141. *Compounds of Potential Pharmacological Interest. Part III.* 2-Substituted 1-Phenylindanes.*

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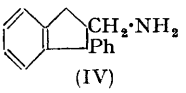
In the search for new analgesics and spasmolytics, two primary amines and one basic ester derived from 1-phenylindane have been synthesised.

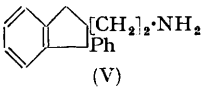
Diphenylmethyl and dialkylaminoethyl ester groupings are examples of important factors contributing to pharmacological activity; they can be found in many highly active compounds such as the analgesic amidone (I), the spasmolytic " Trasentin " (II), and the local anæsthetic procaine (III). The 4-phenylbutylamine system is also important. The

$Et\cdot CO\cdot CPh_2\cdot CH_2\cdot CHMe\cdot NMe_2$ (I) $\quad CHPh_2\cdot CO_2\cdot[CH_2]_2\cdot NEt_2$ (II) $\quad p\text{-}NH_2\cdot C_6H_4\cdot CO_2\cdot[CH_2]_2\cdot NEt_2$ (III)

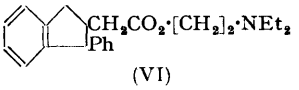
discovery[1,2] of a number of active compounds in the indane series suggested the investigation of indanamines and basic esters derived from 1-phenylindane, particularly (IV), (V), and (VI), since (IV) can be regarded as containing a 3-phenylpropylamine skeleton, and (V) contains a 4-phenylbutylamine skeleton, whilst (VI) is a basic ester of an indanylacetic acid, and all three compounds contain a diphenylmethyl grouping.



(IV)

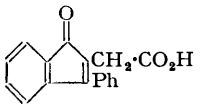


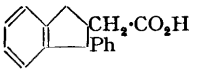
(V)



(VI)

Syntheses of all three compounds started from the little known 1-oxo-3-phenyl-2-indenylacetic acid (VII) which was obtained in three stages from benzophenone through a Stobbe condensation[3] in good yield (average 67% of crude product). As expected, Clemmensen reduction of this αβ-unsaturated acid reduced both the double bond and the carbonyl group, and 1-phenyl-2-indanylacetic acid (VIII) was obtained in almost quantitative yield. The crude acid, melting over a range 105—140°, proved to be a mixture of the two possible geometrical isomers. The lower-melting and more soluble isomer was assigned the *cis*-configuration by analogy with previous facts.[4]

(VII) 



(VIII)

The hydrochlorides of the required amines, *trans*-2-aminomethyl-1-phenylindane (IV) and *trans*-2-2′-aminoethyl-1-phenylindane (V), were obtained from *trans*-1-phenyl-2-indanylacetic acid by standard methods; the former by Hofmann degradation of the corresponding amide, and the latter from the same amide *via* the nitrile. Chlorine and sodium hydroxide solution having proved useless, the Hofmann degradation was successfully accomplished by using Jeffreys's procedure[5] which involves the use of bromine and sodium methoxide, the intermediate urethane being hydrolysed by dry distillation with excess of lime.

Of the available methods for the preparation of basic esters of carboxylic acids, the one involving the interaction of an acid with a chloroalkamine was chosen for the preparation of 2-diethylaminoethyl *trans*-1-phenyl-2-indanylacetate hydrochloride (as VI) since yields are generally good and products are relatively pure. The required chloroalkamine was

* Part II, preceding paper.

[1] Acheson, MacPhee, Philpott, and Barltrop, preceding paper.
[2] Burtner and Cusic, *J. Amer. Chem. Soc.*, 1943, **65**, 262; Levin, Graham, and Kolloff, *J. Org. Chem.*, 1944, **9**, 380; Barltrop, *J.*, 1946, 958; Barltrop and his co-workers, Parts I and II, preceding papers.
[3] (*a*) Johnson, Petersen, and Schneider, *J. Amer. Chem. Soc.*, 1947, **69**, 76: (*b*) Johnson and Goldman, *ibid.*, 1945, **67**, 435.
[4] Cf. Gagnon and Charette, *Canad. J. Res.*, 1941, **19**, *B*, 287.
[5] Jeffreys, *Amer. Chem. J.*, 1899, **22**, 14.

readily obtainable from 2-diethylaminoethanol by reaction with thionyl chloride [6] followed by sodium hydroxide treatment which was conveniently done following Burtner's [7] directions. The chloroalkamine was condensed with *trans*-1-phenyl-2-indanylacetic acid in propan-2-ol by the method of Burtner and Cusic [2] and the required basic ester hydrochloride was obtained in 70% yield.

Experimental

cis- *and* trans-1-*Phenyl*-2-*indanylacetic Acid.*—3-Ethoxycarbonyl-4 : 4-diphenylbut-3-enoic acid was prepared from benzophenone and diethyl succinate by the method described by Johnson, Petersen, and Schneider.[3a] Cyclisation of this acid, followed by hydrolysis, gave 1-oxo-3-phenyl-2-indenylacetic acid.[3b] A solution of this acid (55 g.) in acetic acid (900 c.c.) was heated with amalgamated zinc (130 g.) to gentle reflux. Concentrated hydrochloric acid (1 l.) was slowly added during 1·5 hr. and the mixture was left to cool. Colourless crystals were deposited. The liquid was decanted, diluted with water, and thoroughly extracted with ether. The solid residue was also extracted with ether, and the united ether extracts were washed with water and treated with 5% sodium carbonate solution. Acidification of the alkaline extract gave colourless crystals, m. p. 105—140°, of 1-phenyl-2-indanylacetic acid (49·6 g., 95%), which were collected. Crystallisation from ethanol gave trans-1-*phenyl*-2-*indanylacetic acid* (22·9 g.), obtained on two further crystallisations from ethanol as plates, m. p. 157—158° (Found : C, 80·7; H, 6·5. $C_{17}H_{16}O_2$ requires C, 81·0; H, 6·4%). Addition of water to the ethanolic filtrate and storage overnight at 0° induced crystallisation of the cis-*acid* (18 g.) which, crystallised from toluene, had m. p. 111—115° (Found : C, 80·7; H, 6·6%).

trans-1-*Phenyl*-2-*indanylacetamide.*—A solution of *trans*-1-phenyl-2-indanylacetic acid in benzene was refluxed with an excess of phosphorus trichloride until hydrogen chloride ceased to be evolved. After filtration, most of the benzene was removed and the residue was poured with stirring into an excess of ammonia solution (*d* 0·88). Dilution with water completed precipitation and the *amide* was collected. After three crystallisations from ethanol it had m. p. 173—174° (Found : C, 81·5; H, 7·0; N, 5·1. $C_{17}H_{17}ON$ requires C, 81·3; H, 6·8; N, 5·6%).

trans-2-(N-*Methoxycarbonyl*)*aminomethyl*-1-*phenylindane.*—A solution of *trans*-1-phenyl-2-indanylacetamide (4·7 g.) in methanol (500 c.c.) was added to one from sodium (1·0 g.) and methanol (30 c.c.). Bromine (3·2 g.) was then added slowly with stirring, and the solution was heated at 60—70° for 15 min. Dilute acetic acid was added until the solution was just acid, and the methanol was removed. The solid residue was washed with hot water and triturated with hot ligroin (b. p. 80—100°). After filtering, the filtrate was concentrated and cooled to 0°; the *urethane* (3·9 g.) was deposited. Three crystallisations from ethanol gave prisms, m. p. 103—104·5° (Found : C, 76·2; H, 6·7; N, 5·2. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8; N, 5·0%).

trans-2-*Aminomethyl*-1-*phenylindane Hydrochloride.*—The above urethane (2·9 g.) and a large excess of calcium hydroxide (11 g.) were dry distilled. *trans*-2-Aminomethyl-1-phenylindane, a yellow oil, was collected at 90—120°/0·15 mm. and was immediately dissolved in dry ether. On passage of dry hydrogen chloride through the ethereal solution, the *hydrochloride* (1 g.) was precipitated; this was collected and kept over solid sodium hydroxide for a day. Three crystallisations from ethanol containing a little ethyl acetate yielded plates, m. p. 312—313° (decomp.) (Found : C, 74·2; H, 7·2; N, 5·6. $C_{16}H_{17}N,HCl$ requires C, 74·0; H, 6·9; N, 5·4%).

trans-1-*Phenyl*-2-*indanylacetonitrile.*—A mixture of *trans*-1-phenyl-2-indanylacetamide (13 g.) and phosphoric oxide (4 g.) was dry distilled and the *nitrile* (5 g.), a colourless oil, was collected at 210—212°/10 mm. The compound was purified by washing it with alkali and distilling it, to a colourless oil, b. p. 200—200·5°/7 mm. (Found : C, 87·3; H, 6·2; N, 6·0. $C_{17}H_{15}N$ requires C, 87·5; H, 6·4; N, 6·0%).

trans-2-2'-*Aminoethyl*-1-*phenylindane Hydrochloride.*—*trans*-1-Phenyl-2-indanylacetonitrile (5 g.) in boiling ethanol (75 c.c.) was treated with sodium (11 g.), added in portions. When the reaction was complete, the mixture was allowed to cool, and water was added. The aqueous solution was extracted with ether, and the united ether extracts were treated with 10% hydrochloric acid. The acid solution was made alkaline by the addition of 5% aqueous sodium carbonate, and the liberated base was dissolved in ether. The *hydrochloride* was then obtained by the usual procedure and, crystallised from ethyl acetate, had m. p. 154—157° (Found : Cl, 12·9. $C_{17}H_{19}N,HCl$ requires Cl, 13·0%). The *toluene*-p-*sulphonyl derivative* separated from 5%

[6] Gilman and Shirley, *J. Amer. Chem. Soc.*, 1944, **66**, 888.
[7] Burtner, *ibid.*, 1949, **71**, 2378.

aqueous ethanol as plates, m. p. 135·5—136·5° (Found : N, 3·9; S, 8·2. $C_{24}H_{25}O_2NS$ requires N, 3·6; S, 8·2%).

2-*Diethylaminoethyl* trans-1-*Phenyl*-2-*indanylacetate Hydrochloride*.—2-Diethylaminoethyl chloride hydrochloride was prepared from 2-diethylaminoethanol as described by Gilman and Shirley [6] and converted into the free base.[7] The 2-diethylaminoethyl chloride (3·2 g.) was added slowly with stirring to a hot solution of *trans*-1-phenyl-2-indanylacetic acid (6 g.) in propan-2-ol (40 c.c.), and the mixture was refluxed for 3 hr. The cooled solution was diluted with dry ether, and the precipitated *hydrochloride* (4·6 g., 70%) was collected, washed with ether, and dried. Crystallised thrice from ethyl acetate it had m. p. 127—130° (Found : Cl, 9·5. $C_{23}H_{29}O_2N,HCl$ requires Cl, 9·2%).

A pharmacological examination of these compounds was made by Smith, Kline and French Laboratories, Philadelphia, U.S.A. Compounds (VI) and (VII) were tested for analgesic activity in mice, after intraperitoneal administration, by the Eddy–Leimbach hot-plate procedure. Both compounds produced a significant elevation of the pain threshold, but their activities were rather lower than that of codeine. The effect of adrenaline in raising the arterial blood pressure was greatly augmented by previous administration of the ester (VI).

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