literature are somewhat divergent (Vesely,[5] Colerdi and Moe,[6] Hodgson and Leigh[7]) we synthesized this compound from β-naphthylamine following for the Sandmeyer step the directions of Hodgson and Walker.[8] The 2-chloro-1-nitronaphthalene so obtained had a melting point of 99–99.5°. The mixed melting point with the sample obtained by the decarboxylation of the 6-chloro-nitro-1-naphthoic acid was 98.5–99°. Accordingly our nitro product must be 6-chloro-5-nitro-1-naphthoic acid.

Nitration of Methyl 6-Chloro-1-naphthoate.—A 9.0-g. sample (0.041 mole) of pure methyl 6-chloro-1-naphthoate (m. p. 66°) was treated with 15 cc. of fuming nitric acid (d. 1.49–1.50) and warmed for five minutes on a water-bath. After cooling, a crystalline mass deposited which was collected on a glass filter and washed with a small portion of cold nitromethane. The crystal mass was already almost white, and after one recrystallization from aqueous methanol, pure methyl 6-chloro-5-nitro-1-naphthoate was obtained: yield, 3.3 g. (30%), m. p. 143.5–144°.

Anal. Calcd. for $C_{12}H_8O_4NCl$: C, 54.23; H, 3.03; N, 5.27; Cl, 13.36. Found: C, 54.52; H, 3.23; N, 5.07; Cl, 13.34.

Hydrolysis of the Nitro Ester.—A solution of 0.5 g. of the ester was refluxed in 30 cc. of 20% aqueous potassium hydroxide, to which 4 g. of salt was added. The substance dissolved after one-half hour of vigorous boiling. In acidification, a dark brown precipitate was obtained. This was filtered and twice recrystallized from nitromethane. Greenish-yellow crystals were obtained which melted at 226.5°. A mixed melting point with 6-chloro-5-nitro-1-naphthoic acid above gave 226–226.5°, showing the identity of the two compounds.

Anilide from the Nitro Acid.—A mixture of 0.2 g. of 6-chloro-5-nitro-1-naphthoic acid and 0.5 cc. of thionyl chloride was refluxed for one-half hour. The reaction mixture was treated with 1 cc. of redistilled aniline and dissolved in 15 cc. of benzene. The yellow suspension was washed with water, with dilute hydrochloric acid, with water and with sodium carbonate solution. After evaporation of the benzene, the residue was recrystallized from aqueous ethanol, using charcoal. The slightly greenish crystalline substance had a melting point of 193–193.5°.

Anal. Calcd. for $C_{17}H_{11}O_3N_2Cl$: C, 62.46; H, 3.40; N, 8.57; Cl, 10.85. Found: C, 62.71; H, 3.30; N, 8.68; Cl, 11.10.

Anilide from the Nitro Ester.—(a) A 0.28-g. sample of the ester was treated with three to four-fold excess of anilinomagnesium bromide for ten minutes on the water-bath. (The anilinomagnesium bromide was prepared by addition of 8 g. of aniline to ethylmagnesium bromide, prepared from 2 g. of magnesium and 10 g. of ethyl bromide in 60 cc. of ether, until the very vigorous evolution of ethane ceased.) Ten cc. of dilute hydrochloric acid was added to the mixture and the ether evaporated at room temperature. The dark brown solid residue from the ether layer was separated from the acidic solution by filtration, and it was recrystallized from aqueous ethanol, yielding 0.12 g. of anilide (34%), m. p. 190–191°. This was recrystallized twice (first with charcoal) to give almost colorless crystals, m. p. 193.5–194°, identical with the anilide obtained from the acid.

(b) When 0.3 g. of the ester was heated with 0.2 g. of aniline at 160–170° for twenty minutes, the ester was recovered unchanged, m. p. 143.5–144°.

Amide from the Nitro Acid.—A 0.22-g. sample of 6-chloro-5-nitro-1-naphthoic acid was heated with 1 cc. of thionyl chloride for twenty minutes. The mixture was poured into 10 cc. of ice-cooled 33% ammonium hydroxide. It was cautiously heated on the water-bath for five minutes, then cooled, filtered and recrystallized from aqueous ethanol, m. p. 207–208°.

(5) Vesely, *Ber.*, **38**, 137 (1905).
(6) Colerdi and Moe, *Rend. Int. Lomb.*, **57**, 646 (1924).
(7) Hodgson and Leigh, *J. Chem. Soc.*, 1352 (1937).
(8) Hodgson and Walker, *ibid.*, 1621 (1933).

Anal. Calcd. for $C_{11}H_7O_3N_2Cl$: N, 11.17. Found: N, 10.70.

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RECEIVED JANUARY 5, 1948

9,9-Dibromofluorene and Formation of a Dangerous Skin Irritant

BY JOHN R. SAMPEY AND SCOTT J. CHILDRESS

The preparation of 9-bromofluorene by direct photobromination[1] suggested the preparation of 9,9-dibromofluorene by the addition of a second mole of bromine under strong irradiation.

A solution of 16 g. of fluorene in 150 ml. of carbon tetrachloride was placed in a 250 ml. Vitreosil Erlenmeyer flask equipped with reflux condenser. By the use of a six-inch mercury arc close to the flask, the contents were heated to reflux while a solution of 2 moles of bromine in 50 ml. more solvent was added dropwise through the condenser in thirty minutes. Anhydrous conditions were assumed by a calcium chloride tube and irradiation continued thirty minutes after the addition. Evaporation of the solvent yielded a light gray crystalline product recrystallized from acetic acid, *n*-heptane or absolute alcohol. The yield was 45% of material melting at 115° (uncor.). The literature value for 9,9-dibromofluorene is 114°.[2]

Experiments to further identify the 9,9-dibromofluorene were discontinued when two additional workers to those reported previously,[3] were stricken with a severe dermatitis which has spread over large areas of the body, and which is responding slowly to medical treatment. Intense itching, pus formation, and considerable swelling of the hands, arms and face accompany the irritation.

The authors acknowledge with pleasure the interest of Dr. E. Emmet Reid.

(1) J. R. Sampey and E. E. Reid, THIS JOURNAL, **69**, 234–235 (1947).
(2) H. Staudinger and A. Gaule, *Ber.*, **49**, 1951 (1916).
(3) J. R. Sampey, A. B. King, T. A. Roe, Jr., and S. J. Childress, *Science*, **105**, 621 (1947).

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RECEIVED JULY 21, 1947

Nuclear Substituted 9-(4′-Diethylamino-1′-methylbutylamino)-acridines[1]

BY E. R. SHEPARD AND H. A. SHONLE[2]

At the suggestion of the Committee on Medical Research of the OSRD several years ago, the preparation of a series of nuclear substituted acridines was undertaken. They were prepared in order to study clinically the absorption, excretion and metabolic changes which these materials undergo. In addition, it was of interest to inquire further

(1) Presented before the Division of Medicinal Chemistry at the 109th meeting of the American Chemical Society, Atlantic City, New Jersey, April, 1946.
(2) Deceased, February 24, 1947.

into the relationship of structure and antimalarial activity of the acridines.[3]

The following conclusions can be drawn on the basis of duckling tests[4] on the compounds reported here: (a) A substituent in the 1 position (Fig. 1) appears to be mildly dystherapeutic:

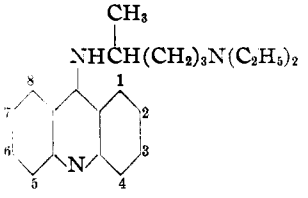

Fig. 1.

(b) One substituent in the 4 or 5 position gives a regular dystherapeutic effect. Since completion of this work, these findings have been supported by Hall and Turner[5] with the amendment that upon substitution in both the 4 and 5 positions, increased activity may be expected.

Experimental

The *o*-chloro-, *o*-bromo and 2,4-dichlorobenzoic acids were obtained commercially. The *o*-chlorobenzoic acid was purified[6] before use.

The anilines with the exception of 2-chloro-4-methoxy and 3,5-dichloroaniline were commercial samples which were distilled or crystallized.

3,5-Dichloroaniline was prepared from 2,6-dichloro-4-nitroaniline by deamination and reduction of the resulting 3,5-dichloronitrobenzene.[7]

2-Chloro-4-methoxyaniline was prepared quite readily in large quantities from technical *p*-anisidine.[8] Phosgene passed into an aqueous solution of pyridine and technical *p*-anisidine gave an 82% yield of N,N'-di-(*p*-methoxy)-phenylurea which was dried and chlorinated in *sym*-tetrachloroethane to give a quantitative yield of the dichlorinated urea. Treatment with 28% ammonium hydroxide at 150–160° for five hours gave a 90–95% yield of 2-chloro-4-methoxyaniline, b. p. 141–144° (25 mm.); N-acetyl derivative, m. p. 113–114.5° (lit.,[8] m. p. 114°).

Diphenylamine-2-carboxylic Acids.—The diphenylaminecarboxylic acids were prepared according to the method of Ullmann.[9] The following more detailed description is typical of the method used for the preparation.

5-Chlorodiphenylamine-2-carboxylic Acid.[10]—One hundred grams (0.52 mole) of 2,4-dichlorobenzoic acid, 60 g. (0.64 mole) of aniline, 82 g. (0.59 mole) of potassium carbonate, 3–5 g. of copper oxide (precipitated powder), and 250 ml. of isoamyl alcohol were refluxed three hours. The hot solution was steam distilled until all of the alcohol and some basic oil came over. The hot residual solution was diluted to 3–4 liters with hot water and decolorized with carbon. The filtrate was acidified with dilute hydrochloric acid, and filtered. The yield was 103–115 g. of crude 5-chlorodiphenylamine-2-carboxylic acid. Since purification was not necessary at this step and would diminish over-all yields, no attempt was made to isolate the pure amino acids.

(3) Corse, Shonle and Bryant, THIS JOURNAL, **68**, 1905, 1911 (1946), reported previous series in which the nucleus was held constant and the side chain was varied.

(4) Performed by K. K. Chen, C. L. Rose and R. C. Anderson of these laboratories, using *Plasmodium Lophurae*.

(5) Hall and Turner, *J. Chem. Soc.*, 694 (1945).

(6) "Organic Syntheses," Coll. Vol. II, p. 16, (1943).

(7) Kremer and Bendich, THIS JOURNAL, **61**, 2659 (1939).

(8) French Patent 738,157.

(9) Ullmann, *Ann.*, **355**, 312 (1907).

(10) Ullmann and Wagner, *ibid.*, **355**, 359 (1907).

The crude amino acids were ring closed to the corresponding 9-chloroacridines[11] and these then reacted with excess 5-diethylamino-2-aminopentane in phenol at 100–110° for one to two hours. The reaction mixtures were decomposed with excess sodium hydroxide solution and extracted with ether. The ether layers were washed and extracted with 5% acetic acid. The bases were liberated from the acetate solutions with sodium hydroxide, taken up in ether and heated eventually at 100° at 15 mm. to remove excess 5-diethylamino-2-aminopentane. Dry hydrogen chloride passed into the solutions of the bases in dry ether gave the anhydrous hydrochlorides which were extremely hygroscopic. The melting points of the anhydrous salts varied widely with slight changes in hydrogen chloride content and were therefore meaningless. Table I lists the acridines prepared in this manner.

TABLE I

9-(4'-DIETHYLAMINO-1'-METHYBUTYLAMINO)-ACRIDINES

Substituents (Fig. 1)	Yield, %[a]	Formula	Nitrogen, % Calcd.	Found[b]
None	71[c]	$C_{22}H_{29}N_3 \cdot 2HCl$	10.29	9.60
2-Cl[d]	34	$C_{22}H_{28}ClN_3 \cdot 2HCl$	9.49	9.68
3-Cl[e]	29	$C_{22}H_{28}ClN_3 \cdot 2HCl$	9.49	9.23
4-Cl	24	$C_{22}H_{28}ClN_3 \cdot 2HCl$	9.49	9.69
4-CH_3	37	$C_{23}H_{31}N_3 \cdot 2HCl$	9.95	9.85
4-OCH_3	15	$C_{23}H_{31}N_3O \cdot HCl$	10.48	10.44
1,3-diCl[g]	7[f]	$C_{22}H_{27}Cl_2N_3 \cdot 2HCl \cdot H_2O$	8.48	8.50
2-OCH_3-4-Cl	30[f]	$C_{23}H_{30}ClN_3O \cdot 2HCl$	8.88	8.81
4-OCH_3-6-Cl	59	$C_{23}H_{30}ClN_3O \cdot 2HCl$	8.88	8.43
4-OCH_3-1-CH_3	38	$C_{24}H_{33}N_3O \cdot HCl$	10.10	9.95
2-Cl-4-CH_3	17[f]	$C_{23}H_{30}ClN_3 \cdot 2HCl$	9.20	8.42
3-Cl-4-CH_3	23[f]	$C_{23}H_{30}ClN_3 \cdot 2HCl$	9.20	8.43
2-Br-4-CH_3	11	$C_{24}H_{30}BrN_3 \cdot 2HCl$	8.38	8.16
2-CH_3O-4,6-diCl	29	$C_{24}H_{29}Cl_2N_3O \cdot 2HCl$	8.28	8.21
4-CH_3-3,6-diCl	15	$C_{23}H_{29}Cl_2N_3 \cdot 2HCl$	8.56	8.59
2,4,6-triCl[h]	2	$C_{22}H_{26}Cl_3N \cdot 2HCl \cdot H_2O$	7.94	7.95

[a] Based on 2-chloro or 2,4-dichlorobenzoic acid unless otherwise noted. [b] The samples were dried *in vacuo* for two weeks over potassium hydroxide before analysis. [c] Based on 9-chloroacridine. [d] Previously reported, U. S. Patent 2,077,249. [e] Previously reported, German Patent 571,449. [f] Based on 2-bromobenzoic acid. [g] Recrystallized from ethanol–water–ether, m. p. 138–142°. [h] Recrystallized from ethanol–water–ether, m. p. 158–161°.

(11) "Organic Syntheses," **22**, 5 (1942).

LILLY RESEARCH LABORATORIES
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Ethyl Acetoacetate 4-Nitrophenylhydrazone and 1-(4'-Nitrophenyl)-3-methylpyrazolone-5

BY WARD C. SUMPTER AND PHIL H. WILKEN

The interaction of equimolecular proportions of ethyl acetoacetate and 4-nitrophenylhydrazine at steam-bath temperature in either the presence or absence of ethanol as a solvent yields ethyl acetoacetate 4-nitrophenylhydrazone (I), m. p. 118°, and not 1-(4'-nitrophenyl)-3-methylpyrazolone-5 (II), m. p. 218°, as stated in the literature.[1]

The nitrophenylhydrazone (I) was converted into the pyrazolone (II) by refluxing a solution of I in glacial acetic acid for five hours at steam-bath temperature. Heating I at steam-bath temperature for fifteen minutes with concentrated hydrochloric acid accomplished the same transformation. Similarly II was obtained when ethyl ace-

(1) Altschul, *Ber.*, **25**, 1853 (1892), via Huntress-Mulliken, "Identification of Pure Organic Compounds, Order 1," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 255.