding paper). This yielded the crystalline acid (0·5 g., 8%), most of the starting material being recoverable.

Nona-1 : 5-*diyne*-1-*carboxyl Chloride* (VI).—The acid (V) (1·4 g.) and oxalyl chloride (5·0 g.) were heated under reflux for 30 minutes. The excess of reagent was removed under reduced pressure, and distillation of the residue gave the acid chloride (1·2 g.) as a pungent yellow liquid, b. p. 95—97°/0·8 mm., n_D^{20} 1·4930. There was a considerable brown solid residue. The distillation was found to be advisable as it facilitated the purification of the product obtained in the following stage.

N-iso*Butylnona*-1 : 5-*diyne*-1-*carboxyamide* (VII).—A solution of *iso*butylamine (2·0 g.) in dry benzene (5 c.c.) was added dropwise during 5 minutes to the acid chloride (VI) (1·1 g.) in benzene (5 c.c.), with ice-cooling and continuous shaking. The clear solution was set aside at room temperature overnight, and was then washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water. The dried extract was evaporated, yielding a residue which completely solidified on cooling. One crystallisation from light petroleum (b. p. 40—60°) gave the N-iso*butylnona*-1 : 5-*diyne*-1-*carboxyamide* (1·02 g.) as long needles, m. p. 72° (Found: C, 76·3; H, 9·5; N, 6·5. $C_{14}H_{21}ON$ requires C, 76·7; H, 9·65; N, 6·4%).

N-iso*Butylnona*-1(cis) : 5(cis)-*diene*-1-*carboxyamide* (cis-cis-*Pellitorine*) (I).—The *N-iso*butyl-amide (0·81 g.) in ethyl acetate (15 c.c.) was shaken with hydrogen in the presence of a palladium–calcium carbonate catalyst (0·08 g.; 5% Pd). Hydrogenation proceeded very rapidly and 2 moles of hydrogen (176 c.c. at 18°/778 mm.) were absorbed in *ca.* 5 minutes. The reaction was interrupted, the catalyst was filtered off, and the solvent was evaporated. Distillation of the residue gave cis-cis-*pellitorine* (0·61 g.) as a somewhat viscous colourless liquid, b. p. 125—126°/5 × 10^{-4} mm., n_D^{20} 1·4855—1·4857 (Found: C, 74·65; H, 11·3; N, 6·2. $C_{14}H_{25}ON$ requires C, 75·3; H, 11·3; N, 6·25%).

N-iso*Butylnonane*-1-*carboxyamide*.—*cis-cis*-Pellitorine (0·12 g.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of platinic oxide until absorption was complete (26·5 c.c. of gas were absorbed at 23°/762 mm., equivalent to 2·0 F). Removal of catalyst and solvent, followed by crystallisation of the solid residue from light petroleum (b. p. 40—60°) at −40°, gave *N-iso*butylnonane-1-carboxyamide as a microcrystalline powder, m. p. 37—37·5° (Gulland and Hopton, *J.*, 1930, 6, give m. p. 36°).

Permanganate Oxidation of cis-cis-*Pellitorine* (I).—This oxidation was carried out with *cis-cis*-pellitorine (200 mg.) and potassium permanganate (750 mg.) in water (20 c.c.) in exactly the manner described by Jacobson (*J. Amer. Chem. Soc.*, 1949, **71**, 366) for natural pellitorine. The material not volatile in steam furnished *N-iso*butyloxamic acid (92 mg., 71%) as long needles, m. p. 103—104°, raised to 106—107° by another crystallisation (Jacobson, *loc. cit.*, gives 77% yield; m. p. 106—107°), and succinic acid (63 mg., 60%) as prisms, m. p. 186° undepressed on admixture with an authentic specimen (m. p. 189°) (Jacobson, *loc. cit.*, gives 69% yield). Titration of the steam-distillate with 0·1N-sodium hydroxide indicated that butyric acid had been obtained in 87% yield. It was identified as its *p*-bromophenacyl ester, m. p. 69° undepressed on admixture with an authentic specimen (m. p. 70°).

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