The Stereochemistry of 2,3-Diphenyl-1-methylpropylamine

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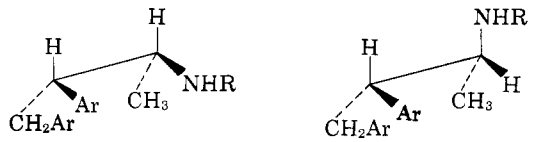
The absolute configuration of *d*-(+)-α-2,3-diphenyl-1-methylpropylamine has been established as 1*S*,2*S* by degradation to two optically active compounds, and synthesis of each of them from stereochemically known starting materials.

Derivatives of 2,3-diphenyl-1-methylpropylamine have been examined recently for their physiological activity and, in particular, their hypocholesterolemic effect.



α β

Ia, Ar = C_6H_5; R = H
b, Ar = *p*-ClC_6H_4; R = $COCH{=}CHCO_2H$
c, Ar = C_6H_5; R = $COCH{=}CHCO_2H$
d, Ar = *p*-ClC_6H_4; R = H

Benzmalecene (Ib, α isomer), for example, has shown activity in both animals and humans,[1] however, not without side effects.

Each of the enantiomorphs of α-dechlorobenzmalecene (Ic) has been tested as a hypocholesterolemic agent, and the (+) isomer was shown to be the active one.[2]

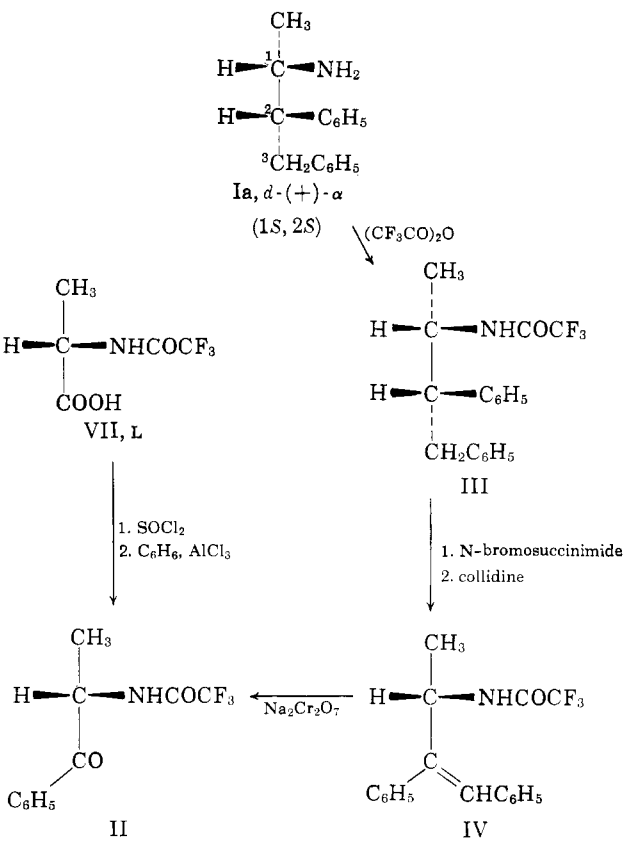
In these and related compounds, prior assignment[1,3] of the prefix "α" has been made arbitrarily to the isomer with the higher melting amine hydrochloride and maleamic acid derivative; the prefix "β" has been assigned to the lower melting derivatives.

The parent amine Ia has previously been prepared by Ishiwata and Suguki[4] and more recently by Schultz, Bicking, and Weibelhaus.[3] The Japanese group was interested in the amine as an intermediate in the synthesis of 1,3-dimethyl-4-benzyl-3,4-dihydroisoquinoline. They made no overt attempt to separate the isomers, although, from the melting point of the hydrochloride (reported[4] as 249° dec), it seems likely that considerable purification toward the less soluble α isomer occurred. Schultz, *et al.*,[3] report the melting points of the isomeric hydrochlorides as 247–248° (α) and 161–162° (β).

We have now directly established the absolute configuration of the *d*-(+)-α-Ia, shown that *d*-(+)-α-Id possesses the same stereochemistry, and thus, indirectly, proven the relative configuration of the β series. The *d*-(+)-α isomer according to the "sequence rule"[5] possesses the 1*S*,2*S* configuration.

The proof of configuration presented herein involves partial degradation of *d*-(+)-α-2,3-diphenyl-1-methylpropylamine to two optically active compounds, each retaining the original configuration at one of the active carbons. Identical compounds have been synthesized from previously established optically active precursors in an unambiguous manner. Carbon 1 was shown to be configurationally related to L-alanine by the method of Scheme I.

SCHEME I



L-Alanine, as its N-trifluoroacetyl derivative (VII), was converted to the corresponding phenyl ketone (II) *via* Friedel–Crafts reaction.[6] The optically active ketone was also obtained by dichromate oxidation of the intermediate IV, obtained from *d*-(+)-α-Ia, thus establishing the configuration at C-1 as *S* (or L).

(1) The biological activity is summarized in the accompanying paper, E. M. Schutz, *et al.*, *J. Med. Chem.*, **10**, 717 (1967).

(2) J. W. Huff, Merck Institute for Therapeutic Research, Rahway, N. J., personal communication.

(3) C. M. Schultz, J. B. Bicking, and V. D. Weibelhaus, British Patent 901,438 (July 18, 1962).

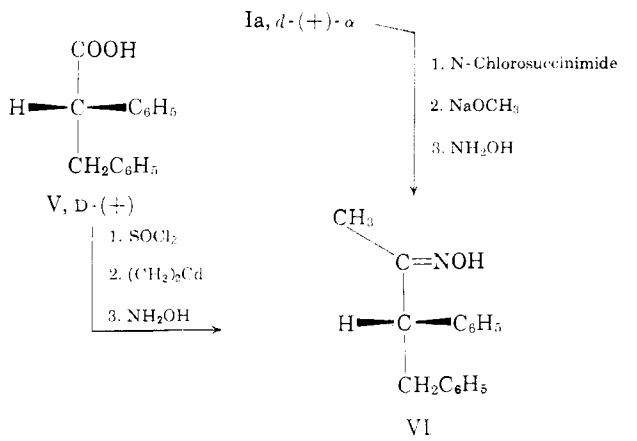
(4) S. Ishiwata and K. Suguki, *J. Pharm. Soc. Japan*, **71**, 1272 (1951); *Chem. Abstr.*, **46**, 5591*i* (1952).

(5) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(6) E. Schallenberg and M. Calvin [*J. Am. Chem. Soc.*, **77**, 2779 (1955)] have shown the optical integrity of amino acids in the conversion to N-trifluoroacetates and then to acid chlorides.

Proof of the configuration at carbon 2 was made less difficult than might be anticipated from an examination of the structure. Pettersson[7] has shown that the dextrorotatory 2,3-diphenylpropionic acid (V) possesses the D absolute configuration. This acid proved to be an ideal starting point, as shown in Scheme II.

SCHEME II



D-2,3-Diphenylpropionic acid (V) was converted to an oxime VI after formation of the methyl ketone in the usual manner with dimethylcadmium. Campbell and Kenyon[8] synthesized optically active 3-phenyl-2-butanone oxime from α-methylphenylacetic acid by the same reaction sequence. In our case, it is quite apparent that considerable racemization occurred during the reactions; the crude oxime initially isolated was only about 30% optically pure.

This oxime (VI), once purified, proved to be identical with the one found from *d*-(+)-α-Ia. Dehydrochlorination of the intermediate N-chloramine to the imine with sodium methoxide must be performed under mild conditions for maximum retention of optical activity. Heating the mixture at reflux with a slight excess of base permits complete racemization of the adjacent carbon atom, presumably through an imine ⇌ enamine tautomerization.

The imine so formed was transformed directly to the corresponding oxime upon addition of an aqueous solution of hydroxylamine. In three different experiments, the crude oxime obtained showed $[\alpha]_D$ +35, +111, and +120°, respectively. In the first experiment, all of the alkoxide was added initially at ice-bath temperature, and the reaction was allowed to proceed overnight, warming to room temperature. The more successful experiments were carried out as described below, wherein sodium methoxide was added slowly at room temperature, permitting reasonable rates of dehydrochlorination without excessive accumulation of base. In all cases, a molar insufficiency of base was used.

The starting material for the degradation studies, *d*-(+)-α-amine (Ia), has been obtained by two pathways which prove the interrelationship of the chloro and dechloro series of compounds.

(7) K. Pettersson, *Arkiv Kemi*, **10**, 297 (1956).

(8) A. Campbell and J. Kenyon, *J. Chem. Soc.*, 25 (1946).

In the first, the straightforward, catalytic reduction[9] of 3,4-diphenyl-2-butanone oxime[4] gave the mixture of diastereoisomeric amines, which were separated as the hydrochlorides.[3] The α-amine was resolved *via* dibenzoyl-L-tartaric acid. The least soluble salt was that of the desired *d*-(+) isomer.

Alternatively, benzmalacene was hydrolyzed with hydrochloric acid to provide *dl*-α-Id as its hydrochloride. The free base was resolved with D-tartaric acid to provide the *d*-(+)-α isomer of Id which was dechlorinated over palladium to give *d*-(+)-α-Ia, identical with the isomer prepared by resolution of the dechloro racemate.

Experimental Section[10]

N-Trifluoroacetyl-L-alanine (VII) was prepared by known methods.[11] After sublimation, the melting point was 66–69°, lit.[11,12] 66–66.5°, 66–68°.

2-Trifluoroacetamidopropiophenone (II) Friedel–Crafts Reaction of VII.—To a stirred mixture of 27 g (0.202 mole) of anhydrous $AlCl_3$ in 90 ml of CS_2 and 40 ml of benzene at 40° was added a solution of N-trifluoroacetyl-L-alanyl chloride in 40 ml of benzene. [The acid chloride had been prepared by treating 0.1 mole of crude (unsublimed) VII with 10 ml (16.4 g, 0.15 mole) of $SOCl_2$ in 100 ml of benzene. After 2 hr of reflux, the solution was evaporated *in vacuo* to a residue.] The addition was completed in 20 min; thereafter, the reaction was refluxed for 3 hr, cooled in an ice bath, and decomposed by the cautious addition of sufficient 6 *N* HCl to provide two clear layers. The organic layer was washed twice with water and the combined aqueous layers were extracted with benzene. The combined organic layers were washed once more (H_2O, 5% $NaHCO_3$, H_2O). After drying the benzene–CS_2 solution (Na_2SO_4), the solvent was removed and the residue, 15.2 g (62% crude yield), crystallized on standing. A portion of the solid was distilled, bp 80–85° (0.05 mm), for analysis. The distillate solidified and was recrystallized from petroleum ether (bp 30–60°). The white plates showed mp 50–51.5°, $[\alpha]_D$ −58.9° (*c* 1.8, dioxane).

Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.89; H, 4.11; N, 5.72. Found: C, 54.12; H, 4.16; N, 5.61.

The **dinitrophenylhydrazone,** crystallized from ethanol–water, showed mp 164–166°, $[\alpha]_D$ −132° (*c* 2, ethanol).

Anal. Calcd for $C_{17}H_{14}F_3N_5O_5$: C, 48.01; H, 3.32; N, 16.45. Found: C, 47.54; H, 3.52; N, 16.27.

N-(1-Methyl-2,3-diphenylpropyl)trifluoroacetamide (III).—A solution of 7.43 g (0.033 mole) of *d*-α-amine (Ia) in 25 ml of anhydrous ethyl ether was treated with 7.6 g (0.036 mole) of trifluoroacetic anhydride in 5 ml of ether at ice temperature with stirring. After 10 min, the solution was raised to 10° and stirred an additional 30 min. The solvent was evaporated *in vacuo* and the solid residue was dissolved in hot hexane and cooled. The waxy filamentous crystals were filtered, washed with hexane, and dried. The crude product was used directly for oxidation to IV. Sublimation of the mother liquid solids gave the analytical sample, mp 64–66°, $[\alpha]_D$ +39.1° (*c* 1.8, dioxane).

Anal. Calcd for $C_{18}H_{18}F_3NO$: C, 67.35; H, 5.65; N, 4.36. Found: C, 67.66; H, 5.65; N, 4.20.

1,2-Diphenyl-3-trifluoroacetamidobut-1-ene (IV).—A solution of 5.65 g (0.0176 mole) of III in 40 ml of benzene was brought to the boiling point. While illuminating with a 250-w infrared heat lamp, a boiling solution of 3.3 g (0.0185 mole) of N-bromosuccinimide in 75 ml of benzene was added. The solution took on a typically reddish brown color, then lightened. Within a few minutes, the reaction was complete as evidenced by a negative test with acidified starch–iodide paper. After cooling, the reaction solution was washed with three 50-ml portions of water

(9) For the general method, see E. Rohrmann and H. A. Shonle, *J. Am. Chem. Soc.*, **66**, 1516 (1944). Anhydrous NH_3 was added to the oxime to enhance yields.

(10) Rotations were determined in a Zeiss Precision photoelectric polarimeter. Melting points were measured on samples in open capillaries in a Thomas-Hoover melting point bath. Temperatures are not corrected. Microanalyses were performed by Mr. R. N. Boos and his associates of these Laboratories.

(11) F. Weygand and R. Geiger, *Chem. Ber.*, **89**, 647 (1956).

(12) W. S. Fones, *J. Org. Chem.*, **17**, 1661 (1952).

and concentrated *in vacuo* to dryness. 2,4,6-Collidine (20 ml) was added to the residue and the resulting solution deposited collidine hydrobromide upon heating at 90° for 2.5 hr. The cooled mixture was distributed between ether and dilute HCl, and the aqueous layers were extracted with ether after washing the ether layer with a fresh portion of acid. The combined ether layer was dried ($MgSO_4$), filtered slowly through a small layer of acid-washed alumina, and concentrated *in vacuo* to a solid residue. Crystallization from ether–petroleum ether gave 2.7 g (48%) of prisms, mp 89–90°. Further recrystallization of the second crop gave analytically pure material, mp 90.5–92°, $[\alpha]_D$ −60.8° (*c* 2, dioxane), λ^{MeOH} 256 mμ (log ε 4.1).

Anal. Calcd for $C_{18}H_{16}F_3NO$: C, 67.69; H, 5.05; N, 4.38. Found: C, 67.63; H, 5.10; N, 4.29.

2-Trifluoroacetamidopropiophenone (II). By Oxidation of IV.—To a stirred solution of 2.7 g (0.0085 mole) of IV in 10 ml of acetic acid and 5 ml of benzene at 15° was added a solution of 4.7 g of $Na_2Cr_2O_7$ in 10 ml of acetic acid. After 20 min stirring, a solution of 1.05 ml of 98% H_2SO_4 in 2 ml of AcOH was added over a 40-min period. After a further 75 min, the reaction was poured into a mixture of benzene and water. The benzene layer was washed with three 25-ml portions of water and finally with 3% $NaHCO_3$. The bicarbonate solution deposited benzoic acid, mp 121°, upon acidification. The benzene layer was evaporated to an oil which smelled of benzaldehyde.

Chromatography on 100 g of acid-washed alumina sufficed to separate the benzaldehyde (20:80 benzene–hexane) from the desired product (50:50 benzene–hexane). Distillation of the product-rich fractions gave the desired ketone which only partly crystallized. The distillate showed $[\alpha]_D$ −51.2° (*c* 2, dioxane). The infrared spectrum was indistinguishable from that of the same ketone prepared by the Friedel–Crafts reaction (*vide supra*).

The **dinitrophenylhydrazone,** prepared as before, showed mp 165–166°, $[\alpha]_D$ −132.5° (*c* 2, EtOH), which was undepressed on admixture with a sample of the previously mentioned DNP. The infrared spectra of the two DNP's were indistinguishable.

Anal. Calcd for $C_{17}H_{14}F_3N_5O_5$: C, 48.01; H, 3.32; N, 16.45. Found: C, 48.07; H, 3.32; N, 16.31.

D-2,3-Diphenylpropionic Acid (V).—Alkylation of phenylacetic acid in liquid ammonia with benzyl chloride[13] gave the racemic acid which was resolved *via* its quinine salt.[14] D-2,3-Diphenylpropionic acid was liberated from the more soluble salt (see Table I).

TABLE I

	Quinine salt of V		V	
	Mp, °C	$[\alpha]_D$, deg (MeOH)	Mp, °C	$[\alpha]_D$, deg (benzene)
Lit.[14]	178–179	...	89	+86
Found	174–176	−86.2	78–80	+99

(+)-3,4-Diphenyl-2-butanone Oxime (VI) from V.—To a solution of 3.1 g (0.0138 mole) of V in 25 ml of anhydrous benzene was added 1.9 ml (0.026 mole) of $SOCl_2$. The solution, protected from moisture, was heated on the steam bath for 1.5 hr, then evaporated to a dry residue *in vacuo*. The acid chloride was dissolved in 20 ml of anhydrous benzene and used below.

To a stirred solution of 7.6 ml of *ca.* 3 *M* MeMgBr (Arapahoe Chemical Co.) in 17 ml of anhydrous ether was added 2.2 g (0.012 mole) of anhydrous $CdCl_2$. The reaction mixture, protected from the atmosphere by N_2, was heated at reflux for 1.5 hr, then 50 ml of dry benzene was added and the solvent was distilled until the vapor temperature reached 79°. The slurry was cooled in an ice bath and to it was added the solution of acid chloride (see above). After heating at reflux 2 hr, the reaction was again cooled in ice, and decomposed in the usual fashion with dilute H_2SO_4. The organic layer was separated and combined with benzene extracts of the aqueous phase. After washing the combined organic layers (H_2O, 5% $NaHCO_3$, H_2O), the solvent was removed *in vacuo*. To the semisolid mass was added 10 ml of ethanol and the mixture was allowed to stand overnight. The insoluble solids were removed and the ethanol filtrate was concentrated to an oil. To it was added 11 ml of methanol and a solution of 1.25 g (0.018 mole) of hydroxylamine hydrochloride and 1.48 g (0.018 mole) of NaOAc in 5 ml of water. The mixture was refluxed 4 hr and cooled, and the methanol was removed under vacuum. The crude oxime [1.9 g, mp 100–120°, $[\alpha]_D$ +54° (*c* 1, dioxane)] was purified by removal of successive crops of near-racemic oxime according to Table II. The mother liquors from the crystallization and recrystallization of crop 5 gave 195 mg of almost optically pure oxime, mp 96–98°, $[\alpha]_D$ +141° (*c* 1.2, dioxane).

TABLE II

Crop no.	Solvent	Wt, mg	$[\alpha]_D$, deg	Mp, °C
1	EtOH	600	+3.9	134–136
2	EtOH	300	+4.3	134–135
3	EtOH–ether	50	+6.4	132–135
4	Ether–petr ether	220	+9.7	132–135
5	Petr ether	400	+132	97–103

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.31; H, 7.16; N, 5.85. Found: C, 80.38; H, 7.15; N, 5.80.

(+)-3,4-Diphenyl-2-butanone Oxime (VI) from *d*-(+)-α-Ia.—A solution of 11.3 g (0.05 mole) of *d*-(+)-α-2,3-diphenyl-1-methylpropylamine in 100 ml of CH_2Cl_2 was cooled in an ice bath. To it was added 6.9 g (0.0517 mole) of N-chlorosuccinimide with stirring. After 10 min, the solution was warmed to room temperature and allowed to stir an additional 2 hr. The solution tested neutral to wet Alk-acid paper. The reaction was washed with two 50-ml portions of water, dried (Na_2SO_4), and concentrated to an oil, 13.4 g (~100%), $[\alpha]_D$ +38.9° (*c* 2.5, dioxane).

Anal. Calcd for $C_{16}H_{18}ClN$: C, 73.97; H, 6.98; N, 5.39. Found: C, 73.88; H, 6.85; N, 5.03.

A portion of the resulting crude oil (10.84 g, 0.0418 mole), was dissolved in 50 ml of ethanol and a solution of 40 mmoles (by titration) of $NaOCH_3$ in 25 ml of ethanol was added dropwise over a period of 3 hr. NaCl precipitated during the reaction. The solvent was removed *in vacuo*, and the residue was taken up in methanol. A solution of 4.2 g (0.06 mole) of hydroxylamine hydrochloride and 5 g (0.061 mole) of NaOAc in 10 ml of water was added and the mixture was stirred and heated for 4 hr under reflux. The methanol was removed *in vacuo*, water was added, and the crude crystalline oxime was isolated by filtration. After washing with water and petroleum ether, the product was dried *in vacuo;* yield 7.8 g (78%), mp *ca.* 90–100°, $[\alpha]_D$ +111° (*c* 2, dioxane).

Fractional crystallization provided the racemic oxime (from ethanol), mp 135–136°. From the mother liquor there was eventually obtained pure (+)-oxime (from ether–petroleum ether), mp 95.5–96.5°, $[\alpha]_D$ +153° (*c* 2, dioxane). The rotation was not increased by continued recrystallization.

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.31; H, 7.16; N, 5.85. Found: C, 80.55; H, 7.28; N, 5.77.

Resolution of *dl*-α-2,3-Diphenyl-1-methylpropylamine (Ia). Isolation of the *d*-(+) Isomer.—A slurry of 69.1 g (0.264 mole) of *dl*-α-2,3-diphenyl-1-methylpropylamine hydrochloride[3] in 400 ml of hexane and 400 ml of water was basified with 23 ml of 50% NaOH. After stirring 3 hr at 40–50°, two clear layers were achieved. The organic phase and a hexane extract of the aqueous phase were washed with water and concentrated to an oil which was dissolved in 450 ml of an 8:1 (volume) acetone–methanol mixture. A solution of 94.6 g (0.264 mole) of dibenzoyl-L-tartaric acid in 530 ml of the same solvent was added. The slurry which formed was heated and stirred at reflux for 2 hr, then recooled to room temperature. The crystalline salt was filtered, washed with acetone, and dried to give 70.15 g (91%, based on one antipode), mp 186–187°, $[\alpha]_D$ −29.9° (*c* 1, MeOH). Purification by hot reslurry in the same solvent system gave 69.7 g (88.2% over-all), mp 188–189°, $[\alpha]_D$ −28.9°. The physical constants were unchanged after further attempts at purification.

To 67.9 g of the above salt was added 600 ml of hexane, 600 ml of water, and 29.4 g of $NaHCO_3$.[15] After 4 hr of stirring at reflux, the aqueous phase was removed and acidified after cooling to provide 37 g of recovered dibenzoyl-L-tartaric acid. The hexane layer gave the optically active *d*-(+)-α-Ia as an oil, 24.3 g

(13) C. R. Hauser and W. R. Dunnavant, *Org. Syn.*, **40**, 38 (1960).

(14) H. Fujimura and Y. Yamikawa, *J. Pharm. Soc. Japan*, **80**, 333 (1960).

(15) When NaOH was used, the resolving agent was hydrolyzed to a mixture of benzoic and tartaric acids.

(92.6%). The amine was best characterized as its hydrochloride, mp 287–288° (from water), $[\alpha]_D$ +93.2° (*c* 1, MeOH).

Anal. Calcd for $C_{16}H_{19}N \cdot HCl$: C, 73.41; H, 7.70; N, 5.35; equiv wt, 261.8. Found: C, 73.27; H, 7.42; N, 5.20; equiv wt, 263.

Conversion of the free amine to its maleamic acid derivative [*d*-(+)-α-Ic] was accomplished in the usual manner.[3] The analytical sample from benzene showed mp 161–162°, $[\alpha]_D$ +60° (*c* 2.5, 0.2 *N* NaOH).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.51; H, 6.68; N, 4.54.

dl-α-2,3-Di(*p*-chlorophenyl)-1-methylpropylamine (Id) from the Hydrolysis of *dl*-α-Ib.—To a stirred refluxing slurry of 17.9 g (0.046 mole) of benzmalecene[3] in 90 of glacial acetic acid was added 90 ml of concentrated HCl over a 20-min period. After 16 hr of continued reflux, the solution was cooled to room temperature and diluted by the slow addition of 180 ml of water. After chilling 1 hr at 0–5°, the crystals were collected and washed with cold water. The hydrochloride of *dl*-α-Id, dried *in vacuo* at 60°, weighed 13.2 g (87%); equiv wt 327 (calcd 330.7). The product decomposes in an ill-defined manner above 265°.

The free base was liberated from its salt by partition between hexane and NaOH as in the case of the dechloroamine above. After work-up of the organic phase, 11.5 g (98%) of an oil was obtained; equiv wt 294 (calcd 294.2).

Resolution of *dl*-α-2,3-Di(*p*-chlorophenyl)-1-methylpropylamine (Id). Isolation of the *d*-(+)-α-Isomer.—A solution of 18.4 g (0.0625 mole) of the preceding free amine and 9.4 g (0.0625 mole) of D-(−)-tartaric acid in 84 ml of methanol was allowed to stand at room temperature for 2 hr, then refrigerated overnight. The crystals were collected and washed with a minimal quantity of cold methanol. The dry salt, 4.46 g, showed mp 191–195°. A second crop, 1.87 g (mp 187–190°), was obtained by crystallization after concentrating the mother liquor to half volume. Purification of the combined crops by reflux in 50 ml of hot absolute ethanol and isolation after cooling provided 5.77 g (41.5% based on one antipode) of *d*-(+)-Id tartrate, mp 192–193.5°, $[\alpha]_D$ +98.4° (*c* 5, MeOH–H_2O, 9:1).

The free amine was liberated as before (hexane–NaOH) to provide an oil in quantitative yield, $[\alpha]_D$ +172° (*c* 5, MeOH).

***d*-(+)-α-2,3-Diphenyl-1-methylpropylamine (Ia) *via* Hydrogenolysis of D-(+)-α-Id.**—A solution of 13.2 g (0.045 mole) of the optically active *d*-(+)-α-Id from above and 8.75 g (0.09 mole) of KOAc in 150 ml of absolute ethanol was hydrogenated over 3 g of 5% Pd–C at room temperature and 2.8 kg/cm². After removal of the catalyst and solvent, the residue was distributed between hexane and NaOH as before. Work-up gave 10.1 g (100%) of an oil which was identical in all respects with the amine obtained *via* resolution of *dl*-α-Ia. The hydrochloride and maleamic acid derivatives exhibited the same physical constants as found previously.

Notes

The Syntheses of 4′-Bromo-10-methyl-1,2-benzanthracene and 4′-Chloro-10-methyl-1,2-benzanthracene[1]

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As part of a program designed to find out more about the mechanism of cancer production by 10-methyl-1,2-benzanthracene (I) the syntheses of all of the aromatic monofluoro-substituted derivatives of I were undertaken. When 4′-fluoro-10-methyl-1,2-benzanthracene (II) was tested, no adequate measure of its carcinogenic activity could be made because of its high toxicity to rats and mice.[3] Because of this finding, the syntheses of 4′-bromo-10-methyl-1,2-benzanthracene[4] (III) and 4′-chloro-10-methyl-1,2-benzanthracene (IV) were undertaken and are described below. Neither III nor IV produced sarcomas in rats when a single dose of 2.28 or 2.66 mg, respectively, was injected subcutaneously in solution in 0.25 ml of trioctanoin (Eastman).[5] In the same experiment an equimolar amount of 10-methyl-1,2-benzanthracene induced sarcomas at the injection site in 11 of 20 rats within 6–14 months (average 9 months) after injection, while in earlier studies this level of 4′-fluoro-10-methyl-1,2-benzanthracene killed all of the rats in 8 weeks.[3]

The reduction of Va[6] by zinc and 90–99% formic acid[7] resulted in good yields of VIa, which, on treatment with methyllithium, afforded high yields of VIIa only when methyl iodide was used to prepare the methyllithium (Scheme I). The conversion of VIIa to III was effected by polyphosphoric acid[8] in 50% yield. Comparable reactions in the chlorinated series (b) led to IV.

Experimental Section[9]

o-(1-Naphthoyl)benzoic acid,[10] mp 173–174°, was prepared in 76% yield by rapidly adding a 1 *M* solution of 1-naphthylmag-

(1) This research was supported by Grants CY-3184 and CY-5480 of the U. S. Public Health Service.

(2) This work formed part of the Ph.D. thesis of N. Venkateswaran to the Ohio State University, 1964.

(3) E. C. Miller and J. A. Miller, *Cancer Res.*, **20**, 133 (1960); see also H. A. Hartmann, E. C. Miller, and J. A. Miller, *Proc. Soc. Exptl. Biol. Med.*, **101**, 626 (1959).

(4) The synthesis of III by B. M. Mikhailov and T. K. Kozminskaya, *Zh. Obshch. Khim.*, **23**, 1220 (1953), is known. Because of the low yield of III obtained and the poor analysis reported (1.7% below theory for C and no Br analysis) an alternate synthesis was sought. The melting point of III reported, *ca.* 183°, agrees well with what we found.

(5) These tests were carried out by Drs. James A. and Elizabeth C. Miller of the McArdle Laboratory for Cancer Research, University of Wisconsin with groups of 20 noninbred female rats from the Charles River Breeding Laboratory; the animals were maintained on Wayne Breeder Blox and the experiment was terminated at 15 months. Benign mammary tumors were found at 12–15 months in 8, 4, and 6 of the rats injected with III, IV, or the solvent alone. Except for the rats killed with mammary tumors no more than one rat from any of these groups died before termination of the experiment.

(6) (a) E. H. Johnson, V. Weinmayr, and R. Adams, *J. Am. Chem. Soc.*, **54**, 3289 (1932); (b) see also G. M. Badger, and A. R. M. Gibb, *J. Chem. Soc.*, 799 (1949), for proof of structure.

(7) R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, **26**, 97 (1961), used 80% formic acid.

(8) Compare M. S. Newman, D. MacDowell, and S. Swaminathan, *ibid.*, **24**, 509 (1959); and C. K. Bradsher and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 393 (1957).

(9) All melting points are uncorrected and taken with standardized thermometers. The phrase "worked up in the usual manner" means that an ether–benzene solution of the products was washed with aqueous acid and/or base and with saturated salt solution and filtered through anhydrous $MgSO_4$. The solvents were then removed by distillation and the residue was treated as indicated. Analyses were performed by (a) by Schwarzkopf Laboratory, Woodside, N. Y., and (b) by Microanalysis, Wilmington, Del.

(10) C. Weizmann, E. Bergmann, and F. Bergmann, *J. Chem. Soc.*, 1367 (1933).