yielded an orange colored oil. A sample of the oil was distilled at 154°/1 mm. to yield compound no. 13b.

Supporting evidence for structure 13a. A 0.003-mole sample of 13a was dissolved in one equivalent of 0.1 *N* hydrochloric acid. After 30 min. bubbles appeared and the solution began to decolorize. After 2 hr. the colorless solution deposited 2-acetylpyrrol, m.p. 91–92°, in quantitative yield.

RESEARCH DIVISION
THE UPJOHN CO.
KALAMAZOO, MICH.

Halogenated Aminobenzaldehydes and Aminostyrylquinolines[1]

CARL TABB BAHNER, WILLIAM CHAPMAN, CLARENCE COOK, OAKLEY CRAWFORD, CHARLES HANNAN, NORVELL HUNT, LYDIA M. RIVES, WARREN YEE, AND WILLIAM EASLEY

Received April 11, 1960

4-(4′-Dimethylaminostyryl)quinolines bearing a halogen atom on the benzene ring of the quinoline portion of the molecule have been prepared from halogen substituted anilines.[2] Additional halogenated styrylquinolines listed in Table I have been prepared, for testing against animal tumors at the Chester Beatty Research Institute. The presence of a bromine atom usually seems to make the compounds less toxic and less active against tumors. Chloride atoms have similar but smaller effect and fluorine atoms have even less effect, but even a fluorine atom in the 2′ position reduces biological activity sharply. The ratio of maximum tolerated dose to minimum effective dose is not necessarily greatest in the most potent compounds and the position of the halogen atom makes a great deal of difference.

EXPERIMENTAL

The 2-chloro-, 2-fluoro-, 3-fluoro-, and 2,5-difluorobenzaldehydes were prepared from the corresponding halodimethylanilines by the method of Campaigne and Archer.[3] 3-Bromo- and 3-chloro-4-dimethylaminobenzaldehyde were prepared by halogenation of 4-dimethylaminobenzaldehyde.[4] Attempts to prepare 3,5-dibromo- and 3-chloro-5-bromodimethylaminobenzaldehyde by treatment of the monohalo compounds with bromine in glacial acetic acid produced crystalline products which seemed to be perbromide hydrobromides of the monohalo compounds. Heating these crystals 3 hr. at 110–130° formed crystalline substances whose composition corresponded to 3,5-dibromo-4-aminobenzaldehyde and 3-chloro-5-bromo-4-aminobenzaldehyde. The loss of the alkyl groups from the dialkylamino group was less surprising in view of Fries[5] report that 2,4,6-tribromo-*N*,*N*-dimethylaniline perbromide hydrobromide on treatment with water in glacial acetic acid formed 2,4,6-tribromo-*N*-monomethylaniline. Molecular models indicate that the crowding of large groups at the amino end of the molecule would produce severe strain, and that even a single bromine or chlorine atom adjacent to the dimethylamino group would cause some strain. It is interesting to note that, although a halogen atom on the benzene ring in the quinoline portion of the styrylquinolines tends to raise the melting point, 4-(4-dimethylamino-3-bromostyryl)quinoline, 4-(4-dimethylamino-3-chlorostyryl)quinoline, and 4-(4-dimethylamino-3-fluorostyryl)quinoline melt approximately 25°, 40°, and 50° lower, respectively, then the unhalogenated parent compound.

3-Bromo- and 3-chlorolepidine, obtained in poor yield by the method of Ellinger,[6] formed styryl derivatives without undue difficulty. In a modification of the Leese method, the picrate was used instead of the hydrochloride, keeping in mind the possible explosive character of the picrate. Numerous efforts to condense 2-chlorolepidine with 4-dimethylaminobenzaldehyde failed, but this base did condense with 4-nitrobenzaldehyde and the resulting nitrocompound was reduced by stannous chloride to 4-(4-aminostyryl)-2-chloroquinoline. 6-Fluorolepidine, b.p. 135° (23 mm.), was prepared from 4-fluoroaniline by William K. Easley, L. Free, and Frank Howell at East Tennessee State College using the method of Campbell and Schaffner.[7] 6-Fluoroquinaldine, m.p. 49.5–51° was provided by Dr. W. F. Little and Mr. Clarence Cook, of the University of North Carolina.

3-Bromo-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared by adding 171 g. (1.07 moles) of bromine in 100 ml. of glacial acetic acid dropwise, with stirring, during 15 min., to 75 g. of 4-dimethylaminobenzaldehyde in 240 ml. of glacial acetic acid, then continuing to stir 45 min. while cooling with an ice bath. The orange crystals were washed well with benzene and dried overnight over sodium hydroxide; yield 216 g., m.p. 128.5–129.3°.

Anal. Calcd. for $C_9H_{10}NOBr.HBr.Br_2$: Oxidizing bromine 34.1%; total bromine 68.18%. Found: Oxidizing bromine 34.19, 34.01; total bromine 68.1, 68.3.[8]

3,5-Dibromo-4-aminobenzaldehyde was prepared by heating 67 g. of the above perbromide 3 hr. at 110–130°. The remaining porous mass was recrystallized from ethanol, from isohexane, and again from ethanol; yield 9.0 g., m.p. 149.5–150.8°; after sublimation m.p. 151.7–152.7°.[10]

Anal. Calcd. for $C_7H_5Br_2NO$: C, 30.14; H, 1.81. Found: C, 30.83; H, 2.10, 1.81.[8]

3-Chloro-4-dimethylaminobenzaldehyde perbromide hydrobromide was prepared similarly from 50 g. of 3-chloro-4-dimethylaminobenzaldehyde; yield 66.4 g., m.p. 125.4–127.1°.

Anal. Calcd. for $C_9H_{10}NOCl.HBr.Br_2$: Oxidizing bromine, 37.61; total halogen 64.84. Found: Oxidizing bromine, 36.68, 36.55; total halogen, 63.7, 63.8.[8]

3-Chloro-5-bromo-4-dimethylaminobenzaldehyde was prepared by heating 51.8 g. of the perbromide 8 hr. at 115°,

(1) The research was supported in part by grants from the American Cancer Society and the National Cancer Institute. Some of the compounds described were prepared in the laboratories of the Chester Beatty Research Institute. A portion of this paper was presented at the Southeastern Regional Meeting, ACS, at Raleigh, N. C., in November 1957.

(2) C. T. Bahner, C. Cook, J. Dale, J. Fain, E. Franklin, J. C. Goan, W. Stump, and J. Wilson, *J. Org. Chem.*, **22**, 682 (1956).

(3) E. Campaigne and W. L. Archer, *Organic Syntheses*, **33**, 27 (1953).

(4) D. L. Brady and R. Truskowski, *J. Chem. Soc.*, 2434 (1923).

(5) K. Fries, *Ann.*, **346**, 193 (1906).

(6) A. Ellinger, *Ber.*, **39**, 2515–2522 (1906).

(7) K. N. Campbell and J. Schaffner, *J. Am. Chem. Soc.*, **67**, 86 (1945).

(8) Analyses by Weiler and Strauss.

(9) C. T. Bahner, C. Cook, J. Dale, J. Fain, F. Hannan, P. Smith, and J. Wilson, *J. Org. Chem.*, **23**, 1060 (1958).

(10) J. J. Blanksma, *Centr.*, **1910**, I, 260 (1910).

TABLE I

HALOGEN SUBSTITUTED STYRYLQUINOLINES

Compound	M.P.	Reaction Method	Reaction Temp.	Reaction Time	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
4-(4-Dimethylaminostyryl)quinolines												
2′-Chloro[f]	159.4–160.6	Leese[g]	150–170	10 min.		$C_{19}H_{17}N_2Cl$	73.90	5.55		73.55	5.50	9.4[b]
										73.62	5.47	9.5
2′-Fluoro	126.3–127.5	Leese	150–160	1 hr.	22.8	$C_{19}H_{17}N_2F$	78.04	5.86		73.29	5.71[a]	
										78.29	5.81	
3′-Bromo	117.4–119.1	Fain[2]	119–120	20 hr.	34	$C_{19}H_{17}N_2Br$	64.56	4.83		64.72	4.83[a]	
										64.80	4.79	
3′-Chloro	103.5–104.6	Fain	115–120	23 hr.	13	$C_{19}H_{17}N_2Cl$	73.90	5.55		73.94	5.61[a]	
										73.73	5.65	
3′-Fluoro	92.1–93.1	Leese	150–160	1 hr.	14	$C_{19}H_{17}N_2F$	78.04	5.86		77.78	6.02[a]	
										78.06	5.82	
2′,5′-Difluoro	107.8–108.5	Leese	150–160	1 hr.	23.5	$C_{19}H_{16}N_2F_2$	73.53	5.20		73.50	5.09[a]	
										73.65	5.12	
3-Bromo	193–194.5	Picrate	95–100	2 hr.		$C_{19}H_{17}BrN_2$	64.56	4.83	7.91	64.59	4.85	7.93[c]
3-Chloro	165.9–167.2	Leese	150	25 min.	23	$C_{19}H_{17}ClN_2$	73.90	5.55	9.07	73.95	5.52	9.10[c]
6-Fluoro	159–160.5	Leese	150–154	1 hr.	9.45	$C_{19}H_{17}N_2F$	78.03	5.86		77.81	5.76[a]	
										77.73	5.77	
2-(4-Dimethylaminostyryl)quinolines												
6-Fluoro	195–196	Leese	155–160	1 hr.	25.2	$C_{19}H_{17}N_2F$	78.04	5.86		77.73	5.68[a]	
										77.85	5.90	
4-(4-Nitrostyryl)quinoline												
2-Chloro	240–241	Leese	130	3 hr.	38.3	$C_{17}H_{11}N_2ClO_2$	65.70	3.57		65.53	3.61[a]	
										65.80	3.77	
4-(4-Aminostyryl)quinoline												
3′,5′-Dibromo	222.5–224.0	Leese	145–150	2 hr.		$C_{17}H_{12}N_2Br_2$	50.52	2.99		50.50	2.98[d]	
										50.39	2.84	
2-Chloro	203–204	$SnCl_2$[e]			9.4	$C_{17}H_{13}N_2Cl$	72.71	4.67		72.43	4.60[a]	
										72.47	4.75	

[a] Analysis by Galbraith. [b] Analysis by Weiler and Strauss. [c] Analysis by Burroughs Wellcome. [d] Calcd. Br 39.6. Found: Br 39.6, 39.2 (analysis by Weiler & Strauss). [e] Reacted in concd. hydrochloric acid at room temperature, then heated at 80–90°, 1 hr. [f] Numbers having a prime refer to positions on the styryl portion of the molecule.

TABLE II

FLUOROALDEHYDES

Name	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
4-Dimethylamino-2-fluorobenzaldehyde	62.9–64.5°	74.3	$C_9H_{10}FNO$	64.66	6.03	64.31	5.83[a]
						64.46	5.83
4-Dimethylamino-2,5-difluorobenzaldehyde	60.8–62.0°	17.3	$C_9H_9F_2NO$	58.37	4.90	58.43	5.00[a]
						58.45	5.20

[a] Analysis by Weiler and Strauss.

recrystallizing the residue repeatedly from ethanol, and subliming in vacuum, m.p. 145.7–147.0°.

Anal. Calcd. for $C_7H_5BrClNO$: C, 35.85; H, 2.15. Found: C, 35.63, 35.48; H, 2.23, 2.33.[8]

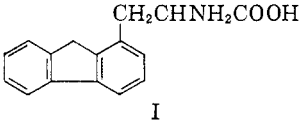
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

Synthesis of *dl*-β-(1-Fluorenyl)alanine

D. C. MORRISON

Received January 26, 1960

In continuation of work begun with the synthesis of *dl*-β-(2-fluorenyl)alanine[1] the corresponding 1-fluorenyl isomer has been prepared. The substance I may be of interest in cancer chemotherapy and as an aromatic amino acid.



I

It was obtained from fluorene-1-carboxylic acid[2] II as starting material by a route similar to that used for the 2-isomer. Reduction of the 1-methyl ester by lithium aluminum hydride gave the 1-carbinol[3] III, which was converted to the corresponding bromide[3] with phosphorus tribromide. The bromide was employed to alkylate the sodium derivative of diethyl acetamidomalonate, and the intermediate ester was hydrolyzed by hydrochloric acid to the amino acid hydrochloride. This salt, when dissolved in dilute alkali and acidified with acetic acid gave the free amino acid. The hydrochloride serves to characterize the compound.

The amino acid was a very sparingly soluble crystalline powder, similar in most physical properties to the 2-isomer. The melting point and that of the hydrochloride were not very sharp as is usually observed with this type of compound.

The infrared spectrum of the free amino acid in a potassium bromide disk showed a wide multicomponent band between 3100–2900 cm.$^{-1}$, probably due to C—H stretching and NH_3^+ stretching. A series of peaks at 1640 (sh), 1613, 1584, 1486, and 1410 cm.$^{-1}$ may be ascribed to C=C stretching, NH_3^+ deformation, and carboxylate ion vibrations but single assignments would be difficult. A very strong band at 759 cm.$^{-1}$ is attributable to C—H out of plane bending.

(1) D. C. Morrison, *J. Org. Chem.*, **24**, 463 (1959).
(2) D. C. Morrison, *J. Org. Chem.*, **23**, 1772 (1958).
(3) L. A. Pinck and G. E. Hilbert, *J. Am. Chem. Soc.*, **68**, 752 (1946).

EXPERIMENTAL

Melting points are uncorrected and were taken on a Fisher-Johns block.

1-Hydroxymethylfluorene. Methyl fluorene-1-carboxylate was prepared by conventional esterification with methanol and sulfuric acid. It was distilled from a small still at 1 mm. pressure and recrystallized from acetone-water. The greater solubility of the ester in organic solvents was an advantage over use of the free acid in reductions. The methyl ester (8.4 g. or 0.038 mole) was treated with lithium aluminum hydride as described for the 2-isomer[1] and gave a nearly theoretical yield (7.4 g.) of crude fluorenyl-carbinol. This melted at 137–146°, and after several recrystallizations from ether–petroleum ether (b.p. 30–60°) had a melting point of 146.5–147.5°. Pinck and Hilbert[3] give 148° corr. The carbinol could also be distilled at 1 mm. to aid in its purification.

1-Bromomethylfluorene. This was prepared by a process similar to that used for the 2-isomer[1] and was obtained in nearly theoretical yield. If insufficient phosphorus tribromide is used, some starting material may be recovered unchanged. The crude product melted at 97–102° and when recrystallized from ether and petroleum ether, this was raised to 100–101.5° with previous sintering; lit.[3] m.p. 104° corr.

Diethyl (1-fluorenylmethyl)acetamidomalonate. A solution of 0.92 g. (0.04 mole) of sodium in absolute ethyl alcohol was treated with 8.7 g. (0.04 mole) of diethyl acetamidomalonate and warmed for solution. Now 10.4 g. (0.04 mole) of the bromide (m.p. 97–102°) was added and the mixture refluxed 16 hr. If variations from the theoretical amounts are used, the product cannot be purified easily. Most of the ethanol was distilled and 3 ml. of acetic acid and an excess of water were added. After leaving overnight on ice, the solid product was filtered, washed with water, and dried. It weighed 15 g. or 94.9%. The ester could be recrystallized from aqueous acetone with difficulty. Slow crystallizations from clear solutions, taking center fractions, were carried out twelve times to obtain a pure product. This was a cream-white powder, m.p. 120–121°.

Anal. Calcd. for $C_{23}H_{25}NO_5$: C, 69.87; H, 6.33. Found: C, 69.91; H, 6.19.

DL-β-*(1-Fluorenyl)alanine hydrochloride.* A solution of 14.8 g. (0.0375 mole) of the crude ester in 150 ml. of glacial acetic acid was heated to boiling under reflux. While boiling, a mixture of 60 ml. of concd. hydrochloric acid and 10 ml. of water was added and reflux continued for 48 hr. Most of the solvent was now distilled and the residue extracted repeatedly with boiling 2*N* hydrochloric acid until nothing further was removed. The extracts were filtered at 90° or higher and the filtrates cooled to obtain the product. This was filtered and the filtrates concentrated to a small volume for a second crop. The combined weight of hydrochloride was 9.3 g. or 85.8%. The hydrochloride could be