243. *The Synthesis of Piperidine Derivatives. Part III.* 5-*Phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane.*

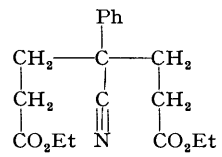
By G. M. Badger, J. W. Cook, and Thomas Walker.

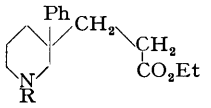
From the products of the hydrogenation of ethyl γ-cyano-γ-phenylpimelate (I) over copper chromite catalyst, *ethyl* β-(3-*phenyl*-1-*ethyl*-3-*piperidyl*)*propionate* (II) and 5-*phenyl*-1-*aza*bicyclo-[3 : 3 : 1]*nonane* (III) have been isolated; (III) has also been obtained, under certain conditions, following hydrogenation of 1 : 3 : 5-tricyano-3-phenylpentane (VII). Hydrogenation of the latter compound has also given 3-phenylpiperidine; in addition, two unidentified *bases* have been isolated and characterised.

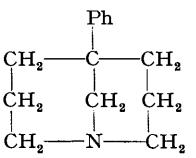
Although Adkins and Connor (*J. Amer. Chem. Soc.*, 1931, **53**, 1094) and more recently, Grundmann (" Newer Methods of Preparative Organic Chemistry," 1948, p. 120) have stated that copper chromite catalyst is ineffective for the reduction of cyanides, Barr and Cook (*J.*, 1945, 438; Part I of this series) found that γ-cyano-esters are readily reduced by hydrogenation over this catalyst to give *N*-alkylpiperidines, in which the *N*-alkyl group is provided by the alcohol used as solvent. Furthermore, Badger, Cook, and Walker (Part II; *J.*, 1948, 2011) have found that oxime-esters are likewise reduced to derivatives of *N*-alkylpiperidines, and indeed these reactions provide new and convenient methods for the preparation of compounds of this type. A preliminary report on the analgesic, antispasmodic, and local anæsthetic activity of some of the derived compounds has been published by Badger *et al.* (*Nature*, 1948, **162**, 21). In continuation of our examination of the structural features associated with biological activity of this nature, we have extended this work to the preparation of a derivative of the *iso*granatanine bridged ring system.

A preliminary investigation of the hydrogenation of ethyl γ-cyano-γ-phenylpimelate over copper chromite was reported by Barr and Cook (*loc. cit.*), who obtained a liquid base for which the structure 3-phenyl-1-ethyl-3-3′-ethoxypropylpiperidine (V) was tentatively suggested. This product gave no solid derivative, however, and it seemed possible that it was not completely homogeneous. The hydrogenation has now been carried out under a variety of experimental conditions, and two pure substances have been isolated and characterised.

In ethanolic solution, under suitable conditions of temperature and pressure, the hydrogenation of the cyano-diester (I) over copper chromite catalyst gave *ethyl* β-(3-*phenyl*-1-*ethyl*-3-*piperidyl*)*propionate* (II) in almost theoretical yield, although in one run, a small quantity of 5-*phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane* (III) (" phenyl*iso*granatanine ") was also isolated by careful fractional distillation.


(I.)


(II, R = Et; II*a*, R = H.)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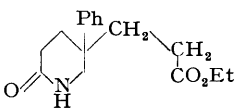
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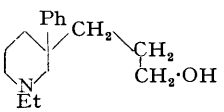
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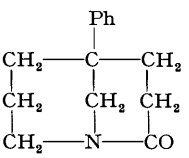

(VI.)

In dioxan solution, hydrogenation gave a mixture of the two products (II) and (III). The relative proportions of the two substances varied somewhat with the experimental conditions, as did the total yield, but the bridged-ring compound (III) was normally obtained in about 20% yield.

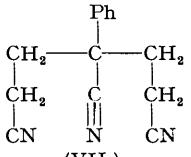
It is clear from the work of Barr and Cook (*loc. cit.*) and of Koelsch (*J. Amer. Chem. Soc.*, 1943, **65**, 2093, 2458, 2459, 2460) that the conversion of γ-cyano-esters into *N*-alkylpiperidines proceeds in four stages: (i) reduction of the cyano-group, (ii) intramolecular condensation with elimination of alcohol to give the piperidone, (iii) reduction of the piperidone to the piperidine, and (iv) alkylation by means of the alcohol used as solvent. Hydrogenations over Raney nickel were found to proceed only as far as the second stage, the piperidones being isolated. In Koelsch's experiments, the piperidones were further reduced with sodium and

butanol. Over copper chromite, however, the reaction proceeded further and *N*-alkylpiperidines were obtained directly from γ-cyano-esters. There is little doubt therefore that the hydrogenation of ethyl γ-cyano-γ-phenylpimelate (I) proceeds through the hypothetical intermediates (IV) and (II*a*). The subsequent course of the reaction is evidently governed by the experimental conditions, the ester (II*a*) reacting in two ways. In dioxan solution, part of the material undergoes a second intramolecular cyclisation with loss of alcohol, to give (VI), which on further reduction gives the bridged-ring compound (III) actually isolated. On the other hand, the hypothetical ester (II*a*) also undergoes *N*-alkylation. Indeed, in ethanolic solution, this *N*-alkylation proceeds almost exclusively, to give (II). Once *N*-alkylation has taken place the second intramolecular cyclisation to give the bridged-ring compound is effectively prevented. Even in dioxan solution the *N*-alkylation takes place to a considerable extent, although the only ethanol present in the reaction mixture is that formed by the intramolecular condensations. This provides another instance of the remarkable ease with which *N*-alkylation of piperidines may be brought about under the influence of copper chromite and high temperatures, a circumstance to which Barr and Cook have already drawn attention.

Two earlier syntheses of the *iso*granatanine ring system have been reported (McElvain and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 2738; Prelog, Heimbach, and Seiwerth, *Ber.*, 1939, **72**, 1319) but both are lengthy and give poor over-all yields. Although the yield in the present method is not good, it provides an alternative method of value for the preparation of further derivatives of this ring system. It is of interest that the recent synthesis of sparteine (Leonard and Beyler, *J. Amer. Chem. Soc.*, 1948, **70**, 2298) involves a somewhat similar intramolecular condensation of 1-carbethoxy-4-keto-3-2′-pyridylpyridocoline with hydrogen and copper chromite, in dioxan.

5-Phenyl-1-aza*bicyclo*[3 : 3 : 1]nonane (III) is a crystalline base, and it has been characterised as the *picrate* and *methiodide*. An attempt to degrade the latter by the Hofmann method was unsuccessful. Treatment with aqueous silver oxide in the usual manner eliminated the methyl group as methyl alcohol, and gave only the original base (III). Ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate (II) was a liquid and it was characterised by the preparation of a crystalline *hydrochloride*, *oxalate*, and *picrolonate*. Hydrolysis of this ester with dilute hydrochloric acid gave the *hydrochloride* of the free acid, also converted into the *oxalate* of the methyl ester. Reduction of the ester with lithium aluminium hydride (Nystrom and Brown, *J. Amer. Chem. Soc.*, 1947, **69**, 1197) gave *3-phenyl-1-ethyl-3-3′-hydroxypropylpiperidine* (V).

Although Huber (*ibid.*, 1944, **66**, 876) found that hydrogenation of basic cyanides over Raney nickel results in the formation of primary amines almost quantitatively, it is well known that the catalytic reduction of cyanides under other experimental conditions normally gives rise to considerable proportions of secondary amine by intermolecular condensation. It therefore seemed of interest to study the hydrogenation of 1 : 3 : 5-tricyano-3-phenylpentane (VII) over copper chromite.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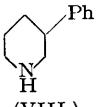
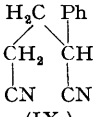

(VIII.)


(IX.)

This hydrogenation has been carried out under a variety of different conditions, and, indeed, it has been found that the course of the reaction is unusually sensitive to changes in solvent, concentration, and the quality of catalyst. In all the experiments a large quantity of ammonia was formed, and varying quantities of 3-phenylpiperidine (VIII) were isolated, depending on the conditions. Two types of copper chromite catalyst were used. For the preparation of catalyst-A, the crude chromate (*Org. Synth.*, **19**, 31) was decomposed by heating in an electric oven at 470—500° for one hour, while for catalyst-B, the chromate was decomposed by heating over a free Bunsen flame until decomposition set in. The latter method was that originally used by Connor, Folkers, and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 1138).

In *cyclo*hexane, over catalyst-B, hydrogenation of 1 : 3 : 5-tricyano-3-phenylpentane gave 3-phenylpiperidine, the remainder of the product being a mixture of high-boiling basic substances, which was not further examined. In dioxan, with the same catalyst, 3-phenylpiperidine was formed, and two additional substances were also isolated. The first was a

crystalline *base*, m. p. 155°, of probable formula $C_{14}H_{17-19}N_2$. It was characterised as the *picrate*, and was unchanged by boiling 70% sulphuric acid. The other product was a *base*, m. p. 247°. Analysis of this base, and of its *picrate*, indicated the presence of oxygen, which can only have arisen from the dioxan used as solvent. This seems to be the first recorded example of the decomposition of dioxan and its interaction with a reactant under such relatively mild conditions of temperature and pressure (230° and 175 atm.). According to Grundmann (*op. cit.*, p. 106), dioxan can be used for hydrogenations over copper chromite at temperatures up to 275°.

With catalyst-A, the hydrogenation proceeded differently. Varying amounts of 3-phenylpiperidine were always obtained, but under certain conditions, some phenylaza*bicyclo*nonane (III) was also isolated.

The formation of 3-phenylpiperidine in these reductions is of interest. It is unlikely that the side chain $\cdot CH_2 \cdot CH_2 \cdot CN$ is eliminated after the piperidine ring has been formed; if this were so one would expect the corresponding side chain to be eliminated in reduction of the cyano-diester (I), which is not observed. It seems more likely that 1 : 3 : 5-tricyano-3-phenylpentane (VII) itself is unstable, and dissociates in the alkaline media, and in the presence of the hydrogenation catalyst, to give the dicyanide (IX) and vinyl cyanide. The tricyanide (VII) is prepared by the Michael addition of vinyl cyanide to benzyl cyanide, and it has been demonstrated by Ingold and Powell (*J.*, 1921, **119**, 1976) that Michael reactions are reversible.

The formation of the compound (III) is perhaps even more surprising. It might be suggested that it is formed in this reaction by a mechanism similar to that usually accepted for the formation of secondary amines by hydrogenation of monocyanides, namely, the interaction of a molecule of primary amine with a molecule of imine with elimination of ammonia, followed by further reduction. It is difficult to extend this mechanism to the formation of a bicyclic compound in which the nitrogen is attached to both rings, however. On the other hand, Winans and Adkins (*J. Amer. Chem. Soc.*, 1932, **54**, 306) found that certain primary amines, in the presence of the usual reduction catalysts and at temperatures above 160°, interact to give ammonia and the corresponding secondary amine, in good yield. High temperatures were used in the present experiments on the hydrogenation of the tricyanide (VII), and in view of the proximity of the reacting groups, the latter type of mechanism seems especially applicable. Moreover Hoerr *et al.* (*J. Org. Chem.*, 1944, **9**, 201) have prepared secondary aliphatic amines from primary amines by catalytic deamination, and more recently, Martin and Martell (*J. Amer. Chem. Soc.*, 1948, **70**, 1817) have described the catalytic deamination of diethylenetriamine to piperazine at temperatures of 150° or higher.

Experimental.

Hydrogenation of Ethyl γ-Cyano-γ-phenylpimelate in Ethanol.—A solution of the cyano-diester (I; 20 g., Barr and Cook, *loc. cit.*) in absolute ethanol (400 c.c.) was shaken with hydrogen and copper chromite (10 g.) for 3 hours at 210° and 175 atm. After removal of the catalyst and the solvent, the resulting oil was treated with hydrochloric acid, in which it all dissolved. The solution was extracted once with ether, and then basified. The product was extracted with ether, and the solution was dried (Na_2SO_4), evaporated, and distilled. *Ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate* (II) was obtained as a colourless viscous oil, b. p. 140°/0·5 mm. (Found : C, 74·9; H, 9·5; N, 4·8; OEt, 16·0. $C_{18}H_{27}O_2N$ requires C, 74·7; H, 9·4; N, 4·8; OEt, 15·55%). The *hydrochloride* formed colourless crystals, m. p. 161°, from ethyl acetate (Found : C, 66·5; H, 8·8; N, 4·5. $C_{18}H_{28}O_2NCl$ requires C, 66·3; H, 8·65; N, 4·3%); the *oxalate* formed small colourless needles, m. p. 198°, from ethanol (Found : C, 63·5; H, 7·6; N, 4·0. $C_{18}H_{27}O_2N,C_2H_2O_4$ requires C, 63·3; H, 7·7; N, 3·7%); the *picrolonate* separated from ethanol as small yellow needles, m. p. 146—148° (Found : C, 61·0; H, 6·1; N, 12·8. $C_{18}H_{27}O_2N,C_{10}H_8O_5N_4$ requires C, 60·7; H, 6·4; N, 12·65%). The pure ester, recovered from the oxalate, was boiled for 1 hour with dilute hydrochloric acid, and the mixture then evaporated in a vacuum. The resulting glass crystallised on standing. Recrystallisation from ethyl acetate containing a little ethanol gave the *hydrochloride* of the free acid, m. p. 170° (after sintering) (Found : C, 60·9; H, 8·2. $C_{16}H_{24}O_2NCl,H_2O$ requires C, 60·85; H, 8·3%). The free acid was water-soluble and was not isolated. Treatment of the acid hydrochloride with methyl alcohol and gaseous hydrogen chloride in the usual way gave an oil which was immediately converted into the *oxalate* of the methyl ester. It formed colourless needles, m. p. 192—193°, from methanol (Found : C, 62·7; H, 7·3; N, 3·9. $C_{19}H_{27}O_6N$ requires C, 62·4; H, 7·4; N, 3·8%). The ethyl ester (II; 1·0 g.) was reduced by adding an ethereal solution dropwise to a stirred solution of lithium aluminium hydride (1 g.) in anhydrous ether. After decomposition by the gradual addition of water (Nystrom and Brown, *loc. cit.*), followed by addition of dilute sulphuric acid, *3-phenyl-1-ethyl-3-3′-hydroxypropylpiperidine* (V) (0·7 g.) was isolated as a colourless viscous oil, b. p. 145°/0·1 mm. (air bath) (Found : C, 77·7; H, 10·2. $C_{16}H_{25}ON$ requires C, 77·7; H, 10·2%).

Hydrogenation of Ethyl γ-Cyano-γ-phenylpimelate in Dioxan.—The dioxan used in these experiments was purified by heating under reflux with sodium for 10 hours, followed by distillation over sodium. The cyano-diester (10 g.) in dioxan (400 c.c.) was hydrogenated over copper chromite (5 g.) for 3 hours at 210° and 175 atm. Fractional distillation of the product, which was all basic,

gave: (*a*) 5-*Phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane* (2·5 g.) as a colourless oil, b. p. 130—135°/0·4 mm., which solidified on standing; after crystallisation from light petroleum it formed colourless needles, m. p. 64° (Found: C, 83·4; H, 9·4; N, 7·0. $C_{14}H_{19}N$ requires C, 83·6; H, 9·45; H, 7·0%); the *picrate* formed yellow needles, m. p. 178°, from ethanol (Found: C, 56·1; H, 4·7; N, 13·0. $C_{14}H_{19}N,C_6H_3O_7N_3$ requires C, 55·8; H, 5·1; N, 13·0%); the *methiodide* formed colourless needles, m. p. 236°, from ethanol (Found: C, 52·8; H, 6·3; N, 4·1. $C_{15}H_{22}NI$ requires C, 52·5; H, 6·4; N, 4·1%). (*b*) A very small quantity of ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate, b. p. 145°/0·4 mm. It was identified by conversion into the oxalate, m. p. and mixed m. p. with the specimen prepared as above 198°. (*c*) A fraction, b. p. 240—280°/0·4 mm., distilled with some decomposition, and was not further examined.

A series of experiments under varying conditions was carried out, and the above record is of one representative experiment. Under different conditions the yield of the two products varied widely. In another experiment in which the cyano-diester (20 g.), in dioxan (400 c.c.), was reduced with hydrogen and copper chromite (5 g.) for 4 hours at 215° and 175 atm., fractional distillation gave 5-phenyl-1-aza*bicyclo*[3 : 3 : 1]nonane (2·0 g.) and ethyl β-(3-phenyl-1-ethyl-3-piperidyl)propionate (7 g.).

Attempted Hofmann Degradation of 5-*Phenyl*-1-*aza*bicyclo[3 : 3 : 1]*nonane*.—A solution of the methiodide (0·4 g.) in water, was shaken with freshly precipitated silver oxide (2 g.) for 4 hours in a tightly stoppered flask. The solid was filtered off and a test of the filtrate with silver nitrate showed the absence of iodide ions and indicated that the reaction had gone to completion. The aqueous solution, on evaporation in a vacuum, gave an oil which was heated in an oil-bath at 200° until all signs of decomposition ceased. Distillation of the product in a vacuum gave 5-phenyl-1-aza*bicyclo*[3 : 3 : 1]-nonane (0·2 g.), identified by conversion into the picrate and methiodide, and by mixed m. p. determinations with authentic specimens.

Reduction of 1 : 3 : 5-*Tricyano*-3-*phenylpentane in Dioxan*.—Many experiments under different experimental conditions were carried out. The details recorded are for typical experiments: under other conditions the yield of the various fractions varied widely.

(1) The tricyanide (VII; 10 g., Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23) in dioxan (400 c.c.) was hydrogenated in the presence of copper chromite-A (5 g.) at 220—230° and 175 atm. for 3 hours. The resulting solution had a strong odour of ammonia. Fractionation of the basic product gave (*a*) 3-phenylpiperidine (1 g.) as a colourless oil, b. p. 85—90°/0·2 mm., (*b*) 5-phenyl-1-aza*bicyclo*-[3 : 3 : 1]nonane (1·5 g.), identified by m. p. and mixed m. p. of the free base, and of its picrate, (*c*) considerable dark brown residue which did not distil below 250°/0·2 mm. and was not further examined.

3-Phenylpiperidine was identified by conversion into its benzoyl derivative, which formed small colourless prisms, m. p. 88°, from ether–ligroin or ethyl acetate (lit. m. p. 89°). The *picrate*, prepared in ethanol, and recrystallised from glacial acetic acid, formed stout yellow needles, m. p. 209—210° (Found: C, 52·1; H, 4·6; N, 14·2. $C_{11}H_{15}N,C_6H_3O_7N_3$ requires C, 52·3; H, 4·6; N, 14·3%). Addition of excess of methyl iodide to 3-phenylpiperidine gave a vigorous reaction. After standing for some hours the excess of methyl iodide was removed. Crystallisation of the residue from ethanol gave 3-*phenyl*-1-*methylpiperidine methiodide* as colourless needles, m. p. 231° (Found: C, 49·5; H, 6·4; N, 4·3. $C_{13}H_{20}NI$ requires C, 49·2; H, 6·3; N, 4·4%). When exposed to the atmosphere in thin films, 3-phenylpiperidine was converted into the carbonate, m. p. 80—81°, which dissolved in dilute hydrochloric acid with effervescence. It decomposed on attempted crystallisation.

(2) The tricyanide (20 g.) in dioxan (400 c.c.) was reduced over copper chromite-A (9 g.) at 230° and 175 atm. for 5 hours. Fractionation gave: (*a*) 3-phenylpiperidine (3 g.) identified as the picrate, (*b*) a viscous oil, b. p. 150—200°/0·5 mm., from which no pure product could be isolated, and (*c*) a considerable residue which did not distil.

(3) The tricyanide (10 g.) in dioxan (400 c.c.) was reduced over copper chromite-B (5 g.) at 230° and 175 atm. for 4 hours. Fractionation of the product gave: (*a*) 3-phenylpiperidine (1 g.) identified as the picrate. (*b*) A colourless viscous oil (2 g.), b. p. 160°/0·5 mm., which solidified on standing; this *base* crystallised from ethyl acetate in colourless needles, m. p. 155° (Found: C, 78·3; H, 8·2; N, 12·9. *M*, Rast, 223. $C_{14}H_{18}N_2$ requires C, 78·5; H, 8·45; N, 13·1%; *M*, 214); the *picrate*, prepared in ethanol and recrystallised from glacial acetic acid, formed yellow needles, m. p. 191° (Found: C, 54·5; H, 4·5; N, 15·8. $C_{14}H_{18}N_2,C_6H_3O_7N_3$ requires C, 54·2; H, 4·75; N, 15·8%); the base was recovered unchanged after boiling with 70% sulphuric acid for 2 hours. (*c*) A few drops of a brown viscous oil, b. p. 240—260°/0·5 mm. A solution of this oil in ethanol deposited colourless needles, m. p. 247°, of a *base* (Found: C, 74·0; H, 6·7; N, 12·5%); its *picrate* crystallised from glacial acetic acid in lemon-yellow needles, m. p. 222° (Found: C, 53·4; H, 4·4; N, 15·8%).

Reduction of the Tricyanide in cyclo*Hexane*.—Hydrogenation of the tricyanide (10 g.) in *cyclo*hexane (400 c.c.) over copper chromite-B (5 g.) at 230° and 180 atm. for 3 hours gave, on fractionation, (*a*) 3-phenylpiperidine (2 g.), identified by mixed m. p. of the picrate, (*b*) a colourless viscous oil (2 g.), b. p. 160—190°/1 mm., from which no solid derivative could be isolated, and (*c*) a brown residue which did not distil below 260°.

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