(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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Received January 13, 1967

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. Expil. 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.

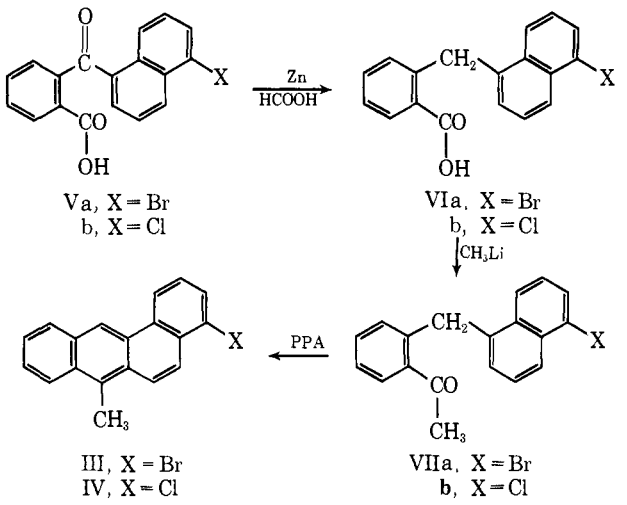
(7) R. L. Letsinger, J. D. Jamison, and A. S. Hussey, *J. Org. Chem.*, **26**, 97 (1961), used 80% formic acid.

(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).

SCHEME I



nesium bromide in 3:2 ether–benzene to a well-stirred warm solution of 163 g of phthalic anhydride in 3 l. of benzene. When tetrahydrofuran (THF) was the solvent for both Grignard reagent and anhydride, the yield fell to 46%.

o-(**5-Bromo-1-naphthoyl**)**benzoic Acid** (**Va**).[6]—A solution of 50 g of *o*-(1-naphthoyl)benzoic acid, 78 g of Br_2, and 2 g of $AlCl_3$ in 400 ml of acetic acid was held at room temperature for 3 hr and at reflux for 48 hr. After distillation of 250 ml of solvent and the usual work-up[9] 46 g (71%) of Va, mp 196.5–198.5° (lit.[6] mp 203–204°), was obtained.

o-(**5-Bromo-1-naphthylmethyl**)**benzoic Acid** (**VIa**).—To a warm solution of 41 g of Va in 750 ml of 95% formic acid was added 80 g of zinc dust.[7] After vigorous stirring at reflux for 48 hr about 600 ml of formic acid was distilled. Acidification of an ether–benzene solution of the products afforded 34.3 g (77%) of VIa as colorless crystals, mp 175–177°.

Anal. Calcd for $C_{18}H_{13}BrO_2$: C, 63.4; H, 3.8; Br, 23.4. Found (a): C, 63.4; H, 3.9; Br, 23.5.

o-(**5-Bromo-1-naphthylmethyl**)**acetophenone** (**VIIa**).—In a typical experiment a solution of 5.0 g of VIa in 500 ml of ether was treated with 136 ml of 0.68 *M* MeLi in ether. After 1 hr the reaction mixture was treated with water and worked up as usual to yield 2.1 g (73% based on unrecovered VIa) of VIIa, mp 74–76°, on recrystallization from alcohol, and 2.1 g of VIa.

Anal. Calcd for $C_{19}H_{15}BrO$: C, 67.3; H, 4.4; Br, 23.5. Found (a): C, 67.5; H, 4.5; Br, 23.8.

The 2,4-dinitrophenylhydrazone of VIIa melted at 178–180°.

Anal. Calcd for $C_{25}H_{19}BrN_4O_4$: N, 10.8; Br, 15.4. Found (b): N, 11.0; B, 15.2.

4'-Bromo-10-methyl-1,2-benzanthracene (III).—In the best of several experiments in which the temperature and time of reaction were varied, a mixture of 5.26 g of VIIa and 100 g of polyphosphoric acid was stirred at 135° for 2 hr. Purification of crude III by recrystallization from benzene yielded 3.3 g (66%) of pure III, mp 183.5–184.5°.

Anal. Calcd for $C_{19}H_{13}Br$: C, 71.0; H, 4.0; Br, 24.9. Found (b): C, 70.9; H, 3.9; Br, 24.8.

The brown 2,4,7-trinitrofluorenone complex,[11] mp 213–215°, was prepared in and recrystallized from benzene.

Anal. Calcd for $C_{32}H_{18}BrN_3O_7$: C, 60.4; H, 2.8; N, 6.6. Found (b): C, 60.3; H, 2.8; N, 6.8.

o-(**5-Chloro-1-naphthoyl**)**benzoic Acid** (**Vb**).—The filtered Grignard reagent prepared in 64% yield from 24.1 g of 1-bromo-5-chloronaphthalene[12] in ether–benzene was added rapidly to a warm solution of 9.3 g of phthalic anhydride in 250 ml of benzene. A conventional work-up yielded 14.2 g (45%) of Vb as colorless crystals, mp 183–184°.[13] Lower yields (25, 33%, respectively) were obtained when the Grignard reagent was prepared by Pearson's technique (use of 1 equiv of ethylene dibromide)[14] or when the reaction was carried out in THF.

o-(**5-Chloro-1-naphthylmethyl**)**benzoic Acid** (**VIb**).—A stirred mixture of 28 g of zinc powder, 14.2 g of Vb, and 500 ml of 90% formic acid was heated at reflux for 18 hr. After the usual work-up 10.3 g (74%) of VIb was obtained as colorless crystals, mp 180–182°, after recrystallization from benzene.

Anal. Calcd for $C_{18}H_{13}ClO_2$: C, 72.9; H, 4.4; Cl, 12.0. Found (a): C, 73.3; H, 4.3; Cl, 11.7.

3-(5-Chloro-1-naphthyl)phthalide.—In one run similar to the above except that 99% formic acid was used, a 64% yield of the phthalide, mp 177–179°, was obtained from the neutral fraction and only a 13% yield of VIb.

Anal. Calcd for $C_{18}H_{11}ClO_2$: C, 73.4; H, 3.8; Cl, 12.0. Found (a): C, 73.8; H, 4.0; Cl, 11.8.

o-(**5-Chloro-1-naphthylmethyl**)**acetophenone** (**VIIb**).—In the best of several experiments, 425 ml of 0.54 *M* MeLi in ether was added to a stirred solution of 33.8 g of VIb in 300 ml of benzene and 1200 ml of ether during 15 min. After a further 30 min a conventional work-up afforded 28.1 g (83%) of VIIb as a pale yellow solid, mp 55–61°, suitable for further use. The analytical sample, mp 59–61°, was obtained with little loss by crystallization from ethanol.

Anal. Calcd for $C_{16}H_{15}ClO$: C, 77.4; H, 5.1; Cl, 12.0. Found (b): C, 77.2; H, 5.2; Cl, 11.9.

4'-Chloro-10-methyl-1,2-benzanthracene (**IV**).—In the best of several experiments a mixture of 5.0 g of VIIb and 100 g of polyphosphoric acid was stirred at 135° for 2 hr. A conventional work-up afforded a solid which on recrystallization from benzene yielded 3.3 g (69%) of pure IV as pale yellow crystals, mp 165.0–166.0°.

Anal. Calcd for $C_{19}H_{13}Cl$: C, 82.5; H, 4.7; Cl, 12.8. Found (a): C, 82.7; H, 4.6; Cl, 12.8.

The 2,4,7-trinitrofluorenone complex formed a red-brown solid, mp 210° dec, from benzene.

Anal. Calcd for $C_{32}H_{18}ClN_3O_7$: C, 64.9; H, 3.1; Cl, 6.0; N, 7.1. Found (a): C, 64.8; H, 3.1; Cl, 5.9; N, 6.8.

(11) M. Orchin and E. O. Woolfolk, *J. Am. Chem. Soc.*, **68**, 1727 (1946).

(12) C. C. Price and S. Voong, *J. Org. Chem.*, **14**, 111 (1949). In one experiment, no improvement in the conversion of 1-bromo-5-aminonaphthalene to the bromochloro compound was observed when the replacement of the amino group was carried out by the method involving a $HgCl_2$ complex of the diazonium salt: H. Von Schwechten, *Ber.*, **65**, 1605 (1932); M. S. Newman and P. H. Wise, *J. Am. Chem. Soc.*, **63**, 2847 (1941).

(13) Reference 6a reports the melting point as 179–180°.

(14) D. E. Pearson, D. Cowan, and J. D. Beckler, *ibid.*, **24**, 504 (1959).

Metabolism of 2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone

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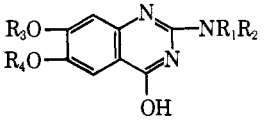
Received February 25, 1967

2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone[1] (**1**) elicits a hypotensive response when administered to humans or animals. To complement pharmacological experiments a limited study of the metabolism of this compound was undertaken.

The strong fluorescence of the compound facilitated the development of an assay for drug in plasma. In aqueous acid **1** exhibits fluorescent maxima at 405 and 445 mμ when activated at 330 mμ. Related com-



1, $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = CH_3$
2, $R_1 = H$; $R_2 = C_2H_5$; $R_3 = R_4 = CH_3$
3, $R_1 = R_2 = H$; $R_3 = R_4 = CH_3$
4, $R_1 = R_2 = C_2H_5$; $R_3 = H$; $R_4 = CH_3$
5, $R_1 = R_2 = C_2H_5$; $R_3 = CH_3$; $R_4 = H$
6, $R_1 = H$; $R_2 = C_2H_5$; (R_3, R_4) = (H, CH_3)
7, $R_1 = R_2 = C_2H_5$; $R_3 = R_4 = H$

(1) H.-J. Hess, T. H. Cronin, and A. Scriabine, submitted for publication; H.-J. Hess and G. F. Holland, Belgian Patent 678,216 (Sept 22, 1966).