Synthesis of Acridines from Diphenylamine-2-carboxaldehydes Prepared *via* the McFadyen-Stevens Reaction

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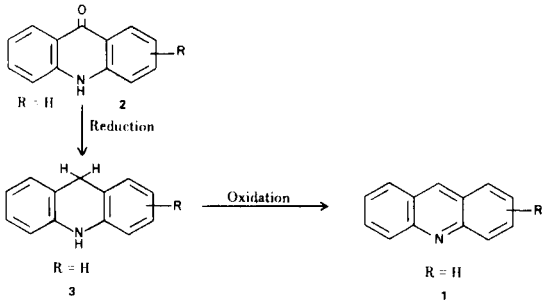
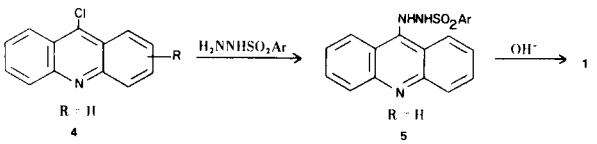
A general synthesis of acridines has been developed using diphenylamine-2-carboxaldehydes. Diphenylamine-2-carboxylic acids are converted to their *p*-toluenesulfonylhydrazides which are decomposed using a modified McFadyen-Stevens reaction to yield an aldehyde derivative which affords the acridine upon treatment with mineral acid.

Although acridine (**1**) was discovered in 1870 by Graebe and Caro (1), and many derivatives have been prepared since that time, no general synthetic method has been developed for the preparation of most acridine derivatives. The most widely used synthesis is the reduction of the appropriate acridone (**2**) to a 9,10-dihydroacridine (**3**) followed by oxidation to the acridine. This

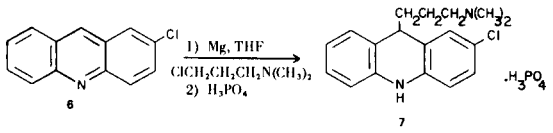


method owes its importance to the easy preparation of acridones from diphenylamine-2-carboxylic acids. Another method which has been widely used since its discovery by Albert (2) is the reduction of 9-chloroacridine (**4**) by first conversion to a 9-arylsulfonylhydrazone (**5**) followed by treatment with base. Catalytic reduction of **4** using



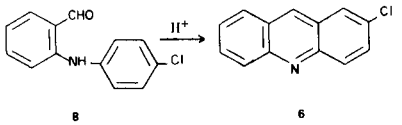
Raney nickel catalyst has also been used in some cases. Both of the above methods have undesirable features and neither has been applied on a general basis for the preparation of acridine derivatives.

Recently we required large quantities of 2-chloroacridine (**6**) as an intermediate in the synthesis of 2-



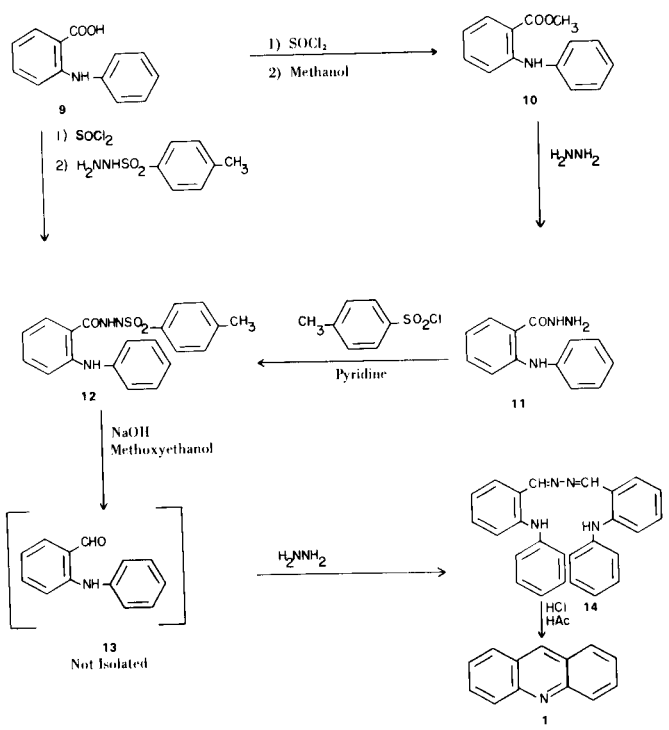
chloro-9-(3-dimethylaminopropyl)acridane, phosphate (7), SK&F 14336-D, a new antipsychotic agent (3).

There are two reported preparations of 2-chloroacridine (4,5) utilizing the above-mentioned methods, both of which proved unacceptable on a large scale because of handling problems and low yields. A synthesis based on ring closure of a diphenylamine-2-carboxaldehyde derivative (**8**) appeared to be most straightforward. However, this group of compounds was not very accessible. Albert (6) prepared diphenylamine-2-carboxaldehyde *via* the McFadyen-Stevens reaction and converted it to acridine in an overall yield of 50%. However, the method had not been extended to any other derivatives. We applied this reaction to the preparation of **6** and with some modification in the preparation and isolation of various intermediates found it to be quite satisfactory on a large scale.



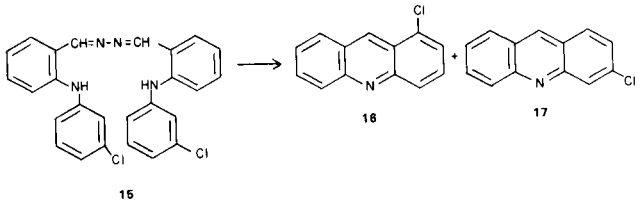
The application of this sequence was then extended to the preparation of other acridines (7,8,9). The general scheme is outlined below.

N-Phenylanthranilic acids (**9**) are well known (10). They are generally prepared from *o*-chlorobenzoic acid and the corresponding substituted aniline in an Ullman-type reaction. Unreported compounds are listed in Table I. Compounds of type **12** are generally unknown,



except the unsubstituted derivative (6) prepared *via* the ester (**10**) and hydrazide (**11**). These compounds can be conveniently prepared in high yield by first converting the acid (**9**) to its acid chloride, followed by reaction with *p*-toluenesulfonylhydrazine in a hydrocarbon solvent. In cases where the acid chloride readily cyclized to the corresponding acridone (3′-methyl, 3′-methoxy), the compounds were prepared *via* an activated ester of **9** which was converted to the hydrazide (**11**) and subsequently to **12**. These compounds are listed in Table II. Decomposition of the *p*-toluenesulfonylhydrazides was carried out in methyl or ethyl cellosolve with aqueous sodium hydroxide. The aldehydes (**13**) were low melting compounds which could be isolated and purified with some difficulty. However, a more convenient procedure which gave better yields and easier isolation was to add hydrazine to the reaction and thus when the aldehyde formed it was converted directly to the azine (**14**) which was insoluble and precipitated. The azines are listed in Table III. Other carbonyl derivatives (semicarbazones, thiosemicarbazones, phenylhydrazones, oximes) could be prepared in the same way. The azines were readily converted to the corresponding acridines by heating for a short time with concentrated hydrochloric acid in acetic acid. Yields were essentially quantitative in most cases (Table IV). Physical data for unreported compounds is given in Table V.

When 3′-substituted azines were cyclized, ring closure could occur in either the *ortho* or *para* position to give a mixture of 1- and 3-substituted acridines. Although both

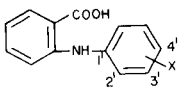


products formed (Table VI) it was not possible in some cases to isolate the minor product. It appeared that both electronic and steric factors influenced the orientation of the ring closure. When the influencing substituent was electron releasing (methoxy, methyl) the major products were 3-substituted compounds. When the substituent was electron withdrawing (nitro), the major product was 1-substitution. Halogen substituents gave slightly more 1-substituted compound, probably due to a slight deactivation effect. The trifluoromethyl compound gave more than a 2:1 ratio of 3-substitution to 1-substitution which must be due to steric factors.

Separation of 1 and 3-haloacridines was based on the difference in solubility of the respective hydrochloride salts in water. The 1-halohydrochlorides were insoluble and precipitated when the acidic reaction mixture was

Table I

N-Phenylanthranilic Acids

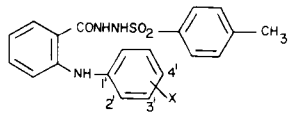


Compound No.	X	Method of Preparation	Yield %	M.p., (°C)	Empirical Formula	Analysis Percent Calcd. C	H	N	Found C	H	N
18	2′-SCH_3	A	27	179-181	$C_{14}H_{13}NO_2S$	64.93	5.05	5.40	65.05	5.07	5.37
19	2′-SO_2CH_3	C	93	230-232	$C_{14}H_{13}NO_4S$	57.72	4.50	4.81	57.56	4.63	4.71
20	4′-SO_2CH_3	C	88	187-188	$C_{14}H_{13}NO_4S$	57.72	4.50	4.81	57.85	4.51	4.77
21	4′-CF_3 (5)	B	32	179-180	$C_{14}H_{10}F_3NO_2$	59.79	3.58	4.98	60.16	3.48	4.87
22	2′-CF_3	B	67.9	207-209	$C_{14}H_{10}F_3NO_2$	59.79	3.58	4.98	59.83	3.62	4.95
23	4′-C_4H_9	A	29	152-153	$C_{17}H_{19}NO_2$	75.81	7.11	5.20	75.50	7.10	5.13

Recrystallization Solvents: benzene - **18, 21, 23**; acetone - **19**; 2-propanol - **20**; toluene - **22**.

Table II

N-Phenylanthranilic Acid, *p*-Toluenesulfonylhydrazides

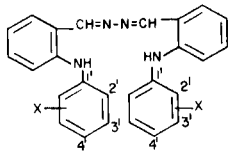


Compound No.	X	Method of Preparation	Reaction Solvent	Yield %	M.p., (°C)	Empirical Formula	Analysis Percent C	H	N	C	H	N
12	H (6)	A	Cyclohexane	91.5	187-188	$C_{20}H_{19}N_3O_3S$						
24	2'-CH_3	A	Benzene	82.5	184-185	$C_{21}H_{21}N_3O_3S$	63.78	5.35	10.63	63.87	5.68	10.46
25	3'-CH_3	B	THF-Pyridine	83	130-131	$C_{21}H_{21}N_3O_3S$	63.78	5.35	10.63	64.06	5.48	11.00
26	4'-CH_3	A	Toluene	59	190-192	$C_{21}H_{21}N_3O_3S$	63.78	5.35	10.63	63.92	5.38	10.56
27	2'-OCH_3	A	Cyclohexane	80	164-166	$C_{21}H_{21}N_3O_4S$	61.30	5.14	10.21	61.31	5.18	10.02
28	3'-OCH_3	B	THF-Pyridine	68	157-158	$C_{21}H_{21}N_3O_4S$	61.30	5.14	10.21	61.02	5.14	10.10
29	4'-OCH_3	A	Toluene	76.5	211-212	$C_{21}H_{21}N_3O_4S$	61.30	5.14	10.21	61.29	5.15	10.58
30	2'-Cl	A	Benzene	98.5	171-173	$C_{20}H_{18}ClN_3O_3S$	57.76	4.36	10.10	57.87	4.69	9.88
31	3'-Cl	A	Cyclohexane	90	159-161	$C_{20}H_{18}ClN_3O_3S$	57.76	4.36	10.10	57.91	4.51	10.00
32	4'-Cl	A	Toluene	95	219-221	$C_{20}H_{18}ClN_3O_3S$	57.76	4.36	10.10	57.80	4.36	9.97
32	4'-Cl	C	Pyridine	92.5	219-221							
33	2'-Br	A	Benzene	93	164-166	$C_{20}H_{18}BrN_3O_3S$	52.18	3.94	9.13	51.96	4.00	8.96
34	3'-Br	A	Cyclohexane	88.6	169-170	$C_{20}H_{18}BrN_3O_3S$	52.18	3.94	9.13	52.15	4.07	8.83
35	4'-Br	A	Toluene	92	220-222	$C_{20}H_{18}BrN_3O_3S$	52.18	3.94	9.13	52.17	4.10	8.85
36	2'-CF_3	A	Benzene	67.5	136-138	$C_{21}H_{18}F_3N_3O_3S$	56.12	4.04	9.34	55.96	3.98	9.20
37	3'-CF_3	A	Toluene	52.5	155-156	$C_{21}H_{18}F_3N_3O_3S$	56.12	4.04	9.34	56.09	3.89	9.10
38	4'-CF_3	A	Cyclohexane	60	190-192	$C_{21}H_{18}F_3N_3O_3S$	56.12	4.04	9.34	56.19	4.16	9.07
39	2'-NO_2	A	Thionyl Chloride-Toluene	83	178-180	$C_{20}H_{18}N_4O_5S$	56.33	4.25	13.14	56.18	4.41	13.20
40	3'-NO_2	A	Toluene	82	203-205	$C_{22}H_{18}N_4O_5S$	56.33	4.25	13.14	56.61	4.36	12.85
41	4'-NO_2	A	Toluene	96.2	220-222	$C_{20}H_{18}N_4O_5S$	56.33	4.25	13.14	56.17	4.21	13.17
42	2'-SCH_3	A	Benzene	62	155-157	$C_{21}H_{21}N_3O_3S_2$	58.99	4.95	9.83	59.09	5.05	9.96
43	4'-SCH_3	A	Benzene	74	171-173	$C_{21}H_{21}N_3O_3S_2$	58.99	4.95	9.83	58.78	4.94	9.73
44	2'-SO_2CH_3	A	Toluene	95.3	182-184	$C_{21}H_{21}N_3O_5S_2$	54.89	4.61	9.14	54.66	4.88	9.13
45	4'-SO_2CH_3	A	Benzene	93.5	169-171	$C_{21}H_{21}N_3O_5S_2$	54.89	4.61	9.14	54.97	4.69	8.83
46	2'-C_6H_5	A	Benzene	72.5	237-239	$C_{26}H_{23}N_3O_3S$	68.25	5.07	9.18	68.19	5.11	8.91
47	4'-C_4H_9	A	Benzene	82.5	151-152	$C_{24}H_{27}N_3O_3S$	65.88	6.22	9.60	65.72	6.27	9.57

Recrystallization Solvents: ethanol - **12**, **34**; ethoxyethanol - **24**, **33**, **46**; 2-propanol - **25**, **27**, **28**, **36**, **37**, **38**, **39**, **42**; acetone-water - **26**, **29**, **35**; ethanol - **30**, **32**, **41**, **44**, **47**; benzene - **31**, 1-butanol - **40**; ethoxethanol-water - **43**; acetone - **45**.

Table III

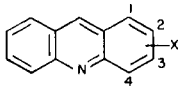
Diphenylamine-2-carboxaldehyde Azines



Compound No.	X	Yield%	M.p., (°C)	Empirical Formula	Analysis Percent Calcd. C	H	N	Found C	H	N
14	H	64	209-212	$C_{26}H_{22}N_4$	79.97	5.68	14.35	79.71	5.71	14.11
49	2'-CH_3	60	229-230	$C_{28}H_{26}N_4$	80.35	6.26	13.39	79.81	6.33	13.05
50	3'-CH_3	70	142-144	$C_{28}H_{26}N_4$	80.35	6.26	13.39	79.96	6.18	13.15
51	4'-CH_3	41.5	203-205	$C_{28}H_{26}N_4$	80.35	6.26	13.39	80.38	6.32	13.26
52	2'-OCH_3	66.5	158-160	$C_{28}H_{26}N_4O_2$	74.64	5.82	12.44	74.53	5.86	12.25
53	3'-OCH_3	80	146-148	$C_{28}H_{26}N_4O_2$	74.64	5.82	12.44	74.36	5.78	12.49
54	4'-OCH_3	50.5	230-232	$C_{28}H_{26}N_4O_2$	74.64	5.82	12.44	74.30	5.82	12.41
55	2'-Cl	68.5	216-217	$C_{26}H_{20}Cl_2N_4$	67.98	4.39	12.20	67.83	4.44	11.91
15	3'-Cl	58.5	168-170	$C_{26}H_{20}Cl_2N_4$	67.98	4.37	12.20	68.22	4.43	11.92
56	4'-Cl	57	237-239	$C_{26}H_{20}Cl_2N_4$	67.98	4.37	12.20	68.30	4.39	11.92
57	2'-Br	69.5	199-200	$C_{26}H_{20}Br_2N_4$	56.95	3.77	10.22	56.87	3.81	9.88
58	3'-Br	61	173-174	$C_{26}H_{20}Br_2N_4$	56.95	3.77	10.22	56.77	3.70	10.09
59	4'-Br	74	252-254	$C_{26}H_{20}Br_2N_4$	56.95	3.68	10.22	56.77	3.70	9.97
60	2'-CF_3	39	191-192	$C_{28}H_{20}F_6N_4$	63.88	3.83	10.64	63.87	3.84	10.66
61	3'-CF_3	74	182-184	$C_{28}H_{20}F_6N_4$	63.88	3.83	10.64	63.79	3.89	10.48
62	4'-CF_3	47.6	238-240	$C_{28}H_{20}F_6N_4$	63.88	3.83	10.64	63.85	3.70	10.62
63	2'-NO_2	20	277-279	$C_{26}H_{20}N_6O_4$	64.99	4.20	17.49	65.31	4.41	17.53
64	3'-NO_2	52	269-271	$C_{26}H_{20}N_6O_4$	64.99	4.20	17.49	64.86	4.30	17.19
65	4'-NO_2	24.2	290-291	$C_{26}H_{20}N_6O_4$	64.99	4.20	17.49	65.11	4.31	17.40
66	2'-SCH_3	73	175-177	$C_{28}H_{26}N_4S_2$	69.68	5.43	11.61	69.42	5.42	11.31
67	4'-SCH_3	70	198-200	$C_{28}H_{26}N_4S_2$	69.68	5.43	11.61	69.34	5.25	11.45
68	2'-SO_2CH_3	68.4	300-302	$C_{28}H_{26}N_4O_4S_2$	61.52	4.70	10.25	61.84	4.81	10.16
69	4'-SO_2CH_3	40	272-273	$C_{28}H_{26}N_4O_4S_2$	61.52	4.79	10.25	61.54	4.98	10.00
70	2'-C_6H_5	64.5	227-229	$C_{38}H_{30}N_4$	84.10	5.57	10.32	84.05	5.71	10.14
71	2'-C_4H_9	52	152-153	$C_{34}H_{38}N_4$	81.23	7.62	11.15	81.00	7.55	11.13

Recrystallization Solvents: all compound recrystallized from ethoxyethanol unless otherwise noted; ethoxyethanol-water -**14**, **49**, **54**, **55**, **69**, **70**; 1-butanol -**15**; 2-propanol -**66**; DMF -**64**, **65**.

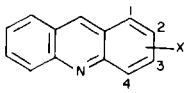
Table IV (Known Acridines)



Compound No.	X	M.p., (°C)	Yield %	Compound No.	X	M.p., (°C)	Yield %
1	H (6)	110-111	95	**17**	3-Cl (2)	126-128	34
72	1-CH_3 (11)	(a)	30	**80**	4-Cl (17)	82-84	94
73	2-CH_3 (11)	135-137	98	**81**	1-Br (18)	108-109	40
74	3-CH_3 (11)	125-126	40	**82**	2-Br (18)	174-176	99
75	4-CH_3 (11)	88-90	95	**83**	3-Br (18)	133-135	31
76	1-OCH_3 (12)	(a)	14	**84**	4-Br (18)	104-106	94
77	2-OCH_3 (13)	102-104	50	**87**	3-CF_3 (5)	169-170	50
78	3-OCH_3 (14)	88-90	70	**89**	1-NO_2 (19)	154-155	56
79	4-OCH_3 (15)	131-135	97	**90**	2-NO_2 (20)	210-212	96
16	1-Cl (16)	98-100 (b)	33	**91**	3-NO_2 (2)	(a)	9
6	2-Cl (16)	173-175	98	**92**	4-NO_2 (6, 19)	163-165	94.5
				93	4-C_6H_5	120-123	90

(a) Compound not isolated, yield determined by glc. (b) Literature m.p. 85° (16). Recrystallization Solvents: benzene -**74**, **83**, **87**; heptane -**78**; hexane -**16**, **17**, **81**; toluene -**6**, **92**; ethanol -**89**.

Table V (Previously Unreported Acridines)

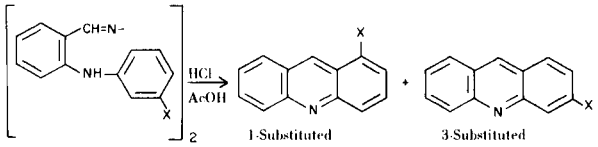


Compound No.	X	Yield %	M.p., (°C)	Empirical Formula	Analysis Percent Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
85	1-CF_3	5	120-121	$C_{14}H_8F_3N$	68.02	3.26	5.67	68.15	3.21	5.84
86	2-CF_3 (5)	43	164-166	$C_{14}H_8F_3N$	68.02	3.26	5.67	68.30	3.15	5.85
88	4-CF_3	94	101-102	$C_{14}H_8F_3N$	68.02	3.26	5.67	68.06	3.41	5.67
94	2-SCH_3 (5)	48	87-89	$C_{14}H_{11}NS$	74.60	3.89	6.22	74.40	5.07	6.37
95	4-SCH_3	98	125-127	$C_{14}H_{11}NS$	74.60	4.89	6.22	74.34	4.89	6.15
96	2-SO_2CH_3	98	199-200	$C_{14}H_{11}NO_2S$	65.35	4.31	5.44	65.66	4.28	5.24
97	4-SO_2CH_3	98	172-174	$C_{14}H_{11}NO_2S$	65.35	4.31	5.44	65.63	4.62	5.42
98	4-C_4H_9	54	74-76	$C_{17}H_{17}N$	86.77	7.28	5.95	86.76	7.51	5.82

Recrystallization Solvents: hexane -**85**, **94**, **98**; ethanol -**86**, **97**; 2-propanol -**88**; benzene -**95**; ethoxethanol -**96**.

Table VI

Ring Closure of 3'-Substitued Azines To Give 1-And 3-Substituted Acridines



Compound No.	Substituent	Product	1-Isomer %	Product	3-Isomer %	Chromatographic Column
64	NO_2	**89**	91.3	**91**	8.7	A
58	Br	**81**	56.6	**83**	43.4	B
15	Cl	**16**	54.3	**17**	45.7	C
61	CF_3	**85**	31.9	**87**	68.1	C
50	CH_3	**72**	30.3	**74**	69.6	B
53	OCH_3	**76**	15.2	**78**	84.8	C

Isomer percentages determined by glc analysis. Columns: A - 6' x 3 mm 10% OV-17 80/100 Chrom Sorb WHP; B - 12' x 2 mm 4% Stabilized DEGS (Diethyleneglycol Succinate) 100/120 Gas Chrom Q; C - 12' x 2 mm 10% Silar 10C on 150/120 Gas Chrom Q.

diluted with water. The basis for the separation of the 1- and 3-trifluoromethyl isomers was that the 3-substituted hydrochloride was not stable in water and precipitated as the free base.

EXPERIMENTAL

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Gas chromatography analyses were done on a Perkin Elmer model 900 gas chromatograph.

N-Phenylanthranilic Acids (Table I).

Method A. *N*-(4'-*n*-Butylphenyl)anthranilic Acid (**23**).

A mixture of 156.5 g (1.0 mole) of *o*-chlorobenzoic acid, 164 g. (1.1 mole) of *p*-*n*-butylaniline, 69 g. (0.5 mole) of anhydrous potassium carbonate, 1 g. of copper-bronze powder, and 350 ml. of isoamyl alcohol was heated at reflux for 4 hours removing water as it formed. The dark mixture was cooled to below 100° and clarified by filtration. Acetic acid (60 ml.) was added and the solution cooled. The product was isolated by filtration and dried to give 78 g. (29.3%) of **23**, m.p. 147-150°.

Method B. *N*-(2'-Trifluoromethylphenyl)anthranilic Acid (**22**).

A mixture of 68.5 g. (0.5 mole) of anthranilic acid, 124 g. (0.55 mole) of *o*-bromobenzotrifluoride, 34.5 g. (0.25 mole) of anhydrous potassium carbonate, 0.5 g. of copper-bronze powder, and 200 ml. of isoamyl alcohol was heated at reflux 5 hours removing water as it formed. The mixture was cooled to below 100° and clarified by filtration. Acetic acid (30 ml.) was added and the mixture cooled. The product was removed by filtration and dried to give 94 g. (67.1%) of **22**, m.p. 205-206°.

Method C. *N*-(2'-Methylsulfonylphenyl)anthranilic Acid (**19**).

To a mixture of 10 g. (0.039 mole) of *N*-(2'-methylthiophenyl)anthranilic acid (**18**) in 160 ml. of acetone was added with mechanical stirring below 35°, 16 ml. of 40% peracetic acid. The

resulting mixture was stirred at room temperature overnight then diluted with 200 ml. of water. The product which separated was removed by filtration and dried to give 10.6 g. (93.4%) **19**, m.p. 229-231°.

N-Phenylanthranilic Acid *p*-Toluenesulfonyl Hydrazides (Table II).

N-(4′-Chlorophenyl)anthranilic Acid *p*-Toluenesulfonyl Hydrazide (**32**).

Method A.

A mixture of 24.9 g. (0.1 mole) of *N*-(4′-chlorophenyl)-anthranilic acid (**21**), 13.1 g. (0.11 mole) thionyl chloride, and 250 ml. toluene was heated at reflux for 1.5 hours during which time complete solution occurred and sulfur dioxide and hydrogen chloride gases were liberated. The solution was cooled to 40-50° and 18.6 g (0.1 mole) of *p*-toluenesulfonylhydrazine added. The resulting mixture was heated at reflux for 5 hours, cooled, and the product removed and dried to give 39.6 g. (95%) of **32**, m.p. 220-222°.

Method B.

A mixture of 12.45 g. (0.05 mole) of *N*-(4′-chlorophenyl)-anthranilic acid, 6.55 g. (0.055 mole) of thionyl chloride, and 125 ml. of toluene was heated under reflux for 1.5 hours, then the solvent was removed on a roto-evaporator. To the crystalline residue was added 100 ml. of anhydrous methanol and the evaporation process was repeated. To the residue (methyl ester) was added 100 ml. of 85% hydrazine hydrate and the mixture was heated at reflux for 1.5 hours during which time solution occurred followed by separation of a yellow solid. The mixture was cooled, diluted with 200 ml. of water, and the product, *N*-(4′-chlorophenyl)anthranilic acid hydrazide, removed and dried to give 13.1 g. (100%), m.p. 160-162°.

Anal. Calcd. for $C_{13}H_{12}ClN_3O$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.86; H, 4.79; N, 15.98.

To a stirred solution of the above hydrazide in 30 ml. of pyridine was added 9.5 g. of *p*-toluenesulfonyl chloride below 60°. The resulting mixture was stirred for 2 hours at ambient temperature, then poured into 200 ml. of 10% hydrochloric acid. The product was removed, washed with water, and dried to yield 19.2 g. (92.5%), of **32**, m.p. 219-221°.

Method C. *N*-(3′-Methoxyphenyl)anthranilic Acid *p*-Toluenesulfonyl Hydrazide (**28**).

To a stirred solution of 12.2 g. (0.05 mole) of *N*-(3′-methoxyphenyl)anthranilic acid (**22**) and 5.8 g. (0.05 mole) of *N*-hydroxysuccinimide in 120 ml. of tetrahydrofuran was added dropwise over 10 minutes a solution of 10.3 g. (0.05 mole) of dicyclohexylcarbodiimide in 60 ml. of tetrahydrofuran. The mixture was stirred for 3 hours and the precipitate (succinimide) was removed and washed with a small amount of tetrahydrofuran. The combined filtrates were concentrated to dryness and to the resulting reddish oil was added 50 ml. of 85% hydrazine hydrate. The mixture was heated on a steam bath for 30 minutes, diluted with 500 g. of ice and water, and the product, *N*-(3′-methoxyphenyl)anthranilic acid hydrazide, removed and dried to yield 13 g. (100%), m.p. 119-120°. The analytical sample was recrystallized from 2-propanol, m.p. 123-125°.

Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.17; H, 5.87; N, 16.27.

To a solution of 12.5 g. (0.048 mole) of the above hydrazide in 120 ml. of pyridine was added in one portion 9.1 g. (0.048 mole) of *p*-toluenesulfonyl chloride and the resulting mixture was stirred for 2 hours at ambient temperature. The mixture was diluted with 320 g. of ice and water and the product removed and dried to give 13.5 g. (67.9%) of **28**, m.p. 157-158°.

Diphenylamine-2-carboxaldehyde and Derivatives (Table III).

4′-Chlorodiphenylamine-2-carboxaldehyde.

A mixture of 104 g. (0.25 mole) of **32**, 50 ml. of 10 *N* sodium hydroxide, 150 ml. of water, and 800 ml. of ethylene glycol was heated on a steam bath with stirring for 2 hours during which time a deep red solution developed. The solution was cooled, diluted with 2 l. of water, and extracted into toluene. The extract was washed with water, dried over magnesium sulfate, and concentrated to give 47 g. of oil which was crystallized from 125 ml. of 2-propanol to give 34 g. (59%), m.p. 66-69°. The analytical sample was recrystallized from toluene, m.p. 68-69°.

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.09; H, 4.43; N, 6.25.

3′Trifluoromethyldiphenylamine-2-carboxaldehyde.

A mixture containing 90 g. (0.2 mole) of **37**, 40 ml. of 10 *N* sodium hydroxide, 140 ml. of water, and 220 ml. of ethylene glycol was heated at reflux for 2 hours, cooled, and diluted with 2 l. water. The product separated as an oil and was extracted into ether. The extract was washed with water, dried over magnesium sulfate, and concentrated to give 41 g. of yellow oil which was crystallized from 100 ml. of 2-propanol to give 26 g. (48.6%) of yellow crystals, m.p. 48-50°. The analytical sample was recrystallized from 2-propanol, m.p. 51-53°.

Anal. Calcd. for $C_{14}H_{10}F_3NO$: C, 63.40; H, 3.80; N, 5.28. Found: C, 63.44; H, 3.75; N, 5.74.

4′-Chlorodiphenylamine-2-carboxaldehyde Azine (**56**).

A mixture of 104 g. (0.25 mole) of **32**, 50 ml. of 10 *N* sodium hydroxide, 250 ml. of water, 400 ml. of ethoxyethanol, and 15 g. of 85% hydrazine hydrate was heated at reflux for 2 hours. Complete solution occurred followed by separation of a yellow solid. The mixture was cooled well and the product removed, washed with 100 ml. of 50% aqueous 2-propanol, and dried to give 42 g. (73.5%) of **56**, m.p. 237-240°.

The following derivatives of 4′-chlorodiphenylamine-2-carboxaldehyde were prepared by substituting the appropriate derivatizing agent for hydrazine:

a. Semicarbazone, yield 36%, m.p. 205-207° (2-propanol).

Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 56.74; H, 4.51; N, 19.41. Found: C, 58.14; H, 4.88; N, 19.16.

b. Thiosemicarbazone, yield 62.5%, m.p. 198-200° (ethanol).

Anal. Calcd. for $C_{14}H_{13}ClN_4S$: C. 55.17; H, 4.30; N, 18.38. Found: C, 55.20; H, 4.46; N, 18.32.

c. Phenylhydrazone, yield 53.5%, m.p. 128-130° (methanol).

Anal. Calcd. for $C_{19}H_{16}ClN_3$: C, 70.91; H, 5.01; N, 13.06. Found: C, 70.65; H, 5.00; N, 12.76.

d. The hydrazone was prepared from the aldehyde and an equimolar amount of hydrazine in methanol, yield 73.5%, m.p. 125-127° (methanol).

Anal. Calcd. for $C_{13}H_{12}ClN_3$: C, 63.55; H, 4.92; N, 17.10. Found: C, 63.86; H, 5.05; N, 16.82.

Acridines (Tables IV, V, VI).

2-Chloroacridine (**6**).

A mixture of 131 g. (0.57 mole) of **56**, 400 ml. of glacial acetic acid, and 122 ml. of concentrated hydrochloric acid was stirred and heated at reflux for 1 hour. The deep red solution was cooled, poured into 1 l. of cold water, and basified (*p*H 10) with 40% sodium hydroxide solution. The product was removed,

washed with water, and dried to give 121 g. (100%) of **6**, m.p. 173-175°.

1-Chloroacridine (**16**) and 3-Chloroacridine (**17**).

A mixture of 15 g. (0.066 mole) of **15**, 50 ml. of glacial acetic acid, and 15 ml. of concentrated hydrochloric acid was stirred and heated at reflux for 1 hour. The mixture was cooled and poured into 200 ml. of ice water. The yellow solid which separated (mostly **16** hydrochloride) was resuspended in water and basified with concentrated ammonia. The precipitate was removed, dried, and recrystallized from 100 ml. of hexane to give 4.5 g. (32.8%) of **16**, m.p. 98-100°. The original acid filtrate was basified with concentrated ammonia and the precipitate was removed, dried, and recrystallized from 200 ml. of hexane to give 4.7 g. (33.6%) of **17**, m.p. 126-128°.

1-Trifluoromethylacridine (**85**) and 3-Trifluoromethylacridine (**87**).

A mixture of 15 g. (0.057 mole) of **61**, 50 ml. of glacial acetic acid, and 15 ml. of concentraed hydrochloric acid was stirred and heated at reflux 1 hour. The dark red solution was cooled, poured into 600 ml. of cold water, and allowed to stand overnight. The precipitate (**87**) was removed and dried to give 7.0 g. (49.6%) of **87**, m.p. 160-165°. The acidic mother liquid was basified with concentrated ammonia and the solid which separated was removed and dried to give 4.0 g., m.p. 105-130° (52% **85** by glc). Four recrystallizations of this material from hexane gave 0.7 g. of white solid (**85**), m.p. 120-121°.

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