

110. *Synthesis of Piperidine Derivatives. Part I.*

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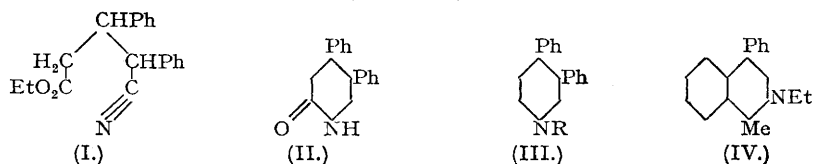
Hydrogenation of γ -cyano-esters in alcoholic solution with copper chromite has been found to give *N*-alkylpiperidines, in which the *N*-alkyl group is provided by the alcohol used as solvent. Similar alkylation occurs in the hydrogenation of phenylacetonitrile in ethanol, and the reaction has been extended to the synthesis of a decahydroisoquinoline derivative (IV).

IN recent years much attention has been devoted to the production of synthetic drugs having antispasmodic or analgesic properties. With analgesics a major objective is a compound of suitable pharmacological action having no tendency to produce the drug addiction shown by morphine and similar substances (compare *U.S. Public Health Reports*, Supplement No. 138, Washington, 1938). Antispasmodics fall into two classes, *viz.*, those preventing spasm by direct action on the muscle cell (*e.g.*, papaverine), and those preventing nervous stimulation of the muscle cell (*e.g.*, atropine). It is useful to be able to treat spasm clinically without the need to determine in each case the mechanism by which it is produced, and compounds are now known which show the combined action of both types of antispasmodic (compare Raymond, *J. Amer. Pharm. Assoc.*, 1943, **32**, 249; Blicke, *Ann. Rev. Biochem.*, 1944, **13**, 549). A compound which is claimed to be a potent antispasmodic and also a highly efficient analgesic is pethidine (ethyl 4-phenyl-1-methylpiperidine-4-carboxylate hydrochloride; also termed dolantal, dolantin, or demerol). This compound, introduced by Eisleb and Schaumann (*Deut. med. Wochenschr.*, 1939, **65**, 967), has received extensive clinical use (see, *e.g.*, Batterman, *Arch. intern. Med.*, 1943, **71**, 345; Schumann, *Amer. J. Obstet. Gynec.*, 1944, **47**, 93; Woolfe and Macdonald, *J. Pharm. Exp. Ther.*, 1944, **80**, 300). Contrary to early expectation, pethidine appears to resemble morphine in causing drug addiction (Hecht, Noth, and Yonkman, *J. Amer. Med. Assoc.*, 1943, **121**, 1307; Himmelsbach, *J. Pharm. Exp. Ther.*, 1943, **79**, 5).

The pharmacological interest attaching to piperidine derivatives led us to investigate methods of synthesis of new compounds of this series, especially 3-arylpiperidines which are structurally related to pharmacologically active β -arylethylamines. While our experiments were in progress, Koelsch published a series of papers on very similar lines (*J. Amer. Chem. Soc.*, 1943, **65**, 2093, 2458, 2459, 2460). However, our methods and results have some novel features, and certain substituted piperidines are obtained very simply by our procedure, which we wish therefore to record. More recently, Bergel *et al.* (*J.*, 1944, **261**, **265**, **269**) have described other syntheses of piperidine derivatives of pharmacological interest.

Koelsch's synthetic method consisted essentially in the catalytic hydrogenation by Raney nickel of

γ -cyano-esters (type I) to α -piperidones (type II), followed by reduction with sodium and butyl alcohol. Appropriate γ -cyano-esters were obtained by the Michael reaction, which we also used. It was found that hydrogenation in alcoholic solution, with Adkins's copper-chromium oxide catalyst ("copper chromite") led to further reduction of the intermediate α -piperidones (type II), and also alkylation by the solvent to tertiary amines (type III). For instance, in two operations, phenylacetonitrile and ethyl cinnamate were converted into 3:4-diphenyl-1-alkylpiperidines (III; R = Me, Et, or Bu), the alkyl group being determined by the solvent used for hydrogenation of the intermediate ethyl γ -cyano- β -diphenylbutyrate (I).



Copper chromite does not appear to have been used previously for the hydrogenation of nitriles. Indeed, Adkins and Connor (*J. Amer. Chem. Soc.*, 1931, 53, 1094) state that "the copper chromite catalyst is not active toward cyanides." Probably the α -piperidone (II) is an intermediate (it was isolated when dioxan was used as a solvent), and the elimination of oxygen from such a structure accords with the known facility with which oxygen-containing groups are hydrogenated by copper chromite. That the products were tertiary and not secondary amines was shown by the failure to give acyl derivatives, by the formation of different products in different alcoholic solvents, and by the fact that they all differed from the two stereoisomeric 3:4-diphenylpiperidines (III; R = H) described by Koelsch (*loc. cit.*). Moreover, the m. p. of the product obtained by hydrogenation in methanol agrees with that given by Koelsch for the *N*-methyl derivative of one of his stereoisomerides. When hydrogenation of (I) was carried out in dioxan solution there was obtained 3:4-diphenyl-1-ethylpiperidine (III; R = Et) in addition to the α -piperidone (II). Evidently alkylation takes place with such ease that the small amount of alcohol formed during the reduction and cyclisation of the ester (I) suffices. Alkylation of other amines by alcohols and catalysts has been reported (compare Schwogler and Adkins, *J. Amer. Chem. Soc.*, 1939, 61, 3499), and it was also observed in the hydrogenation of phenylacetonitrile in ethanol by copper chromite. This gave a mixture of β -phenyltriethylamine and bis-(β -phenylethyl)ethylamine. Compounds of the latter type are powerful antispasmodics (Külz, Rosenmund, *et al.*, *Ber.*, 1939, 72, 19, 2161; compare Blicke *et al.*, *J. Amer. Chem. Soc.*, 1939, 61, 91, 93, 771).

By hydrogenation of suitable γ -cyano-esters with copper chromite we have also prepared 4-phenyl-3-*p*-anisyl-1-ethylpiperidine, 4-carbethoxy-3-phenyl-1-ethylpiperidine, 3-phenyl-3- γ -ethoxypropyl-1-ethylpiperidine, and 4-phenyl-1-methyl-2-ethyldecahydroisoquinoline (IV).

The pharmacological examination of some of our new bases will be reported elsewhere. Derivatives of 3- and 4-arylpiperidines have been found already to have antispasmodic activity (Fellows and Cunningham, *Federation Proc.*, 1942, 1, 151; Eisleb, U.S.P., 2,248,018).

EXPERIMENTAL.

Ethyl γ -Cyano- β -diphenylbutyrate (I).—(a) The Michael reaction between phenylacetonitrile (80 g.) and ethyl cinnamate (120 g.) in presence of pure sodium hydroxide (28 g.) (2 hours' heating at 100°) (compare Avery and McDole, *J. Amer. Chem. Soc.*, 1908, 30, 596) gave ethyl γ -cyano- β -diphenylbutyrate, m. p. 98—99° (68 g.), a benzene-soluble cyano-acid, m. p. 154—156° (raised to 163° by recrystallisation) (65 g.), and the benzene-insoluble γ -amido- β -diphenylbutyric acid, m. p. 205° (24 g.). The amido-acid, when heated above its m. p., gave $\alpha\beta$ -diphenylglutarimide, m. p. 221—223° (Found: C, 77.0; H, 5.5; N, 5.7. Calc. for $C_{17}H_{15}O_2N$: C, 77.0; H, 5.7; N, 5.3%) (compare Avery and Maclay, *ibid.*, 1929, 51, 2833).

(b) Condensation of phenylacetonitrile (100 g.) with ethyl cinnamate (150 g.) by sodium ethoxide (14 g.) in ethanol (100 c.c.), without cooling, gave ethyl γ -cyano- β -diphenylbutyrate, m. p. 99° after crystallisation from industrial alcohol (80% yield). Concentration of the mother-liquors gave a solid which, after crystallisation from acetone, formed colourless prisms, m. p. 207—208°. This was evidently ethyl 4-cyano-3:4:5-triphenylcyclohexanone-2-carboxylate, formed from 1 mol. of phenylacetonitrile and 2 mols. of ethyl cinnamate (Found: C, 79.55; H, 5.8; N, 3.2. $C_{28}H_{25}O_3N$ requires C, 79.4; H, 6.15; N, 3.3%). A similar product has been described by Avery (*ibid.*, 1928, 50, 2512). The resin obtained by evaporation of the mother-liquors from which this solid was isolated gave, by hydrolysis with boiling alcoholic potash, the amido-acid, m. p. 205°, mentioned under (a).

This procedure for the Michael reaction was much more satisfactory for the preparation of the cyano-ester, m. p. 99°, than that of Koelsch (*ibid.*, 1943, 65, 438), who obtained this ester in much smaller yield (39%), together with a stereoisomeric cyano-ester (m. p. 59—60°) which we have not encountered.

Ethyl γ -cyano- β -diphenylbutyrate was hydrolysed by alcoholic potash to the cyano-acid, m. p. 163.5° (Avery, *loc. cit.*), which was hydrolysed further by concentrated sulphuric acid (12 parts) at room temperature (3 days). The product (m. p. ca. 180°) gave, by crystallisation from acetic acid or alcohol, fine colourless needles, m. p. 225° (decomp.), of γ -amido- β -diphenylbutyric acid, stereoisomeric with that described above (Found: C, 72.3; H, 6.2; N, 4.9. $C_{17}H_{15}O_3N$ requires C, 72.1; H, 6.0; N, 4.95%).

Ethyl δ -Acetamido- β -diphenylvalerate.—Hydrogenation of ethyl γ -cyano- β -diphenylbutyrate (5 g.) in acetic anhydride (100 c.c.) with Adams's platinum catalyst (0.1 g.) was slow and incomplete. After 6 days the acetic anhydride was decomposed with ice and dilute sodium hydroxide. Recrystallisation of the resulting solid from ethanol gave unchanged cyano-ester and the more soluble ethyl δ -acetamido- β -diphenylvalerate, which formed a colourless microcrystalline powder, m. p. 74—75° (Found: C, 73.7; H, 7.3; N, 4.3. $C_{21}H_{25}O_3N$ requires C, 74.3; H, 7.4; N, 4.1%). The hydrochloride of the corresponding amino-acid has been described by Avery and McDole (*ibid.*, 1908, 30, 1425).

Stereoisomeric 3:4-Diphenyl-1-ethylpiperidines (III; R = Et).—A solution of ethyl γ -cyano- β -diphenylbutyrate, m. p. 99° (I; 20 g.) in ethanol (250 c.c.) was agitated with hydrogen and copper chromite (Connor, Folkers, and Adkins,

ibid., 1932, **54**, 1138) (6 g.) at 200° and 175 atm. for 2 hours. The filtered solution was concentrated and poured into dilute hydrochloric acid, and the small amount of neutral product was extracted with ether. The acid solution was made alkaline, and the basic products (obtained in 95% yield) were extracted with ether. The oil remaining after distillation of the ether was dissolved in dilute ethanol. The solution deposited crystals (8 g.) of 3 : 4-diphenyl-1-ethylpiperidine-A, which, after several recrystallisations from ethanol, formed colourless prisms, m. p. 71° (Found : C, 85.9; H, 8.4; N, 5.6. $C_{19}H_{23}N$ requires C, 86.0; H, 8.7; N, 5.3%). The oil obtained by dilution of the mother-liquors was distilled (b. p. 153—157°/1 mm.), dissolved in ether, and the solution treated with alcoholic hydrogen chloride. The precipitated hydrochloride was recrystallised from ethanol-ether, giving colourless needles of the hydrochloride, m. p. 273°, of 3 : 4-diphenyl-1-ethylpiperidine-B (Found : C, 76.3; H, 7.9; N, 4.7. $C_{19}H_{23}NCl$ requires C, 75.5; H, 7.95; N, 4.6%). This hydrochloride, which was sparingly soluble in hot water, was treated with alkali, and the base distilled. 3 : 4-Diphenyl-1-ethylpiperidine-B (4 g.) formed a colourless liquid, b. p. 155°/1 mm., which crystallised on standing and then had m. p. 30° (Found : C, 85.9; H, 8.55; N, 5.1. $C_{19}H_{23}N$ requires C, 86.0; H, 8.7; N, 5.3%).

The hydrochloride of 3 : 4-diphenyl-1-ethylpiperidine-A, was prepared from the pure base as described for the isomeride. It crystallised from water in colourless needles, m. p. 268° (decomp.), and was more soluble than its isomeride (Found : C, 75.8; H, 7.8; N, 4.7. $C_{19}H_{23}NCl$ requires C, 75.5; H, 7.95; N, 4.6%). The chloroplatinate formed an orange, microcrystalline powder (from ethanol containing hydrochloric acid), m. p. 148—151° [Found : C, 48.7; H, 5.0; Pt, 20.25. ($C_{19}H_{23}N$), H_2PtCl_6 requires C, 48.5; H, 5.1; Pt, 20.7%]. 3 : 4-Diphenyl-1-ethylpiperidine-A was recovered unchanged after treatment with boiling acetic anhydride, with benzoyl chloride in pyridine, and with benzenesulphonyl chloride and aqueous alkali. With methyl iodide in boiling benzene it gave, in 90% yield, 3 : 4-diphenyl-1-methyl-1-ethylpiperidinium iodide as a colourless crystalline powder (from acetone-ethanol-ether), m. p. 209—210° (Found : C, 59.5; H, 6.2. $C_{20}H_{26}NI$ requires C, 59.0; H, 6.4%).

When dioxan was used as the solvent in the hydrogenation of ethyl γ -cyano- β -diphenylbutyrate with copper chromite there was obtained an oil which deposited a small amount of colourless needles, m. p. 192—193°, insoluble in dilute acid. This agrees with the m. p. given by Koelsch (*loc. cit.*, p. 2094) for his α -form * of 4 : 5-diphenyl-2-piperidone (II) (Found : C, 81.6; H, 6.7. Calc. for $C_{17}H_{17}ON$: C, 81.3; H, 6.8%). In another experiment in dioxan the basic hydrogenation product (only 20% yield) was an oil which, on standing, deposited some crystals, m. p. 30—32°. The major portion did not crystallise, and was treated with ethanolic hydrogen chloride in ethereal solution. This gave the hydrochloride, m. p. 268°, of 3 : 4-diphenyl-1-ethylpiperidine (Found : C, 75.7; H, 7.8; N, 4.6%).

3 : 4-Diphenyl-1-ethylpiperidine-A (m. p. 68°) was also formed by hydrogenation of $\alpha\beta$ -diphenylglutarimide in ethanol with copper chromite at 200° and 200 atm. It was identified by mixed m. p. determinations, both of the base and its picrate, m. p. 213°.

3 : 4-Diphenyl-1-methylpiperidine (III; R = Me).—This was obtained by hydrogenation of the cyano-ester (I; 10 g.) in methanol (250 c.c.) with copper chromite (2 g.) for 2 hours at 200° and 180 atm. The crystalline base (4 g.) had m. p. 80—81° in agreement with the value given by Koelsch (*loc. cit.*, p. 2095) for the compound obtained by methylation of his α -3 : 4-diphenylpiperidine (Found : C, 86.1; H, 8.4. Calc. for $C_{18}H_{21}N$: C, 86.1; H, 8.4%).

3 : 4-Diphenyl-1-n-butylpiperidine (III; R = Bu).—This was formed by hydrogenation of the cyano-ester (I) (10 g.), in *n*-butanol (250 c.c.) under the usual conditions. The base, obtained in 50% yield, formed colourless elongated plates, m. p. 58—59° (from ethanol) (Found : C, 86.15; H, 9.2; N, 4.9. $C_{24}H_{27}N$ requires C, 86.0; H, 9.2; N, 4.8%), and gave a hydrochloride which crystallised from ethanol-ether and then water in colourless needles, m. p. 211—212° (Found : C, 76.65; H, 8.45. $C_{24}H_{28}NCl$ requires C, 76.4; H, 8.6%).

4-Phenyl-3-p-anisyl-1-ethylpiperidine.—Condensation of *p*-methoxyphenylacetoneitrile (Kindler and Peschke, *Arch. Pharm.*, 1933, **271**, 431) and ethyl cinnamate by sodium ethoxide (compare Koelsch, *ibid.*, p. 439) gave in nearly theoretical yield ethyl γ -cyano- β -phenyl- γ -p-anisylbutyrate as colourless needles (from methanol), m. p. 85° (Found : C, 74.5; H, 6.6. $C_{20}H_{21}O_3N$ requires C, 74.3; H, 6.5%). By alkaline hydrolysis the corresponding cyano-acid was obtained as fine colourless needles (from aqueous acetic acid), m. p. 197—198° (Found : C, 73.3; H, 5.9. $C_{18}H_{17}O_3N$ requires C, 73.2; H, 5.8%). Hydrogenation of the ester (20 g.) in ethanol (250 c.c.) with copper chromite (5 g.) under the usual conditions gave, in 55% yield, 4-phenyl-3-p-anisyl-1-ethylpiperidine as colourless prisms (from ethanol), m. p. 57° (Found : C, 81.2; H, 8.3; N, 4.8. $C_{20}H_{23}ON$ requires C, 81.4; H, 8.5; N, 4.75%). The hydrochloride formed colourless prismatic needles (from ethanol-ether), m. p. 238° (Found : C, 72.3; H, 8.1. $C_{20}H_{24}ONCl$ requires C, 72.3; H, 7.85%).

4-Carboxy-3-phenyl-1-ethylpiperidine.—The following procedure for the Michael condensation of ethyl maleate with phenylacetoneitrile gave ethyl γ -cyano- γ -phenylmethylsuccinate in 75% yield, which is considerably higher than that (46—58%) reported by Koelsch (*loc. cit.*, p. 438) : A solution of sodium ethoxide (1 g. of sodium in 20 c.c. of ethanol) was added in small portions to a mixture of ethyl maleate (90 g.) and phenylacetoneitrile (60 g.) in a well-lagged flask. Heat was evolved, and each new addition of sodium ethoxide was made when the temperature began to fall. The mixture was kept for 36 hours, poured into water, and the product extracted with ether and distilled (b. p. 185°/1 mm.).

A solution of ethyl γ -cyano- γ -phenylmethylsuccinate in ethanol was hydrogenated with copper chromite under the conditions already described. The product was a mixture of the neutral α -4-carboxy-5-phenyl-2-piperidone, m. p. 162—163°, described by Koelsch (*loc. cit.*, p. 2095), and the basic 4-carboxy-3-phenyl-1-ethylpiperidine, which formed a colourless liquid, b. p. 102°/0.4 mm. (Found : C, 73.5; H, 9.2; N, 5.25. $C_{17}H_{23}O_2N$ requires C, 73.6; H, 8.9; N, 5.4%). This base has a structural resemblance to pethidine. When hydrogenation was carried out in methanol solution only a small yield of basic product was obtained.

3-Phenyl-3- γ -ethoxypropyl-1-ethylpiperidine.—A solution of γ -cyano- γ -phenylpimelonitrile (20 g.) (from phenylacetoneitrile and acrylonitrile; Bruson and Riener, *J. Amer. Chem. Soc.*, 1943, **65**, 23) in ethanol (400 c.c.) saturated with hydrogen chloride was kept at room temperature overnight, during which ammonium chloride crystallised, and was then boiled for an hour. The resulting ethyl γ -cyano- γ -phenylpimelate (22.5 g.) formed a colourless liquid, b. p. 162°/0.4 mm. (Found : C, 68.3; H, 7.1; N, 4.7. $C_{18}H_{23}O_4N$ requires C, 68.1; H, 7.25; N, 4.4%). The base formed by hydrogenation of this ester (10 g.) in ethanol (250 c.c.) with copper chromite (4 g.) at 200° and 180 atm. (3 hours) formed a colourless viscous liquid (5.5 g.), b. p. 126°/0.4 mm. Analysis indicated that it is 3-phenyl-3- γ -ethoxypropyl-1-ethylpiperidine (Found : C, 78.3; H, 10.8; N, 5.3. $C_{18}H_{23}ON$ requires C, 78.6; H, 10.5; N, 5.1%).

4-Phenyl-1-methyl-2-ethyldecahydroisquinoline (IV).—A solution of sodium ethoxide (from 4 g. of sodium and 80 c.c. of ethanol) was added gradually to a mixture of 1-acetyl- Δ^1 -cyclohexene (Darzens, *Compt. rend.*, 1910, **150**, 709) (20 g.) and phenylacetoneitrile (20 g.). After being kept at room temperature for 4 hours the mass was poured into 10% hydrochloric acid (250 c.c.). The resulting α -2-acetylcyclohexylphenylacetoneitrile crystallised from ethanol in colourless rhombs (22.5 g.), m. p. 120° (Found : C, 80.3; H, 7.9; N, 5.9. $C_{16}H_{19}ON$ requires C, 79.7; H, 7.9; N, 5.8%). Hydrogenation of this nitrile (10 g.) in ethanol (500 c.c.) with copper chromite (3 g.) at 200° and 160 atm. (2 hours) gave a colourless liquid base (9.5 g.), b. p. 135°/1 mm., the composition of which corresponded with structure (IV) (Found : C, 84.2; H, 10.4; N, 5.6. $C_{18}H_{23}N$ requires C, 84.1; H, 10.5; N, 5.45%). It gave a picrate, m. p. 187—190° (from benzene-ethanol) (Found : C, 59.4; H, 6.3; N, 11.4. $C_{18}H_{23}N, C_6H_5O_7N_3$ requires C, 59.3; H, 6.2; N, 11.5%).

* This was recently shown to have the *cis*-configuration (Koelsch and Raffauf, *J. Amer. Chem. Soc.*, 1944, **66**, 1857).

Hydrogenation of Phenylacetonitrile.—(a) A solution of the nitrile (20 g.) in ethanol (300 c.c.) was hydrogenated with copper chromite (5 g.) at 200° and 160 atm. The filtered solution was concentrated, and the basic products were extracted with dilute hydrochloric acid, and liberated from the acid extract by means of sodium hydroxide. The mixture of bases thus obtained was distilled into 2 fractions having b. p. 100—110°/10 mm. (16.2 g.) and b. p. 140—150°/0.4 mm. (5.3 g.). From the former was obtained, in good yield, the *picrate*, m. p. 94°, of β -phenyltriethylamine. This formed long, canary-yellow, prismatic needles (from ethanol) (Found: C, 53.3; H, 5.5; N, 13.7. $C_{18}H_{22}O_7N_4$ requires C, 53.2; H, 5.5; N, 13.8%). Addition of ethanolic hydrogen chloride to an ethereal solution of some of the higher-boiling fraction gave a small amount of a sparingly soluble hydrochloride, m. p. 240—255°, after sintering. This was derived from a minor constituent and was not obtained by similar treatment of the base recovered from the pure picrate [compare (b) below]. This high-boiling fraction (1.1 g.) gave with ethanolic picric acid the *picrate* (1.7 g.) of bis-(β -phenylethyl)-ethylamine. This picrate formed lemon-yellow rhombic needles, m. p. 121—122° (Found: C, 59.9; H, 5.3; N, 11.7. $C_{24}H_{26}O_7N_4$ requires C, 59.7; H, 5.4; N, 11.6%), and the base recovered from it formed a hydrochloride, m. p. 134—136° (Külz *et al.*, *Ber.*, 1939, **72**, 2161, and Blicke and Zientz, *J. Amer. Chem. Soc.*, 1939, **61**, 773, give m. p. 137°). The formation of these two principal products of hydrogenation was confirmed by repetition of the experiment.

(b) Another hydrogenation of phenylacetonitrile was carried out in the same manner, except that half of the ethanol was replaced by ethyl acetate. The basic products were distilled at 11 mm. into 2 fractions, b. p. 103—107° (5.7 g.) and 176—183° (3.6 g.) Addition of ethanolic hydrogen chloride to an ethereal solution of the former precipitated a colourless crystalline *hydrochloride*, m. p. 183—184°, easily soluble in water but obtained crystalline by addition of ether to its solution in ethanol. Analysis indicated that this was the hydrochloride of β -phenyldiethylamine (Found: C, 64.9; H, 8.5; N, 7.7. $C_{16}H_{18}NCl$ requires C, 64.6; H, 8.7; N, 7.5%). The picrate prepared from this had m. p. 131—132°. The higher-boiling fraction gave, with dilute hydrochloric acid, a sparingly soluble hydrochloride which crystallised from water in colourless plates, m. p. 262—263°. This same hydrochloride (2 g.) had already been obtained in the extraction of the bases from the crude products of hydrogenation. The m. p. of the salt is in approximate agreement with the value (268—269°) given by Buth, Külz, and Rosenmund (*Ber.*, 1939, **72**, 24) for the m. p. of the hydrochloride of bis-(β -phenylethyl)amine. The analysis of our specimen was not in accord with this view of its structure (Found: C, 74.5; H, 8.2; N, 4.8. Calc. for $C_{18}H_{20}NCl$: C, 73.4; H, 7.65; N, 5.4%), but the base regenerated from the pure hydrochloride formed a *picrate* which crystallised from ethanol in short, orange needles, m. p. 151—152° and gave satisfactory analytical figures (Found: C, 58.4; H, 5.3; N, 12.8. $C_{22}H_{22}O_7N_4$ requires C, 58.1; H, 4.9; N, 12.3%).

It appears from these results that dilution of the solvent ethanol with ethyl acetate in the hydrogenation of phenylacetonitrile over copper chromite, hinders ethylation of the resulting amines.

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