139. *Compounds of Potential Pharmacological Interest. Part I. Acyl Derivatives of 1-Amino-3-phenylindane.*

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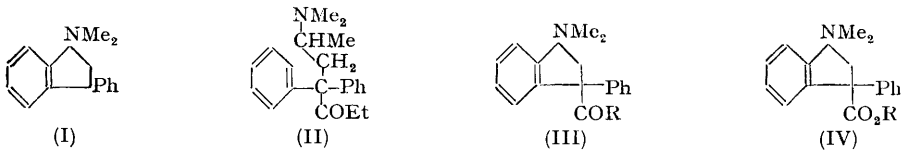
As part of a search for new analgesics, 1-cyano-3-dimethylamino-1-phenylindane (VII; R = Me) has been synthesised (i) by cyclising β-cyano-ββ-diphenylpropionic acid to the indanone and then reducing and alkylating the oxime, and (ii) by brominating and aminating 1-cyano-1-phenylindane (X). Two isomeric forms of the amine (VII; R = Me) were obtained from (X) depending on the techniques adopted for its synthesis and bromination. Only one of these isomers could be converted into 3-dimethylamino-1-ethoxycarbonyl-1-phenylindane. Unsuccessful attempts to prepare 1-acyl-3-dimethylamino-1-phenylindanes, which are cyclic analogues of amidone, are described. Ethyl-lithium reacts with 1-cyano-3-dimethylamino-1-phenylindane, and ethylmagnesium iodide reacts with the oxime of 1-cyano-1-phenyl-3-indanone by replacing the nitrile group with hydrogen.

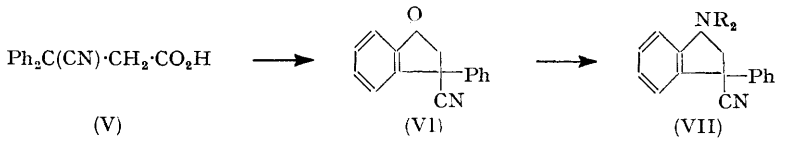
In Part IV [1] the synthesis and pharmacological properties of alkyl derivatives of 3-phenyl-1-indanylamines will be described, and attention will be drawn to the marked analgesic properties of 1-dimethylamino-3-phenylindane (I). Because of the superficial resemblance between the 3-phenylindane (I) and amidone (II), it became important to prepare the ketones (III), which are cyclic members of the amidone series and the esters (IV; R = Et), which are related cyclically to Bockmühl and Ehrhart's amino-esters.[2a]

The synthesis of these compounds was first attempted through the reaction sequence (V) ⟶ (VII). β-Cyano-ββ-diphenylpropionic acid (V) was readily obtained by alkylating

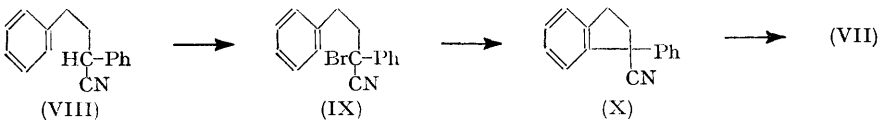
[1] Acheson, Philpott, MacPhee, Hunt, and Barltrop, to be published.
[2] (*a*) Bockmühl and Ehrhart, G.P. 711,069; *Chem. Abs.*, 1943, **37**, 4075. (*b*) *Idem*, *Annalen*, 1949, **561**, 71; May and Mosettig, *J. Org. Chem.*, 1948, **13**, 459.

diphenylacetonitrile with ethyl bromoacetate and sodamide in liquid ammonia and hydrolysing the product. Under precisely defined conditions, the corresponding acid chloride could be cyclised in excellent yields to 3-cyano-3-phenylindan-1-one (VI), the





oxime of which was reduced with sodium amalgam to 3-amino-1-cyano-1-phenylindane (VII; R = H) in 55% yield. Catalytic hydrogenation of the oxime and the Leuckart reaction provided unsatisfactory methods of transforming the ketone (VI) into the base (VII; R = H). Methylation of the primary base (VII; R = H) with formic acid and formaldehyde gave poor yields of the tertiary amine, and at this point an alternative synthesis of 1-cyano-3-dimethylamino-1-phenylindane became available through the reactions (VIII) ⟶ (X) ⟶ (VII).



Phenylacetonitrile was smoothly alkylated with phenethyl bromide by means of sodamide in liquid ammonia. The resulting 2 : 4-diphenylbutyronitrile (VIII) was brominated and the crude 2-bromo-2 : 4-diphenylbutyronitrile (IX) was cyclised under a variety of conditions to give 1-cyano-1-phenylindane (X), which was brominated and treated with dimethylamine to give the base (VII; R = Me); but three apparently different bases were obtained according to the method of preparing and brominating the indane (X). The use of aluminium chloride as a catalyst for cyclisation of the bromide (IX) was investigated closely and optimum conditions were defined under which it was possible to obtain the product (X) in 49% yield from (VIII). The product (X) from this reaction was designated indane-A. Ferric chloride appeared to be almost as effective as aluminium chloride and gave a 44% yield of indane-B, but stannic chloride at 80° gave a 75% yield of indane-C. The indanes-A, -B, and -C were brominated smoothly in carbon tetrachloride and the resulting bromo-compounds were converted, without purification, into the bases (VII; R = Me). From indane-A was obtained 1-cyano-3-dimethylamino-1-phenylindane hydrochloride (β), so called because it was different from the α-compound obtained earlier from the ketone (VI). The β-compound persistently melted over a range in spite of repeated crystallisation. The product from indane-B was a mixture of the β-compound and a higher-melting, more insoluble hydrochloride [1-cyano-3-dimethylamino-1-phenylindane hydrochloride (γ)]. The product from indane-C was exclusively the γ-compound, which was also obtained from indane-A if the bromination was catalysed by a trace of benzoyl peroxide. An analysis of the m. p.s and mixed m. p.s of the hydrochlorides and picrates of the bases (see Experimental section) showed that there were in fact only two distinct isomers, the α- and the γ-compound, and that the β-compound is an impure form of the α-compound probably contaminated with a little of the less soluble γ-compound which could not readily be removed by recrystallisation. The α-compound must be an indane because of its preparation from the indanone (VI), and the γ-compound must also be cyclic and therefore an indane from the fact that it resists catalytic hydrogenation. Thus there can be little doubt but that the α- and the γ-compound are *cis–trans*-isomers of 1-cyano-3-dimethylamino-1-phenylindane (VII; R = Me) and the question arises how different

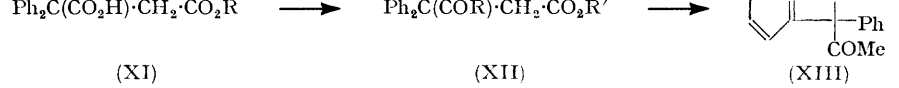
specimens of (X), which can exist in only one form, can give rise to *cis–trans*-isomers of (VII; R = Me) when brominated and aminated under apparently identical conditions.

The simplest explanation is in terms of the remarkable fact mentioned above, that indane-A prepared from the aluminium chloride cyclisation gives rise to the α- or γ-isomer depending on whether the bromination is effected in the presence or absence of benzoyl peroxide. If the cyclisation catalysed by the weaker catalyst stannic chloride be postulated to be incomplete, giving the indane-C (X) contaminated by traces of olefins, which autoxidise to peroxides which behave similarly to benzoyl peroxide in influencing the stereochemical course of the bromination reaction, then we have an explanation of the differing behaviour of indanes-A and -C. One must further postulate that in the case of indane-B, prepared through the agency of ferric chloride, so little peroxide was formed that the normal and the peroxide-catalysed reaction occurred at comparable rates.

As would be expected from the sterically hindered position of the nitrile group, esterification of the α-base (VII; R = Me) was successful only under forcing conditions. In addition to the ester (IV; R = Et) a small quantity of the acid (IV; R = H) was isolated. A similar reaction with the γ-isomer gave no ester but mainly starting material together with a small quantity of the amide.

Several unsuccessful attempts were made to prepare ketones of the type (III). Although diphenylmethane may be metalated at the methylene group, our efforts to prepare the corresponding 3-lithio-derivative of the indane (I) with butyl-lithium and then to condense it with propionyl chloride led only to recovery of starting material. Since reaction with butyl-lithium followed by carboxylation gave none of the amino-acid (IV; R = H), it is clear that no metalation occurred under these conditions. The next attempts proceeded from the reaction between the amino-nitrile (VII; R = Me) and organometallic compounds. With Grignard reagents either starting material or non-basic degradation products were obtained depending on the reaction temperature, but with ethyl-lithium a base was obtained in which it appeared that the cyano-group had been removed, giving an indanylamine (I), different from the specimen described in Part IV,[1] and to which it is presumably related by *cis–trans*-isomerism. The replacement of a nitrile group by hydrogen is not new, and a similar degradation of amino-nitriles in which the cyano-group is linked to a quaternary carbon atom has been reported previously,[2b] but only in the presence of sodamide and potassium hydroxide. Since the completion of this work, two instances have been reported of loss of a nitrile group occurring in the presence of Grignard reagents. The first is conversion of 4 : 5-bis(dimethylamino)-2 : 2-diphenylvaleronitrile by ethylmagnesium iodide at 100° into 3 : 4-bis(dimethylamino)-1 : 1-diphenylbutane instead of the expected ketone,[3] and the second a similar reaction at 120° with 9-cyano-9-2′-dimethylaminoethylfluorene.[4] Both these compounds are closely related to the substance (VII; R = Me) used in the present instance and the conditions closely parallel those prevailing in a similar reaction with the oxime of the cyano-ketone (VI) described below.

Because of these anomalies in the final stage of the preparation of the ketone (III), it became necessary to devise a synthesis in which the acyl group was introduced before ring-closure to the indane. The reaction sequence (XI) ⟶ (XIII) appeared promising.



(XI) (XII) (XIII)

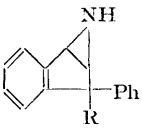
αα-Diphenylsuccinic acid was prepared by the hydrolysis of the cyano-acid (V) and esterified to give a mixture of the monoester (XI; R = Et) and the diester.[5] Thionyl chloride gave the acid chloride (XII; R = Cl, R′ = Et) which on reaction with dimethylcadmium gave the required ethyl γ-oxo-ββ-diphenylvalerate (XII; R = Me, R′ = Et) together with an acid $C_{18}H_{20}O_3$ which appears to be the *iso*alkanoic acid (XIV) formed by

[3] Schultz, *J. Amer. Chem. Soc.*, 1952, **74**, 5793.
[4] King, Meltzer, and Doczi, Abs. Papers 123rd Meeting Amer. Chem. Soc., 1953, 15L.
[5] Salmon-Legagneur, *Compt. rend.*, 1939, **208**, 1507.

the attack of dimethylcadmium on the less hindered carbonyl group of αα-diphenylsuccinic anhydride which results from the action of heat on the acid chloride. A second route to the ketone (XII; R = Me) lay through the diazo-ketone (XII; R = CHN_2), which was obtained by reaction between the acid chloride and diazomethane and on reduction with hydriodic acid gave a hydrated form of the keto-ester (XII; R = Me, R′ = Et). The keto-group of this ester was sterically hindered, and no dinitrophenylhydrazone was obtained. It therefore follows that the acid chloride from which it was derived must have the structure (XII; R = Cl, R′ = Et) and not the alternative (XII; R = OEt, and COCl instead of CO_2R') although Chase and Hey [6] have shown that the methyl ester (XI; R = Me) rearranged in thionyl chloride and gave the alternative acid chloride. All attempts to form the diketone (XIII) from the keto-acid (XII; R = Me, R′ = H) and its derivatives gave only traces of ketonic material.

The final work in this series involved the reaction of ethylmagnesium iodide with the oxime of the cyano-ketone (VI), which from the results of Campbell *et al.*[7] was expected to give the imine (XV; R = CN or CEt:NH) and thence a series of phenyl-1- and -2-indanyl-

(XIV) $Ph_2C(CO_2H)\cdot CH_2\cdot CMe_2\cdot OH$



(XV)

amines. The product obtained, however, was the base (XV; R = H), the nitrile group having been lost (see above).

A pharmacological examination of 3-dimethylamino-1-ethoxycarbonyl-1-phenylindane hydrochloride (IV; R = Et) was undertaken through the courtesy of Dr. G. E. Ullyot by Smith, Kline and French Laboratories, Philadelphia, U.S.A. The salt failed to show analgesic activity in rats after intraperitoneal injection (d'Amour-Smith method) at dose levels of 20—50 mg./kg. It produced stimulation in all animals at 50 mg./kg.

Experimental

β-Cyano-ββ-diphenylpropionic Acid.—Sodium (3·45 g.) was dissolved in liquid ammonia in the presence of a trace of ferric nitrate. When the blue colour had been discharged, a dry ethereal solution of diphenylacetonitrile [8] (29·1 g.) was added. The intensely yellow solution was cooled in acetone–solid carbon dioxide and treated with ethyl bromoacetate (25·5 g.), dropwise and with agitation. A vigorous reaction occurred with discharge of the colour. Evaporation of the solvents gave a partly crystalline material which was hydrolysed by boiling ethanolic potassium hydroxide for ½ hr. When cold, the precipitated solid was collected, dissolved in water, and acidified. β-Cyano-ββ-diphenylpropionic acid (23 g.) was collected and dried. Concentration of the alcoholic filtrate, dilution with water, and acidification yielded more acid (4 g.). On crystallisation from ethanol, the acid formed plates, m. p. 178° (Found : C, 76·6; H, 5·2. Calc. for $C_{16}H_{13}O_2N$: C, 76·5; H, 5·2%).

3-Cyano-3-phenylindan-1-one.—β-Cyano-ββ-diphenylpropionic acid (12·0 g.) and thionyl chloride (16 c.c.) were heated together under reflux for 1½ hr. Distillation of the thionyl chloride under reduced pressure gave a solid acid chloride, which was dissolved in dry tetrachloroethane (40 c.c.) and treated with pulverised aluminium chloride (12·8 g.) in small portions with cooling. The mixture was agitated occasionally, set aside overnight, shaken for 3 hr., then poured on ice and concentrated hydrochloric acid (25 c.c.) and extracted with ether. The extracts were washed with dilute hydrochloric acid, sodium carbonate solution, and water, and the solvents were removed by steam-distillation. The residual yellowish gum was isolated with ether and distilled. *3-Cyano-3-phenylindan-1-one* (8·7 g., 79·4%) was collected at 150—155°/0·1 mm. A specimen, crystallised from ethanol, gave colourless rhombs, m. p. 81° (Found : C, 82·3; H, 4·75; N, 6·2. $C_{16}H_{11}ON$ requires C, 82·3; H, 4·75; N, 6·0%).

1-Cyano-3-hydroxyimino-1-phenylindane.—The above ketone (8·7 g.) was boiled under reflux in aqueous ethanol with hydroxylamine hydrochloride (6·0 g.) and sodium acetate

[6] Chase and Hey, *J.*, 1952, 553.
[7] Campbell *et al.*, *J. Org. Chem.*, 1943, **8**, 103; 1944, **9**, 184.
[8] Ginsburg and Baiser, *J. Amer. Chem. Soc.*, 1949, **71**, 2254.

(15·0 g.) for 2 hr. The solution was cooled and poured into water (1 l.). 1-*Cyano*-3-*hydroxyimino*-1-*phenylindane* slowly solidified; it crystallised from aqueous ethanol (very slow cooling) as needles (8·5 g., 92%), m. p. 176·5° (Found: C, 77·2; H, 4·9; N, 7·0. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·9; N, 7·1%).

3-*Amino*-1-*cyano*-1-*phenylindane*.—(*a*) A solution of the above oxime (1·0 g.) in methanol (50 c.c.), acidified with 20% acetic acid (4 c.c.), was stirred vigorously and reduced with 3½% sodium amalgam (50 g.), added in portions during 1 hr., the solution being kept acid by the dropwise addition of 20% acetic acid. The solution, separated from mercury, was further acidified with hydrochloric acid and evaporated to small bulk under reduced pressure. Water was added, and the solution washed with ether, basified, and extracted with ether. The dried extracts, on treatment with dry ethereal hydrogen chloride, yielded a precipitate of 3-amino-1-cyano-1-phenylindane hydrochloride (0·6 g., 55%), which was collected and dried *in vacuo* over sodium hydroxide. The hydrochloride was converted into a *picrate* which crystallised from ethanol in needles, m. p. 220° (decomp.) (Found: C, 57·2; H, 3·55; N, 15·0. $C_{16}H_{14}N_2,C_6H_3O_7N_3$ requires C, 57·0; H, 3·7; N, 15·1%).

(*b*) A solution of the oxime (1·0 g.) in ethanol saturated with ammonia was hydrogenated at 100 atm. and room temperature in the presence of Raney nickel (0·5 g.). Working up in the usual way gave the amine hydrochloride (1·0 g., 91·5%) which was converted into a picrate identical with described above. This result was not reproducible, and, in general, only partial reduction was effected. Hydrogenation over Adams catalyst in ethanol containing hydrochloric acid gave only microscopic yields.

A Leuckart reaction conducted with 3-cyano-3-phenylindan-1-one (1·3 g.), ammonium formate (1·74 g.), and formic acid (2 c.c.) at 150° for 4 hr. gave, after hydrolysis of the substituted formamide, only 50 mg. of the picrate of the required amine. Starting material (0·8 g.) was recovered.

2 : 4-*Diphenylbutyronitrile*.—Sodium (6 g.) was dissolved in liquid ammonia in the presence of a trace of ferric nitrate. When the blue colour had disappeared, benzyl cyanide (30 g.) was added, the solution being cooled in acetone–solid carbon dioxide to modify the otherwise vigorous reaction. To this cooled, deep red solution, an ether solution of phenethyl bromide (48·2 g.) was added dropwise with stirring. The red colour was not discharged. Water was added to the semisolid residue after the evaporation of the ammonia, and the whole extracted with ether. The residue from the dried extracts was distilled *in vacuo* and 2 : 4-*diphenylbutyronitrile* (36·8 g., 65·3%) collected at 132°/0·16 mm. (Found: C, 86·8; H, 7·2; N, 5·4. $C_{16}H_{15}N$ requires C, 86·9; H, 6·8; N, 6·3%). The highest yield obtained by this method was 71·4%. A lower yield (43%) was obtained when the benzyl cyanide and phenethyl bromide were mixed and then added to the sodamide in liquid ammonia.

1-*Cyano*-1-*phenylindane*.—(*a*) A solution of bromine (14·6 g.) in dry tetrachloroethane was added to one of 2 : 4-diphenylbutyronitrile (19·7 g.) in the same solvent. After 1½ hr. at 80°, bromination was complete, giving a straw-coloured solution of 2-bromo-2 : 4-diphenylbutyronitrile, which was immediately cyclised, by treatment at 0° with pulverised aluminium chloride (13 g.) in portions with agitation. The mixture was kept at 0° for 1 hr., with occasional agitation, then allowed to come to room temperature and kept for 40 hr. The mixture was poured on ice and concentrated hydrochloric acid (26 c.c.), and the layers were separated. The aqueous layer was extracted with benzene and the combined organic solutions were dried and distilled. 1-*Cyano*-1-*phenylindane* (9·7 g., 49%) was collected at 122°/0·2 mm. (Found: C, 87·7; H, 6·3; N, 6·0. $C_{16}H_{13}N$ requires C, 87·7; H, 5·9; N, 6·4%). This specimen is designated indane-A. All variations of the above conditions caused a lower yield.

(*b*) The tetrachloroethane solution of 2-bromo-2 : 4-diphenylbutyronitrile, prepared as above from 2 : 4-diphenylbutyronitrile (8·05 g.), was cooled to 0° and treated with anhydrous ferric chloride (6·5 g.), with agitation. The mixture was kept at 0° for 1 hr. and then allowed to remain at room temperature overnight. The product, worked up as above, gave 1-cyano-1-phenylindane-B (3·5 g., 43·5%), apparently identical with the indane-A described above.

(*c*) 2-Bromo-2 : 4-diphenylbutyronitrile in tetrachloroethane was kept for 3 hr. at 80° with stannic chloride (1 mol.), then overnight at room temperature. Working up gave 1-cyano-1-phenylindane-C (6·05 g., 75·3%), apparently identical with the specimens described above.

1-*Cyano*-3-*dimethylamino*-1-*phenylindane*.—(*a*) 3-Amino-1-cyano-1-phenylindane (1·2 g.), formic acid (5 c.c.), and 40% aqueous formaldehyde (1 c.c.) were heated together on the steam-bath. When the vigorous evolution of carbon dioxide had abated, the solution was boiled for 5 min. under reflux, cooled, basified with potassium hydroxide, and extracted with ether. The residue from the dried extracts was dissolved in dilute hydrochloric acid and treated at 0° with

aqueous sodium nitrite. The resulting solution was washed with ether, basified, and extracted with ether. The dried extracts were treated with dry ethereal hydrogen chloride, and 1-*cyano*-3-*dimethylamino*-1-*phenylindane hydrochloride* (α) precipitated as an orange gum. After drying *in vacuo* over sodium hydroxide it crystallised from *tert.*-butyl alcohol in colourless needles, m. p. 215—217° (Found: C, 70·3; H, 6·55; N, 8·9. $C_{18}H_{18}N_2$,HCl,$\frac{1}{2}H_2O$ requires C, 70·2; H, 6·5; N, 9·1%). The *picrate*, recrystallised from ethanol, had m. p. 223° (decomp.) (Found: C, 58·9; H, 4·5; N, 14·1. $C_{18}H_{18}N_2$,$C_6H_3O_7N_3$ requires C, 58·6; H, 4·3; N, 14·3%).

(*b*) 1-Cyano-1-phenylindane-A (8·5 g.) and bromine (1·95 c.c.) were heated under reflux in carbon tetrachloride until reaction was complete (4—6 hr.). Evaporation under reduced pressure gave crude 3-bromo-1-cyano-1-phenylindane. This compound (5·5 g.), dissolved in dry dioxan, was cooled to −15° and treated with similarly cooled dimethylamine (2·5 g.). The mixture was allowed to react at room temperature for 1 week in a sealed pressure-bottle. The solution was filtered from the precipitated dimethylamine hydrobromide (3·2 g.) and evaporated under reduced pressure. The residual oil was dissolved in ether, filtered, and extracted with dilute hydrochloric acid. The acid solution was strongly basified and extracted with ether. 1-Cyano-3-dimethylamino-1-phenylindane hydrochloride (β) was precipitated from the dry ether solution with dry hydrogen chloride and recrystallised from ethyl acetate–ethanol after drying *in vacuo* over sodium hydroxide. It formed colourless needles, m. p. 193—212°, mixed m. p. with α-hydrochloride 193—208° (Found: C, 72·5; H, 6·3; N, 9·35. Calc. for $C_{18}H_{18}N_2$,HCl: C, 72·35; H, 6·4; N, 9·4%). The picrate, recrystallised from ethanol, had m. p. 195—198°, mixed m. p. with α-picrate 195—198° (Found: C, 58·6; H, 4·5; N, 14·5%).

(*c*) 3-Bromo-1-cyano-1-phenylindane prepared from indane-B (3·5 g.) was allowed to react with dimethylamine (2·4 c.c.) as in the previous experiment. After filtration, evaporation, and dissolution in ether, the refiltered solution was extracted with dilute hydrochloric acid. A copious precipitate was formed which was collected and recrystallised from ethyl acetate–ethanol, giving colourless needles of 1-cyano-3-dimethylamino-1-phenylindane hydrochloride (γ), m. p. 221° (decomp.), mixed m. p. with β-hydrochloride 173°, with α-hydrochloride 182°, with γ-hydrochloride (below) 220° (decomp.).

The residual acid solution above was strongly basified and extracted with ether and 1-cyano-3-dimethylamino-1-phenylindane hydrochloride (β) precipitated in the usual way. Crystallisation from ethyl acetate–ethanol gave needles, m. p. 193—212°, mixed m. p. with β-hydrochloride 193—212°.

(*d*) A similar experiment with the bromocyanophenylindane prepared from indane-C gave needles of 1-cyano-3-dimethylamino-1-phenylindane hydrochloride (γ), m. p. 216—218°, mixed m. p. with γ-hydrochloride (below) 219—220°.

The residual acid solution was basified and extracted with ether. From this the γ-hydrochloride was obtained in the usual way, m. p. 216—218°. The picrate, recrystallised from ethanol, had m. p. 184°, mixed m. p. with γ-picrate (below) 179°, with β-picrate 172—176°.

(*e*) 1-Cyano-1-phenylindane-A (8·5 g.) and bromine (1·95 c.c.) were heated under reflux in dry carbon tetrachloride in the presence of a trace of benzoyl peroxide. The reaction was complete in 6 hr. Evaporation of the solvent under reduced pressure gave the bromo-derivative as a red gum which was dissolved in dioxan and treated with dimethylamine (3 mols.). The mixture was slowly warmed to 60° and allowed to cool overnight. After filtration, evaporation, and dissolution in ether, the refiltered solution was extracted with dilute hydrochloric acid. There was some precipitate which dissolved on addition of more water. The acid solution was strongly basified and extracted with ether. 1-Cyano-3-dimethylamino-1-phenylindane hydrochloride (γ) was prepared from this in the usual way, as needles, m. p. 221° (Found: C, 71·8; H, 6·4; N, 9·1%). The *γ-picrate*, recrystallised from ethanol, had m. p. 181°, mixed m. p. with β-picrate 172—176°, with α-picrate 168—185° (decomp.) (Found: C, 58·4; H, 4·2; N, 13·8. $C_{18}H_{18}N_2$,$C_6H_3O_7N_3$ requires C, 58·6; H, 4·3; N, 14·3%). The free base had *M* 202 ($C_{18}H_{18}N_2$ requires *M*, 262).

3-*Dimethylamino*-1-*ethoxycarbonyl*-1-*phenylindane*.—A solution of 1-cyano-3-dimethylamino-1-phenylindane (β) (2·0 g.) in dry ethanol (25 c.c.) was saturated at 0° with dry hydrogen chloride, then heated in a sealed tube for 24 hr. at 125°. Two immiscible layers had formed but the whole was evaporated under reduced pressure and dried *in vacuo* over sodium hydroxide. The residual gum was dissolved in chloroform and filtered from the precipitated ammonium chloride. Evaporation of the chloroform gave a sticky gum which was dissolved in water, basified with sodium carbonate, and extracted with ether. 3-*Dimethylamino*-1-*ethoxycarbonyl*-1-*phenylindane hydrochloride* was precipitated with hydrogen chloride in the usual way and dried *in vacuo* over sodium hydroxide; recrystallised from ethyl acetate–ethanol, it had m. p. 205° (Found:

C, 69·3; H, 7·0; N, 4·1. $C_{20}H_{23}O_2N$,HCl requires C, 69·4; H, 7·0; N, 4·05%). The *picrate* had m. p. 193—194° (Found: C, 58·4; H, 4·8; N, 10·3. $C_{20}H_{23}O_2N$,$C_6H_3O_7N_3$ requires C, 58·0; H, 4·9; N, 10·4%).

The residual sodium carbonate solution (above) was acidified with dilute hydrochloric acid and evaporated to dryness. The resulting semisolid mass was extracted with chloroform, and the solution filtered, dried, and evaporated, giving 3-dimethylamino-1-phenylindane-1-carboxylic acid as a sticky gum, which was converted into a *picrate*, m. p. 198° (from ethanol) (Found: C, 56·2; H, 4·6; N, 10·8. $C_{18}H_{19}O_2N$,$C_6H_3O_7N_3$ requires C, 56·4; H, 4·35; N, 11·0%).

Only slightly impure starting material was obtained by heating the nitrile in saturated ethanolic hydrogen chloride under reflux for 7 hr. and then for 4 hr. in a Carius tube at 100°.

Attempted Hydrolysis of 1-Cyano-3-dimethylamino-1-phenylindane (γ).—As in the previous experiment, 1-cyano-3-dimethylamino-1-phenylindane hydrochloride (γ) (2·0 g.) was heated with ethanolic hydrogen chloride in a sealed tube at 140° for 17 hr. Working up as previously gave a hydrochloride, m. p. 194—195°, from which was obtained a small amount of *3-dimethylamino-1-phenylindane-1-carboxyamide picrate*, which, crystallised from ethanol, had m. p. 186° (Found: C, 54·6; H, 4·6; N, 12·7. $C_{18}H_{20}ON_2$,$C_6H_3O_7N_3$,H_2O requires C, 54·6; H, 4·7; N, 13·3%).

Attempted Preparation of 3-Dimethylamino-1-phenyl-1-propionylindane.—A solution of ethyllithium was prepared in dry ether from lithium (0·78 g.) and ethyl bromide (6·1 g.) and siphoned under nitrogen through a muslin filter into a nitrogen-filled flask. Ether and unchanged ethyl bromide were distilled off, and dry ether was added to the residue, followed by an ethereal solution of 1-cyano-3-dimethylamino-1-phenylindane (β) (2·62 g.) dropwise with stirring. The mixture was boiled for 17 hr. under nitrogen and poured on ice, and the ethereal layer separated, combined with the ethereal washings from the aqueous layer, and extracted with hydrochloric acid. The acid solution was heated on the steam-bath for 2 hr., cooled, filtered from a little dark oil, and basified strongly, and the basic material isolated with ether and converted into a *hydrochloride*, which crystallised from ethanol–ethyl acetate–ether in needles, m. p. 181°, mixed m. p. with hydrochloride of starting material 166°, with 1-dimethylamino-3-phenylindane hydrochloride[1] (m. p. 190°) 160—170° (Found: C, 70·9, 71·0; H, 7·5, 7·3; N, 5·0, 4·8. $C_{17}H_{19}N$,HCl,H_2O requires C, 70·0; H, 7·5; N, 4·8%). The *picrate* crystallised from ethanol (Found: C, 59·1; H, 4·6; N, 12·1. $C_{17}H_{19}N$,$C_6H_3O_7N_3$ requires C, 59·1; H, 4·7; N, 12·0%).

A reaction conducted between the nitrile and ethylmagnesium iodide in toluene at 97° for 18 hr. led to recovery of the starting material, and another similar reaction in anisole at 150° for 20 hr. gave no basic material.

Ethyl γ-Oxo-ββ-diphenylvalerate.—(*a*) Ethyl hydrogen αα-diphenylsuccinate[5] (7·45 g.) was converted into the half ester chloride by reaction with thionyl chloride followed by evaporation under reduced pressure. Methylmagnesium chloride (from magnesium, 1·15 g., and methyl chloride in ether) was treated at 0° with cadmium chloride (5·0 g.) and stirred until a negative test with Michler's ketone was obtained. A dry ethereal solution of the acid chloride was added to the cooled solution of dimethylcadmium, yielding a sticky solid. The mixture was heated under reflux for 4 hr. and set aside overnight. It was then decomposed with ice and dilute hydrochloric acid, and the ether layer separated. The aqueous layer was extracted with ether, and the combined ether solutions were washed with dilute hydrochloric acid, water, and then sodium carbonate solution until all acid had been removed. The ether solution was dried (K_2CO_3) and the residue distilled *in vacuo* to give the *valerate* (2·5 g., 33·8%), b. p. 143—145°/0·07 mm. (Found: C, 77·0; H, 6·7. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

A similar experiment under more drastic conditions was carried out on the acid chloride from the half-ester (15·4 g.). A toluene solution of this was added to an ether–toluene solution of dimethylcadmium [prepared from methylmagnesium chloride (7 g. of magnesium) and anhydrous cadmium chloride (30·3 g.)], and the ether was distilled off until the internal temperature was 70°. The mixture was heated under reflux for 3 hr. and set aside overnight. A non-acidic brown gum was isolated by the procedure above and hydrolysed to a yellow oily acid (6·3 g.). Purification by acidification of the sodium carbonate extracts gave *γ-hydroxy-γ-methyl-αα-diphenylvaleric acid* which, crystallised from ethanol, had m. p. 202—203° (Found: C, 76·5; H, 7·4%; *M*, 252. $C_{18}H_{20}O_3$ requires C, 76·1; H, 7·0%; *M*, 284).

(*b*) To a stirred mixture of ether (80 c.c.) and 40% potassium hydroxide solution (24 c.c.), cooled to 5°, *N*-nitrosomethylurea (8 g.) was added in portions. Then the solution was stirred at 5° for 10 min., the layers were separated, and the ether solution of diazomethane (containing 2·24 g.) dried (KOH). This solution was stirred at 0° and an ether solution of the half-ester acid

chloride (from 5·0 g. of the half-ester above) added dropwise. The yellow solution was stirred at 0° for ½ hr., then at room temperature for 3 hr., and set aside overnight. The ether was evaporated to 25°, to give a yellow semicrystalline material which was kept at −5°. A solution of this diazo-ketone (0·5 g.) in dry chloroform was shaken with 55% hydriodic acid (2 c.c.). A gas was evolved and the chloroform layer was separated, dried, and evaporated *in vacuo*. The residual gum was dissolved in ether, decolorised by a little sodium thiosulphate solution, washed with sodium hydrogen carbonate solution, dried, and evaporated. The residual brown gum, crystallised from aqueous methanol, gave the *keto-ester* as needles, m. p. 97° (Found: C, 73·2; H, 6·6. $C_{19}H_{20}O_3,H_2O$ requires C, 72·6; H, 7·0%).

Reaction between Ethylmagnesium Iodide and 1-*Cyano*-3-*oximino*-1-*phenylindane*.—Ethylmagnesium iodide was prepared from ethyl iodide (5·0 g.) and magnesium (0·8 g.) in ether, the ether replaced by toluene (10 c.c.), and the whole heated at 130—140°. A solution of 1-cyano-3-oximino-1-phenylindane (1·0 g.) in dry toluene (10 c.c.) was slowly added to the hot solution during 15 min. and heating was continued for a further 20—30 min. The solution was cooled, hydrolysed with ice and ammonium chloride, and extracted with ether. The basic material was isolated by extracting the ethereal solution with acid and then basifying. 1 : 2-*Imino*-3-*phenylindane picrate* crystallised from ethanol in plates, m. p. 202—203° (decomp.) (Found: C, 59·2; H, 4·0; N, 11·7. $C_{17}H_{17}N,C_6H_3O_7N_3$ requires C, 59·5; H, 4·3; N, 12·1%).

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