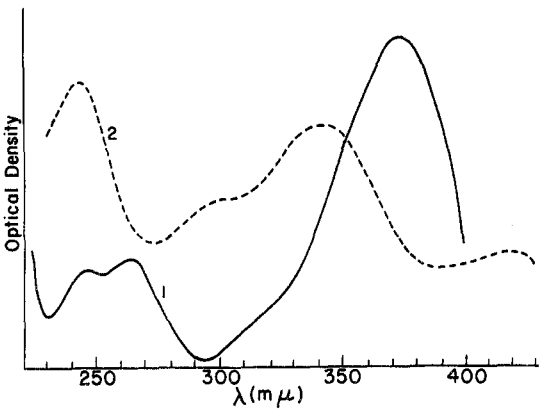


Fig. 2. Ultraviolet spectra of 2′-hydroxy-3,4-dimethoxychalcone in (1) ethanol, (2) 0.002*M* sodium ethoxide

length region undergoes a marked increase in intensity. A low intensity band may appear in the 400 mμ region (Fig. 2).

Spectral procedures for detecting *o*-dihydroxyl and 2′-hydroxyl groups in chalcones have been reported previously. Thus, chalcones which contain an *o*-dihydroxyl grouping in the B-ring give a characteristic bathochromic shift with boric acid–sodium acetate.[5] 2′-Hydroxychalcones form complexes with aluminum chloride in alcoholic solution,[2,6] the λ_{max} of the long wave-length band undergoing a bathochromic shift of 40–60 mμ (Table II). It is important that a large excess of aluminum chloride be employed in this test for a 2′-hydroxyl.[7] In Table II, it will be noted that 2′,3′,4′-trihydroxychalcone derivatives give a remarkably consistent bathochromic shift of only 37 mμ with aluminum chloride. This suggests that these compounds form aluminum complexes of a different type from those given by other 2′-hydroxychalcones.

Acknowledgment. The authors are indebted to Dr. T. A. Geissman for specimens of many of the chalcones used in this study.

(5) L. Jurd, *Arch. Biochem.*, **63**, 376 (1956).

(6) E. C. Bate-Smith and T. Swain, *J. Chem. Soc.*, 2185 (1953).

(7) L. Jurd and T. A. Geissman, *J. Org. Chem.*, **21**, 1395 (1956).

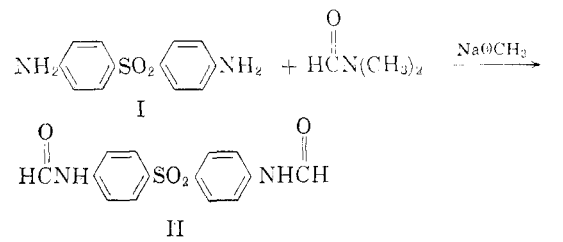
Potential Cancerocidal Agents. III. Formanilides[1,2]

GEORGE R. PETTIT, MALDA V. KALNINS, THOMAS M. H. LIU, EVAN G. THOMAS, AND KEVIN PARENT

Received October 27, 1960

As part of a study directed at defining the scope of a new procedure[3] for the preparation of formanilides it was considered of importance to submit several of these substances for evaluation as cancer chemotherapeutic agents.[4] One of the first compounds prepared was 2,5-dimethoxyformanilide (Table I) and this substance was subsequently found to inhibit growth of the Ehrlich Ascites tumor in preliminary screening studies.[5] Consequently, it appeared desirable to prepare a number of related formanilides.

Initial emphasis was placed on the preparation of alkylated, alkoxy, and halogenated derivatives of formanilide (Table I). In each case, the corresponding aniline was formylated (*cf.*, I → II) employing dimethylformamide in the presence of sodium methoxide.[3] Acylation was conveniently accomplished using excess dimethylformamide and



a 2:1 molar ratio of sodium methoxide to amine Generally the reaction was complete after fifteen to thirty minutes at reflux and was accompanied by evolution of dimethylamine. The structure of the first product, *p*-chloroformanilide (Table I), prepared by this new reaction was suggested on the basis of its infrared spectrum and elemental composition. Unequivocal evidence for this structure was obtained following comparison (infrared spectra and mixture melting point) with an authentic specimen of *p*-chloroformanilide.[6]

Although the substances illustrated in Table I

(1) Refer to G. R. Pettit and M. V. Kalnins, *J. Org. Chem.*, **25**, 1365 (1960) for the preceding contribution.

(2) This investigation was aided by Grant No. T-79A from the American Cancer Society and in part by a Frederick Gardner Cottrell grant from the Research Corporation.

(3) Consult: G. R. Pettit and E. G. Thomas, *J. Org. Chem.*, **24**, 895 (1959) for a preliminary report of this reaction.

(4) The known inhibition of Sarcoma 180 by *N*-methylformamide emphasized the advisability of a concurrent biological investigation. An account of the tumor inhibitory activity of *N*-methylformamide has been prepared by D. A. Clarke, F. S. Philips, S. S. Sternberg, R. K. Barclay, and C. C. Stock, *Proc. Soc. Exptl. Biol. Med.*, **84**, 203 (1953). This substance has also been shown to prolong the survival time of mice with Leukemia L1210 and inhibit the growth of Adrenocarcinoma E0771; H. E. Skipper, F. M. Schable, V. Binns, J. R. Thomson, and G. P. Wheeler, *Cancer Research*, **15**, 143 (1955). An increase in the survival time of mice bearing Ehrlich Ascites tumor following treatment with *N*-methylformamide has been reported by A. Furst, W. C. Cutting, and H. Gross, *Cancer Research*, **15**, 294 (1955).

(5) Evaluation of 2,5-dimethoxyformanilide (NSC 30098) is being carried out by the Cancer Chemotherapy National Service Center, National Cancer Institute, Bethesda, Md.

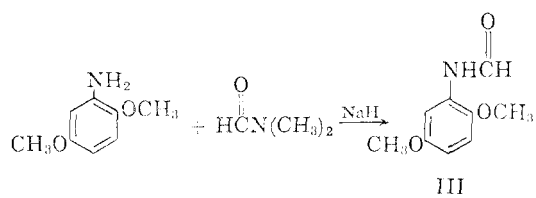
(6) M. D. Farrow and C. K. Ingold, *J. Chem. Soc.*, **125**, 2552 (1924).

TABLE I

R_1	R_2	R_3	R_4	R_5	Yield, %[a]	Solvent[c]	M.P.[d]	Formula
CH_2CH_3					97	1	73.5–74.5 (70)[e]	$C_9H_{11}NO$
OCH_3					44[b]	1	84 (84)[f]	
		OCH_3			41		80–81 (80–81)[f]	
F					70	2	44	C_7H_6NOF
	F				35	2	63–64	C_7H_6NOF
		F			78	2	67–68 (66)[g]	
	CF_3				52	3	54–55	$C_8H_6F_3NO$
	Cl				48	4	56–57.5[h] (57–58)[i]	
		Cl			79	5	102–103.5[h] (100–102)[j]	
I					68	4	113–113.5	C_7H_6INO
CH_3	CH_3				62	6	103.5–104.5	$C_8H_{11}NO$
	CH_3	CH_3			51	2	68–69	$C_8H_{11}NO$
CH_3		OCH_3			63[b]	7	104–105	$C_9H_{11}NO_2$
OCH_3		OCH_3			35	8	140–141	$C_9H_{11}NO_3$
OCH_3			OCH_3		48	6	79–80	$C_9H_{11}NO_3$
OCH_2CH_3			OCH_2CH_3		36[b]	1	95.5–96	$C_{11}H_{15}NO_3$
	F	CH_3			53	2	68–69	C_8H_8FNO
	F			CH_3	56	2	88–89	C_8H_8FNO
		F		CH_3	41	2	91–92	C_8H_8FNO
	Cl	F			73	2	94–95	C_7H_5ClFNO
	CF_3		CF_3		54	1	124–125	$C_9H_5F_6NO$
	CF_3	Cl			58	2	108–109	$C_8H_5ClF_3NO$
Cl			CF_3		35[b]	8	110–111	$C_8H_5ClF_3NO$
	Cl	CH_3			68.5	4	97–97.5	C_8H_8ClNO
	Cl			CH_3	93	4	134–134.5	C_8H_8ClNO
Cl				CH_3	79[b]	7	167.5–168	C_8H_8ClNO
Cl	Cl				42[b]	1	151	$C_7H_5Cl_2NO$
	Cl	Cl			71	9	109.5–110 (110–112)[k]	
Cl			Cl		40[b]	1	148	$C_7H_5Cl_2NO$
	Cl		Cl		54	1	130	$C_7H_5Cl_2NO$
Br				Br	86	1	199.5–201	$C_7H_5Br_2NO$
	Br	Br			95	10	132–133	$C_7H_5Br_2NO$
OCH_3		Cl	OCH_3		96	7	108–109	$C_9H_{10}ClNO_3$
	CH_3O	Cl		OCH_3	89	1	103–104	$C_9H_{10}ClNO_3$
	Cl	OCH_3		OCH_3	76	8	184–185	$C_9H_{10}ClNO_3$
Cl		Cl	Cl		56[b]	7	169–169.5	$C_7H_4Cl_3NO$

[a] Yields are based on the crystalline product isolated following dilution of the reaction mixture with water unless otherwise noted. [b] The yield after one or more recrystallizations. [c] The formanilide was recrystallized from ethanol-water (1), benzene–petroleum ether (2), chloroform–petroleum ether (3), methanol (4), acetone (5), carbon tetrachloride (6), methanol-water (7), ethanol (8), benzene–carbon tetrachloride (9), or benzene (10). [d] Melting point of the analytical sample unless indicated otherwise. The melting point in parentheses has been previously reported. [e] R. B. Kelly, W. I. Taylor, and K.

were readily prepared by the dimethylformamide–sodium methoxide procedure, the reaction usually led to complex mixtures when applied to nitroanilines. The difficulty experienced with nitro compounds was attributed to additional reactions involving methoxide and was not further investigated. Attempts to formylate, for example, 3,4-dichloroaniline with dimethylformamide in the absence of sodium methoxide or by substituting sodium hydroxide for the alkoxide were unsuccessful. Heating at reflux for periods up to ninety hours resulted only in recovery of starting aniline. Formylation of 2,5-dimethoxyaniline with dimethylformamide using either sodium amide or hydride in place of sodium methoxide resulted in increased yield of formanilide III. These experiments served to approximately define the base requirements of the reaction and were not pursued further in the present study.



III

The dimethylformamide–sodium methoxide formylation reaction was easily extended to the synthesis of *N*-phenyl-*p*-aminoformanilide, 4,4′-diformamidodiphenylsulfone (II), α-formamidonaphthalene, and 8-formamido-2-naphthol from the corresponding amines.

TABLE I (*Continued*)

Carbon		Hydrogen		Bromine		Chlorine		Fluorine		Nitrogen	
Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
72.46	72.35	7.43	7.49							9.93	9.36
60.42	59.99	4.35	4.30							10.07	10.27
60.42	60.37	4.35	4.29								
50.80	51.02	3.19	3.27					30.13	29.89	7.40	7.41
34.04	33.71	2.45	2.27							5.67	5.84
72.45	72.13	7.30	7.31							9.38	9.41
72.45	72.43	7.30	7.26							9.38	9.54
65.44	65.31	6.71	6.56							8.48	8.59
59.65	59.48	6.12	6.05							7.72	7.90
59.65	59.44	6.12	6.18							7.72	7.73
63.10	62.97	7.22	7.06							6.69	6.83
62.73	62.86	5.26	5.45					12.41	12.11	9.15	8.98
62.73	62.89	5.26	5.05					12.41	12.26	9.15	9.01
62.73	62.94	5.26	5.37							9.15	8.87
48.43	48.81	2.90	3.10					10.95	10.28	8.07	7.61
42.04	42.22	1.96	2.12							5.45	5.39
42.99	42.74	2.25	2.58							6.27	6.26
42.99	42.44	2.25	2.45							6.27	6.30
56.65	56.60	4.75	4.66							8.26	8.11
56.65	56.89	4.75	4.76							8.26	7.90
56.65	56.56	4.75	4.78							8.26	8.04
44.24	44.30	2.65	2.91							7.37	7.34
44.24	44.28	2.65	2.85			37.32	37.21			7.37	7.21
44.24	44.39	2.65	2.66							7.37	7.20
30.14	30.00	1.81	1.78	57.29	57.07					5.02	4.73
30.14	30.10	1.81	1.87	57.29	57.00					5.02	4.90
50.13	49.82	4.67	4.77							6.49	6.18
50.13	49.85	4.67	4.64			16.44	16.27			6.49	6.26
50.13	50.13	4.67	4.55			16.44	16.56			6.49	6.32
37.45	37.72	1.79	2.01							6.24	6.39

Wiesner, *J. Chem. Soc.*, 2094 (1953). [f] S. Sugasuwa and H. Shigehara, *Yakugaku Zasshi*, **62**, 531 (1942); *Chem. Abstr.*, **45**, 2861 (1951). [g] H. Rheinboldt and A. Levy, *Univ. Sao Paulo, Faculdade filosof., cienc. e letras, Bol. No. 129, Quimica* No. **3**, **69** (1951); *Chem. Abstr.*, **46**, 7552 (1952). [h] Melting point of the crude product. [i] O. C. M. Davis, *J. Chem. Soc.*, **95**, 1397 (1909). [j] *Cf.* Ref. 6. [k] C. W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

EXPERIMENTAL[7]

General formylation procedure. The following general procedure was employed for preparation of the formanilides described in Table I. Sodium methoxide[8] (0.3 mole) was added to the amine (0.15 mole), dissolved in 150 ml. of dimethylformamide[9] and the resulting mixture was heated at reflux for 30 min. Dimethylamine[10] was rapidly evolved during the first 15 to 20 min. The hot reaction mixture was diluted with 300 to 800 ml. of water, cooled and usually refrigerated overnight before collecting the product.[11]

(7) The infrared spectrum of each pure compound was recorded and found to be consistent with the assigned structure. Melting points were observed using open Kimble glass capillaries and are uncorrected. Microanalyses were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Several of the fluorine-containing anilines were generously provided by L. F. Loutrel, Jr., Maumee Chemical Co.

(8) Dry sodium methoxide prepared in the laboratory was found to be the most reliable reagent. Several recently purchased, and previously unopened, commercial samples of sodium methoxide gave comparable results. The formylation reaction failed when poorer quality alkoxide was used.

(9) Commercial dimethylformamide was conveniently dried by allowing it to remain for 48 hr. in contact with Fischer Scientific Co. Molecular Sieve Type 4A. This procedure is based on unpublished experiments performed by Dr. J. L. Wolfhagen of this laboratory. Additional purification was found to be unnecessary.

(10) In several cases the amine was guided into dilute hydrochloric acid solution and identified as dimethylamine hydrochloride.

(11) The yield of several formanilides appreciably soluble in the aqueous mixture was improved by removing *ca.* half of the reaction solvent *in vacuo* before dilution. When carefully purified amine starting material was employed, the crude formamide was generally unaccompanied by a detectable (melting point determination) amount of impurity.

Formylation of 2,5-dimethoxyaniline in the presence of sodium hydride or sodium amide. To a solution of 2,5-dimethoxyaniline (12.1 g.) in 150 ml. of dimethylformamide (under nitrogen) was added 6.8 g. of a 53% dispersion of sodium hydride in oil.[12] The mixture was heated at reflux for 20 min., cooled (ice-bath) and then cautiously treated with water. After hydrolyzing the remaining sodium hydride, the mixture was diluted to *ca.* 1 l. with water and refrigerated for 16 hr. The crystalline 2,5-dimethoxyformanilide weighed 10.3 g. (62%), m.p. 78–79.5° (*cf.*, Table I).

When an equivalent quantity of commercial (Fisher Scientific Co.) sodium amide was substituted for sodium hydride and the reaction repeated exactly as described above, 8.7 g. (52%) of 2,5-dimethoxyformanilide, m.p. 79–80°, was isolated.

Each of the following formamides was prepared using the general sodium methoxide-dimethylformamide procedure. N-Phenyl-p-aminoformanilide. The crude product prepared from 27.6 g. of *p*-aminodiphenylamine recrystallized from methanol-water as purple crystals (18.7 g., 59%), m.p. 170–171°. Two additional recrystallizations from methanol-water (Norit-A) gave pure colorless leaflets melting at 174.5–175°.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.66; H, 5.75; N, 13.12.

4,4′-Diformamidodiphenylsulfone (II). Conversion of 4,4′-diaminodiphenylsulfone (I, 40 g.) to the crude light brown diformyl derivative, m.p. 242–250° (48 g., 98%), was accomplished in the usual manner. Repeated recrystallization from methanol-water (Darco) led to a colorless crystalline analytical sample, m.p. 273–273.5° (lit.,[13] m.p. 260.5°).

Anal. Calcd. for $C_{14}H_{12}N_2O_4S$: C, 55.26; H, 3.97; N, 9.21; S, 10.53. Found: C, 55.22; H, 3.92; N, 9.10; S, 10.59.

α-Formamidonaphthalene. The crude formamide derivative prepared from 20 g. of α-naphthylamine weighed 19.7 g. (82.5%) and melted at 131–135°. Recrystallizing the reddish-brown product from benzene (Norit-A) gave colorless needles (19.0 g., 79.5%), m.p. 138.5–139.5° (lit.,[14] m.p. 138.5°).

8-Formamido-2-naphthol. Before collecting the formamide (8.8 g., 73%) derived from 10 g. of 8-amino-2-naphthol, the reaction mixture was cooled and adjusted to *p*H 5 with hydrochloric acid. Two recrystallizations from methanol-water (Darco) gave colorless needles melting at 205.5–207° dec. (lit.,[15] m.p. 205–207° dec.).

Department of Chemistry
University of Maine
Orono, Me.

(12) Metal Hydrides, Inc.

(13) V. A. Zasosov, *Zhur. Obshchei Khim.*, **17**, 471 (1947); *Chem. Abstr.*, **42**, 534 (1948).

(14) G. Tobias, *Ber.*, **15**, 2447 (1882).

(15) H. E. Fierz-David and W. Kuster, *Helv. Chim. Acta.*, **22**, 82 (1939).

4-(4-Dimethylaminostyryl)quinolines with a Methyl Group on the Styryl Ring[1]

Carl Tabb Bahner, William Chapman, Jr., Harold Lyons, and Lydia M. Rives[1]

Received May 23, 1960

A series of 4-(4-dimethylaminostyryl)quinolines carrying a methyl group on the quinoline ring has been reported.[2] The series has been extended to include compounds carrying methyl groups on the ring in the styryl group. These compounds are of especial interest because of indications that the hydroxylation of certain positions of such compounds as *p*-aminodiphenyl *in vivo* is involved in their carcinogenetic effects.[3] It seemed that the methyl groups might modify the biological effects of the styrylquinolines by blocking or increasing hydroxylation at certain positions, or by steric effects. Melting points and analyses of the new compounds are shown in Table I.

The substituted 4-dimethylaminobenzaldehydes required were prepared from the corresponding substituted *N,N*-dimethylanilines by the method of Campaigne and Archer[4] or the method of Vilsmeier and Haack.[5] Attempts to prepare 4-dimethylamino-3,5-dimethylbenzaldehyde by these methods and by the method of Adams and Coleman[6] were unsuccessful.

The compounds have been tested against Walker 256 tumors by Professor Alexander Haddow and

(1) This research was supported in part by grants from the American Cancer Society and the National Institutes of Health. We are also grateful for the use of the laboratory facilities of the Chester Beatty Research Institute and for the assistance of Mr. David Hakim in the preparation of one of the compounds reported.

(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 (1957).

(3) A. L. Walpole, M. H. C. Williams, and D. C. Roberts, *Brit. J. Ind. Med.*, **9**, 255–263 (1952).

(4) E. Campaigne and W. L. Archer, *Org. Syntheses*, **33**, 27 (1953).

(5) A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

(6) R. Adams and G. H. Coleman, *Org. Syntheses*, **2**, 17 (1922).

TABLE I

4-(4-Dimethylaminostyryl)quinolines

Substituent	M.P.	Method	Reaction Time	Reaction Temp.	Yield, %	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2′-Methyl-[a]	163.5–164.5	$ZnCl_2$[2]	30 hr.	120	20	83.29	6.99	9.71	83.2 83.1	6.6 6.8	9.60[b]
3′-Methyl-	191.0–193.0	Leese[7]	1 hr.	140–160	4	83.30	6.99	9.71	83.26 83.56	6.85 6.70	[c]
2′,6′-Dimethyl-	140.6–141.9	Leese	40 min.	155–165	50	83.40	7.33	9.26	83.27	7.29	9.03[b]
2′,6′-Dimethyl-3-methyl-	130	Leese	3 hr.	155–170		83.50	7.64	8.85	83.82	7.35	8.91[b]

[a] Positions marked by a (′) are on the benzene ring of the styryl group. [b] Analyses by Burroughs Wellcome Laboratories. [c] Analyses by Galbraith Laboratories.