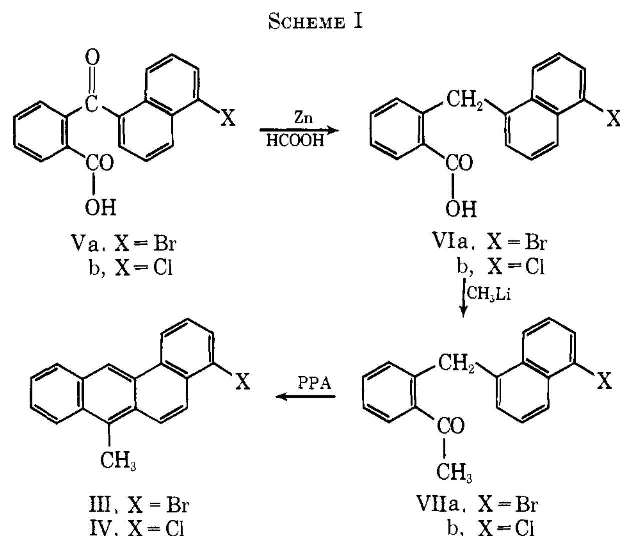
SCHEME I



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 $C_{15}H_{13}BrO_2$: 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 $C_{19}H_{15}ClO$: 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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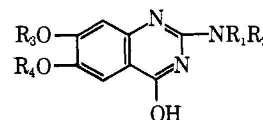
2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone[1] (**1**) elicits a hypotensive response when administered to humans or animals. To complement pharmacological experiments a limited study of the metabolism of this compound was undertaken.

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).

pounds differed in their fluorescence spectra. When activated at 330 mμ, the N-monoethyl derivative[1] **2** showed a fluorescence maximum at 405 mμ, compound[1] **3** at 390 mμ, derivative **4** at 415 and 455 mμ, and the 6,7-dihydroxy derivative[1] **7** at 410 mμ.

Oral administration of 10 mg/kg (capsules) to four dogs[2] yielded peak plasma concentrations[3] within 0.5–2 hr of about 4 μg/ml. These concentrations decreased with rapid but variable rates with a half-life approximating 1 hr. Blood pressure determinations suggested that a drug plasma concentration of about 0.3 μg/ml had to be reached before a hypotensive response could be detected. However this effect persisted even after the level had dropped below 0.3 μg/ml.

The rapid decrease of blood plasma concentration *in vivo* could be due to rapid excretion, metabolism, or deposition of drug in other body compartments. Very little unchanged drug was found in urine. To distinguish between rapid metabolism and deposition of drug in tissues, five rats were dosed intravenously with **1**. After certain time intervals the animals were sacrificed, plasma was collected, and the total carcasses were homogenized and assayed for total body contents of drug (Table I). Although drug disappeared from the total bodies somewhat more slowly than from plasma, the decrease of drug plasma concentrations seemed to be mainly due to metabolic degradation rather than deposition of drug in other body compartments.

TABLE I

DRUG CONCENTRATIONS IN PLASMA AND TOTAL DRUG IN CARCASSES OF RATS (140 G) AFTER 1.4 mg iv

Rat	Time, hr	Drug plasma concn, μg/ml	Total drug found in carcasses, μg
1	1	5.6	360
2	1	3.3	219
4	2	0.9	107
5	4	0.21	93.3
6	4	0.10	59.5

2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone (**1**) was administered orally to humans in two dosage forms. Peak drug plasma concentrations were obtained with capsules after about 2 hr, but with a syrup within 0.5–1 hr. Maximum blood concentrations again were very variable. The highest found was 2 μg/ml after a dose of 300 mg of syrup. Drug plasma half-life was shorter than had been found in dogs, approximating 0.5 hr or even less. As had been the case in the dog studies, it appeared that drug plasma concentration in humans generally also had to reach about 0.3 μg/ml before a decrease in blood pressure occurred.

The search for drug metabolites in human urine yielded five derivatives, **2–6**, besides the parent drug. The sum of these metabolites found in a 24-hr urine sample was estimated to constitute less than 10% of the administered dose.

Metabolite **2** was the only drug derivative found after *in vitro* experiments with rat liver homogenates.

(2) This experiment was carried out in collaboration with Dr. A. Scriabine.

(3) The canine plasma protein binding of the drug (**1**) as determined with Toribara tubes (T. Y. Toribara, *Anal. Chem.*, **25**, 1286 (1953)) was found to be 61% at a concentration of 2 μg/ml.

Experimental Section

Assay of 2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone (1).—Plasma (10 ml) was adjusted to pH 9.5–10 by addition of aqueous NaOH and extracted three times with benzene (15 ml each). The benzene solution was concentrated to 5 ml and extracted twice with 0.1 *N* HCl (4 ml each). The aqueous extract was diluted to 10 ml for fluorometry (Aminco-Bowman). This assay was capable of detecting 0.03 μg of drug/ml of plasma and responded linearly to concentrations between 0.03 and 3 μg/ml. The fluorescence of extracts of plasma from medicated animals was that of unchanged drug.

Carcasses were homogenized with 0.1 *N* HCl (300 ml) in a Waring Blendor. The homogenate was centrifuged, the supernatant was collected, and the residue was rehomogenized with 0.1 *N* HCl (300 ml). After centrifugation, the combined supernatants were adjusted to pH 10 with 30% NaOH and the drug was extracted similarly to the procedures described above.

Identification of Metabolites.—Isolation and purification of metabolites followed conventional routes of extraction and thin layer chromatography (tlc). The tlc systems employed silica gel HF and solvent mixtures of either benzene-acetone-acetic acid (10:10:1) or ethyl acetate-diethylamine (19:1).

Metabolite **2** was identified by comparison of its tlc mobilities, fluorescence, and ultraviolet curves with those of an authentic sample.[1] Metabolite **3** was identical with an authentic sample[1] by the same criterion as well as by its infrared absorption spectrum. Metabolite **4** had the same tlc mobility as a monodemethyl derivative of **1** obtained by treatment of **1** with hydrobromic acid. Metabolite **5** appeared to be an isomer of **4** and was converted to drug (tlc) by treatment with diazomethane. The structure **6** is tentative since a conversion of **6** to **2** with diazomethane was not proven unambiguously.

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Carboranes. III. Boron-Containing Acridines[1]

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In a continuation of work designed to synthesize biologically active carboranes[3] and to incorporate a carrier into a carborane molecule which would promote its localization into tumors for neutron-capture therapy, acridines have been considered. As a basis for this work certain acridines have selectively localized in tumor nuclei under *in vivo* conditions[4] intercalcating with the nucleic acids[5] and recently nitrogen mustard containing acridines have shown high antitumor activity.[6] Boron was first incorporated into an acridine

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(2) Supported in part by National Institutes of Health, Division of Environmental Sciences, U. S. Public Health Service Environmental Health Training Grant No. 2TIES 1306.

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