305. *Synthetic Analgesics. Part VIII. Further Attempts to prepare 3-Phenylpiperidine Derivatives.*

By A. W. D. Avison and A. L. Morrison.

Some unsuccessful attempts are described to prepare 3-cyano-3-phenyl-1-methylpiperidine which was required for conversion into esters or ketones related to metadine.

In addition, the Mannich reaction with benzyl ketones was studied and found to take place in only one instance, *viz.*, between benzyl methyl ketone, formaldehyde, and methylallylamine. The resulting unsaturated amino-ketone (X), which had weak analgesic properties, could not be converted into a piperidine derivative.

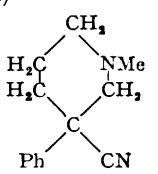
Finally, 3-phenyl-1 : 2-dimethyl-1 : 4 : 5 : 6-tetrahydropyridine has been prepared from the action of methylamine on 1-chloro-4-phenylhexan-5-one.

Originally efforts to prepare 3-phenyl-3-piperidyl ketones (see Part VII, preceding paper) were based on many unsuccessful attempts to make a 3-cyano-3-phenylpiperidine for subsequent treatment with a Grignard reagent, and also on the use of the Mannich reaction by means of which the ketone grouping would have been introduced before piperidine ring formation.

1-Chloro-3-bromopropane was condensed with phenylmalononitrile, and the resulting halogen compound (I) treated with benzylmethylamine to give the basic dinitrile (II). Hydrogenation of the latter product proceeded sluggishly and none of the desired piperidine derivative (IV) was obtained.

$$\underset{\text{(I.)}}{CH_2Cl\cdot CH_2\cdot CH_2\cdot CPh(CN)_2} \longrightarrow \underset{\text{(II.)}}{Ph\cdot CH_2\cdot NMe\cdot CH_2\cdot CH_2\cdot CPh(CN)_2}$$

$$\underset{\text{(III.)}}{CH_2Cl\cdot CH_2\cdot CH_2\cdot CPh(CN)\cdot CH_2\cdot OH}$$

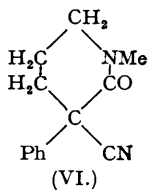


(IV.)

Ethyl δ-chloro-α-cyano-α-phenylvalerate (see preceding paper) was next reduced selectively to the cyano-alcohol (III) by means of lithium aluminium hydride. Attempts to replace the hydroxyl with halogen using thionyl chloride or phosphorus tribromide were unsuccessful and (III) itself did not condense with methylamine to give (IV).

Ethyl δ-chloro-α-cyano-α-phenylvalerate reacted readily with aqueous methylamine in the cold to give the methylamide (V) which cyclised in good yield on treatment with sodium ethoxide to form 3-cyano-3-phenyl-1-methyl-2-piperidone (VI). In neither (V) nor (VI) could the amide group be reduced selectively with lithium aluminium hydride.

$$\underset{\text{(V.)}}{CH_2Cl\cdot CH_2\cdot CH_2\cdot CPh(CN)\cdot CO\cdot NHMe} \xrightarrow{NaOEt}$$



(VI.)

$$\underset{\text{(VII.)}}{Me\cdot NH\cdot CH_2\cdot CHPh\cdot CN}$$

$$\underset{\text{(VIII.)}}{CH_2{:}CPh\cdot CN}$$

A final attempt in this group required the preparation of 2-methylamino-1-phenylethyl cyanide (VII) by the action of methylamine and formaldehyde on phenylcyanoacetic acid (cf. Mannich and Ganz, *Ber.*, 1922, **55**, 3486). This acid, obtained readily by alkaline hydrolysis of its ethyl ester, had m. p. 74°, not 92° as reported by Hessler who first described the compound (*Amer. Chem. J.*, 1904, **32**, 127). Reaction with formaldehyde and aqueous methylamine at 0° gave a basic (VII) (hydrochloride, m. p. 160—161°) and a neutral product, the bulk of which polymerised on attempted distillation and which proved to be 1-phenylvinyl cyanide (VIII) formed by decomposition of (VII).

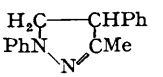
Unfortunately (VII) which was intended to be condensed with 1 : 3-dibromopropane in the presence of sodamide to complete the piperidine ring proved too unstable for this purpose.

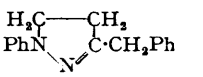
It will be apparent that 3-cyano- and 3-carbalkoxy-3-phenylpiperidines and especially 3-phenyl-3-piperidyl ketones may be regarded as Mannich bases. This led to attempts at two other synthetic approaches. First, it was desired to produce a compound such as (IX; X = halogen) which could possibly suffer cyclisation with sodamide. Accordingly, methyl-3-chloropropylamine was prepared from 1-chloro-3-bromopropane and methylamine, but this could not

$CH_2X{\cdot}CH_2{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CHPh{\cdot}CO{\cdot}R$ (IX.)

$CH_2{:}CH{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CHPh{\cdot}CO{\cdot}R$ (X.)

(XI.)





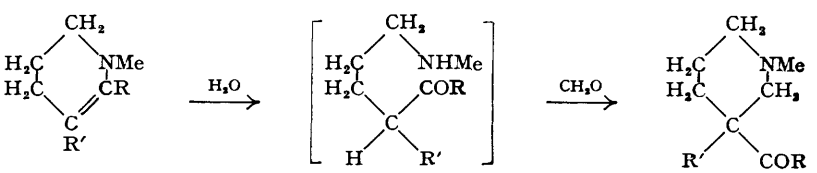
(XII.)

be induced to react with formaldehyde and methyl benzyl ketone in the Mannich reaction. On the other hand methylallylamine condensed readily to give the compound (X; R = Me). The structure of the product was taken to be that shown by virtue of (i) the general rule that $-CH_2-$ is more reactive than CH_3- in a Mannich reaction (Blicke, *Org. Reactions*, **1**, p. 308) and (ii) the colour produced in Feigl and Zappert's test for a methyl ketone (Feigl, " Spot Tests," p. 288). This view was confirmed by treatment with phenylhydrazine which splits out methylallylamine to give the pyrazoline (XI) (cf. Mannich and Bauroth, *Ber.*, 1924, **57**, 1108; Jacob and Madinaveitia, *J.*, 1937, 1929; Levvy and Nisbet, *J.*, 1938, 1053; Harradence and Lions, *J. Proc. Roy. Soc. New South Wales*, 1939, 247). Had the Mannich reaction involved the terminal methyl group, the pyrazoline obtained would have been (XII), but a Kuhn–Roth oxidation showed the presence of a methyl group.

The hydrochloride of (X; R = Me) had slight analgesic activity in the rat. The Mannich product (X; R = Et) from benzyl ethyl ketone and methylallylamine could not be obtained under a variety of conditions. The difficulty of carrying out the Mannich reaction with benzyl ketones (the above is apparently the first example reported) is not readily explained in the absence of a satisfactory theory of the mechanism of this type of condensation. It may be noted that β-tetralone, itself a " benzyl " ketone, was found by Mosettig and May (*J. Org. Chem.*, 1940, **5**, 528) not to undergo the Mannich reaction with formaldehyde and 1 : 2 : 3 : 4-tetrahydro*iso*quinoline.

All attempts to bring about addition of hydrogen bromide to the double bond of (X; R = Me) in the presence of benzoyl peroxide in the hope of obtaining (IX; R = Me, X = Br) were unsuccessful.

The second type of approach was based on the observation of Lipp (*Ber.*, 1892, **25**, 2194, 2197; 1905, **38**, 2276, 2471) that the tetrahydropyridine (XIII; R = Me, R′ = H) on treatment with formaldehyde gave 1-methyl-3-piperidyl methyl ketone (XIV; R = Me, R′ = H). If, in this earliest example of the Mannich reaction, R′ is made Ph, the application to the problem under discussion is obvious.



(XIII.) (XIV.)

In order to obtain the required intermediate (XIII; R′ = Ph, R = Me) 1-cyano-1-phenylpropan-2-one was treated with sodamide and 1-chloro-3-bromopropane to give the chloropropyl compound (XV). Instead of the expected hydrolysis of the nitrile group and consequent

decarboxylation, cleavage took place at the keto-group to give 4-chloro-1-phenylbutyl cyanide. However, it was believed that in view of its somewhat less reactive methylene group a benzyl ketone might be capable of being alkylated with sodamide and 1-chloro-3-bromopropane without giving exclusively a *cyclo*butane derivative as experienced by Case (*J. Amer. Chem. Soc.*,

$CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CPh(CN){\cdot}COMe$ (XV.) $CH_2Cl{\cdot}CH_2{\cdot}CH_2{\cdot}CHPh{\cdot}COMe$ (XVI.)

1934, **56**, 715) with benzyl cyanide. This view was confirmed by the preparation of (XVI) by this means, though in rather low yield. Treatment of this δ-chloro-ketone with aqueous methylamine (cf. Lipp, *loc. cit.*) gave the required tetrahydropyridine (XIII; R = Ph, R′ = Me). In view of unsatisfactory yields the synthesis was not carried further.

Experimental.

4-Chloro-1 : 1-dicyano-1-phenylbutane (I).—Phenylmalononitrile (7·4 g.) (Hessler, *Amer. Chem. J.*, 1904, **32**, 123) was added with stirring and cooling to a solution of sodium ethoxide (1·2 g. of sodium in 30 ml. of absolute alcohol), followed by 1-chloro-3-bromobutane (8·2 g.) in absolute alcohol (20 ml.). The mixture was then refluxed for 10 hours, sodium bromide separating. It was next concentrated *in vacuo* and the residue treated with ether and water. The ethereal solution together with a further ethereal washing of the aqueous part was washed with water, dried, and concentrated. Distillation gave the *chloro-nitrile* (5·7 g.) as a practically colourless oil, b. p. 111°/0·2 mm. (Found: N, 13·5. $C_{12}H_{11}N_2Cl$ requires N, 12·8%).

4-Benzylmethylamino-1 : 1-dicyano-1-phenylbutane (II).—The above chloro-compound (5·65 g.) was added slowly to a solution of sodium iodide (3·9 g.) in boiling acetone (40 ml.). Benzylmethylamine (6·3 g.) was then added and the reaction mixture boiled under reflux with stirring for 20 hours. After concentration *in vacuo* and treatment of the residue with excess of 2N-sodium hydroxide with cooling, the product was extracted with ether. The extract was washed, dried, and concentrated, and the residue distilled, to give the basic *nitrile* (5·0 g.), a pale golden-brown syrup, b. p. 156—157°/0·3 mm. (Found: C, 78·6; H, 6·6; N, 13·4. $C_{20}H_{21}N_3$ requires C, 79·2; H, 6·9; N, 13·9%).

This material absorbed hydrogen only slowly and incompletely in the presence of palladised charcoal giving rise to a non-homogeneous high-boiling product which was not investigated.

5-Chloro-2-cyano-2-phenylpentan-1-ol (III).—A solution of lithium aluminium hydride (2·3 g.) in dry ether (130 ml.) was added slowly under dry nitrogen to a stirred ethereal solution of ethyl δ-chloro-α-cyano-α-phenylvalerate (26·6 g. in 70 ml.). After the vigorous reaction had subsided the reaction mixture was cooled in ice and treated cautiously with cold 2N-sulphuric acid until strongly acid. The layers were separated, the aqueous layer was washed once with ether, and the combined ethereal extracts were washed with water and dried. The *cyano-alcohol* was obtained as a clear syrup (22·5 g.) on concentrating the ethereal solution and carefully drying it *in vacuo* (Found: Active H, 1·0 atom per mole. $C_{12}H_{14}ONCl$ requires Active H, 1·0 atom per mole). Attempts at distillation at 0·5 mm. usually resulted in decomposition and distillates giving inconsistent analyses, although in some cases distillation was possible giving a pale yellow oil of b. p. 155—159°/0·5 mm. (Found: N, 6·2; Cl, 15·4. $C_{12}H_{14}ONCl$ requires N, 6·0; Cl, 15·9%).

Treatment of this compound with thionyl chloride or phosphorus tribromide in the presence of tertiary bases gave none of the desired halogenated products.

Reaction with methylamine at 140° for 8 hours did not yield any piperidine derivative.

N-Methylamide of δ-Chloro-α-cyano-α-phenylvaleric Acid (V).—Ethyl δ-chloro-α-cyano-α-phenylvalerate (13·3 g.) was shaken with aqueous methylamine solution (30 ml. of 33%) for 3 hours. The *N-methylamide* separated as a white solid (10·1 g.), m. p. 100—104°. Recrystallisation from benzene–light petroleum (b. p. 40—60°) raised the m. p. to 108—110° (Found: C, 62·3; H, 6·1; N, 10·6. $C_{13}H_{15}ON_2Cl$ requires C, 62·3; H, 6·0; N, 11·1%).

3-Cyano-3-phenyl-1-methyl-2-piperidone (VI).—The above amide (26·5 g.) dissolved in alcohol (120 ml.) was added to sodium ethoxide from sodium (2·4 g.) and alcohol (60 ml.), and the solution heated to gentle reflux on the water-bath for 1½ hours. After cooling and filtration from the separated sodium chloride, the alcoholic solution was concentrated and the residue dissolved in ethyl acetate. The extract was washed twice with water and distilled. The *piperidone* derivative (18·7 g.) was collected as a colourless, viscous syrup, b. p. 167—170°/0·2 mm. (Found: C, 73·3; H, 7·0; N, 12·7. $C_{13}H_{14}ON_2$ requires C, 72·9; H, 6·6; N, 13·0%).

Attempted selective reduction of (V) or (VI) with lithium aluminium hydride gave only mixtures of basic products from which a pure compound was not isolated.

Phenylcyanoacetic Acid.—Ethyl phenylcyanoacetate (18·9 g.) was dissolved in 2N-aqueous sodium hydroxide (100 ml.) and kept at room temperature for 6 hours. On acidification (Congo-red paper) with concentrated hydrochloric acid with ice-cooling, a white solid separated (13·9 g.). The analytical specimen was recrystallised from benzene and then from ether–light petroleum (b. p. 40—60°), whereafter it melted at 74° (Found: C, 66·9; H, 4·9; N, 8·7. Calc. for $C_9H_7O_2N$: C, 67·0; H, 4·4; N, 8·7%).

2-Methylamino-1-phenylethyl Cyanide (VII).—Phenylcyanoacetic acid (13·5 g.) was treated with 33% aqueous methylamine (7·8 ml.) with cooling in ice and then with 40% formaldehyde solution (6·3 ml.), slight carbon dioxide evolution occurring. The mixture was kept close to 0° for 24 hours, whereafter the smells of methylamine and formaldehyde had disappeared. Addition of 2N-hydrochloric acid (50 ml.) then caused vigorous evolution of carbon dioxide. The acidified reaction mixture was extracted twice with ether to remove non-basic material, the aqueous part made alkaline with 2N-aqueous ammonia (60 ml.), and the oil which was precipitated was extracted by washing 4 times with ether. The ethereal

solutions were washed with water, dried, and concentrated to give the required base as a pale yellow oil (4·9 g.) with an ammoniacal smell. This crude base was converted into the *hydrochloride*, m. p. 160—161° (Found : C, 61·4; H, 6·9; N, 14·3. $C_{10}H_{13}N_2Cl$ requires C, 61·0; H, 6·6; N, 14·2%), by taking it up in ether and treating it with excess of alcoholic hydrogen chloride. Recrystallisation was from absolute alcohol.

1-*Phenylvinyl Cyanide* (VIII).—This *compound* was isolated from the above reaction mixture by washing the ethereal extract of non-basic substances with dilute sodium carbonate solution and then with water. Drying and concentration of the extract gave a pale yellow oil (4·8 g.). On attempted distillation only a few drops of colourless oil, b. p. *ca.* 100°/12 mm., could be obtained (Found : N, 10·9. C_9H_7N requires N, 10·9%). The residue would not distil, merely becoming increasingly viscous without appreciable darkening as the temperature was raised.

1-*Allylmethylamino*-2-*phenylbutan*-3-*one* (X; R = Me).—Benzyl methyl ketone (13·4 g.) was dissolved in absolute alcohol (30 ml.) and mixed with allylmethylamine (7·8 g.) dissolved in alcoholic hydrogen chloride (10 ml.). Paraformaldehyde (3 g.) was added and the mixture refluxed for 1 hour, a further quantity (3 g.) of paraformaldehyde being then added and the refluxing continued for 3½ hours longer. Concentration of the reaction mixture under reduced pressure gave a pasty solid which was triturated with acetone (50 ml.) and filtered off. The white solid (11·7 g.) had m. p. 145—150° and, on recrystallisation from acetone–alcohol, the pure ***hydrochloride*** melted sharply at 150° (Found : C, 66·5: H, 7·7; N, 5·4; Cl, 13·7. $C_{14}H_{20}ONCl$ requires C, 66·3; H, 7·9; N, 5·5; Cl, 14·0%). The recrystallised product gave a pale violet colour when subjected to Feigl and Zappert's test for a methyl ketone (Feigl, " Spot Tests," p. 288).

1 : 4-*Diphenyl*-3-*methyl*-Δ^2-*pyrazoline* (XI).—The above hydrochloride (3 g.) was treated with anhydrous sodium acetate (3 g.) and phenylhydrazine (3 g.) in a mixture of absolute alcohol (10 ml.) and glacial acetic acid (10 ml.) according to the procedure of Levvy and Nisbet (*J.*, 1938, 1053). Sodium chloride was filtered off and the resulting solution boiled gently for 7 hours under reflux. After 4 days at ordinary temperature crystals separated. These were collected and recrystallised from methanol. The *pyrazoline* was obtained as yellow plates, m. p. 159—160° (Found : N, 12·6; *C*-Me, 7·8. $C_{16}H_{16}N_2$ requires N, 11·9; *C*-Me, 6·4%).

Action of Hydrogen Bromide on (X; R = Me).—The hydrochloride of (X; R = Me) (1·75 g.) was suspended in carbon tetrachloride (125 ml.), and benzoyl peroxide (0·06 g.) added. The mixture was then saturated with dry hydrogen bromide and left for 14 days. It was then boiled for 3 hours and filtered. The solid (1·95 g.) had m. p. 158—161°. On recrystallisation from alcohol the *hydrobromide* of (X; R = Me) was obtained with m. p. 166° (Found : C, 56·6; H, 6·8; N, 4·9. $C_{14}H_{20}ONBr$ requires C, 56·7; H, 6·7; N, 4·7%).

A modification of the above procedure using the free Mannich base dissolved in benzene was tried. In the presence of a trace of benzoyl peroxide, dry hydrogen bromide was passed over the surface of the gently boiling solution. Once again, only unsaturated hydrobromide could be isolated.

Methyl-3-*chloropropylamine*.—1-Chloro-3-bromopropane (15·9 g.) and 26% alcoholic methylamine (24 ml.) were mixed with ice-cooling and then kept at room temperature for 16 hours. Considerable separation of methylamine hydrobromide had taken place and this was completed by addition of dry ether. The filtered solution was then treated with dry hydrogen chloride and concentrated under reduced pressure. The residue was dried in a vacuum over phosphoric oxide and then suspended in dry ether–acetone, filtered very rapidly, and transferred to a desiccator. The *methyl*-3-*chloropropylamine hydrochloride* was extremely hygroscopic and a melting point was not determined (Found : Cl^-, 23·8. $C_4H_{11}NCl_2$ requires Cl^-, 24·6%).

This hydrochloride was treated with formaldehyde and benzyl methyl ketone as described for the *N*-allyl compound but no crystalline products were obtained. The result was equally unsatisfactory when an aqueous medium was employed (cf. Mannich and Braun, *Ber.*, 1920, **53**, 1875).

Condensation of 1-*Cyano*-1-*phenylpropan*-2-*one and Trimethylene Chlorobromide*.—1-Chloro-3-bromopropane (23·7 g.) was added to the sodio-derivative from 1-cyano-1-phenylpropan-2-one (*Org. Synth.*, **18**, 66) (12·0 g.) and sodamide (3·0 g.) in dry toluene (100 ml.). The mixture was heated under reflux with stirring for 30 hours. It was then cooled and washed thoroughly with cold water. The toluene solution was then concentrated and the residue distilled, a fraction (5·0 g.) boiling at 120—140°/0·2 mm. being collected. This pale yellow, viscous oil (XV) was subjected to hydrolysis by boiling for 10 hours with 20% sulphuric acid, and the product characterised by condensation with dimethylamine. The 4-dimethylamino-1-phenylbutyl cyanide was an oil, giving a *picrate*, m. p. 109—110° (Found : C, 52·9; H, 5·0; N, 16·5. $C_{13}H_{18}N_2,C_6H_3O_7N_3$ requires C, 52·9; H, 4·9; N, 16·3%).

1-*Chloro*-4-*phenylhexan*-5-*one* (XVI).—Benzyl methyl ketone (10·0 g.) and 1-chloro-3-bromopropane (11·7 g.) were dissolved in dry toluene (50 ml.), and powdered sodamide (3·0 g.) added with stirring and cooling. The orange-coloured solution was stirred at room temperature for 1½ hours and then heated gradually to the b. p. (3 hours) and kept there for 1 hour. The mixture was cooled and poured into water. The toluene solution was washed thoroughly with water and concentrated. Distillation gave rise to the required ketone (2·5 g.) as the fraction, b. p. *ca.* 146°/12 mm., giving a 2 : 4-*dinitrophenylhydrazone*, m. p. 116—117° (Found : C, 54·8; H, 4·6; N, 14·4. $C_{18}H_{19}O_4N_4Cl$ requires C, 55·3; H, 4·8; N, 14·4%).

3-*Phenyl*-1 : 2-*dimethyl*-1 : 4 : 5 : 6-*tetrahydropyridine* (XIII; R = Me, R′ = Ph).—The above chloro-ketone (2·4 g.) was treated with 33% aqueous methylamine (5·5 ml.) and alcohol (10 ml.). The mixture was heated in a sealed tube for 16 hours at 140°. The basic product gave a very hygroscopic *hydrochloride* which could not be recrystallised successfully (Found : C, 67·7; H, 8·0; N, 5·7. $C_{13}H_{18}NCl,\frac{1}{2}H_2O$ requires C, 67·1; H, 8·1; N, 6·0%).

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