Notes

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4-(*p*-Dimethylaminostyryl)quinolines[1]

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Received November 26, 1956

Recent observations at the Medical Division of the Oak Ridge Institute of Nuclear Studies[2,3] and the Wistar Institute of Anatomy and Biology[4,5] of the effects of 4-(*p*-dimethylaminostyryl)quinoline (I)[6,7] on tumors have encouraged the preparation of other similar compounds. A systematic study of the effects of small variations in structure upon the antitumor activity and toxicity of such compounds, similar to the studies of Browning, Cohen, Ellingworth, and Gulbransen[8] on trypanocidal styrylquinoline salts and the study of Haddow, Harris, Kon, and Roe[9] on the stilbenes, is being undertaken.

The compounds listed in Table 1 have been synthesized according to plan to include at least one example of substitution of each possible position on the quinoline ring by a methyl or benzo-group.

TABLE I

4-(*p*-DIMETHYLAMINOSTYRYL)QUINOLINE

Position of Substitution	Yield, %	M.P., °C. (corr.)	Analyses[a] Calcd. C	Calcd. H	Found C	Found H
3-Methyl	55	166	83.29	6.99	83.40, 83.26	7.13, 6.95
6-Methyl	20	157			83.21, 83.07	7.05, 6.86
7(or 5)-Methyl	43	153			83.26, 83.33	7.10, 7.08
8-Methyl	44	154[b]			83.40, 83.30	7.07, 6.98
3,6-Dimethyl	10	98	83.40	7.33	83.77, 83.66	7.28, 7.43
3,8-Dimethyl	18	146			83.35, 83.50	7.28, 7.29
5,7-Dimethyl	45	172			83.29, 83.53	7.40, 7.48
5,8-Dimethyl	15	159			83.77, 83.51	7.29, 7.21
6,7(or 5,6)-Dimethyl[c]		226			83.59, 83.35	7.29, 7.20
6,8-Dimethyl		145			83.26, 83.27	7.30, 7.28
7,8-Dimethyl	21	153			83.52, 83.38	7.23, 7.48
2,3-Benzo[d]	20	256	85.15	6.21	85.48, 85.53	6.34, 6.56
5,6-Benzo	69	163			85.25, 85.37	6.23, 6.10
7,8-Benzo[d,e]	27	184				
6-Iodo	35	205	57.01	4.28	56.83, 56.91	4.38, 4.39
6-Bromo	41	178	64.60	4.85	64.53, 64.52	5.09, 4.89
6-Chloro	47	165	73.90	5.55	73.86, 73.86	5.49, 5.53
7(or 5)-Chloro	40	145			74.04, 73.95	5.61, 5.59
8-Chloro	46	196			74.04, 74.05	5.74, 5.71

[a] Carbon and hydrogen analyses by Galbraith Microanalytical Laboratories, Knoxville, Tenn. [b] A sample prepared by heating *p*-dimethylaminobenzaldehyde with 8-methyllepidine in the presence of a smaller amount of zinc chloride 6 hr. at 180–200° melted at 196.5–198°. *Anal.* Found: C, 83.24, 83.46; H, 6.79, 6.79. The difference between the two samples is being investigated further. [c] The 5,6-dimethyl structure for this compound seems much less probable. [d] Prepared by the method of Clapp and Tipson. [e] R. J. Gobeil and C. S. Hamilton, *J. Am. Chem. Soc.*, **67**, 511 (1945).

Since halogen atoms differ from methyl groups in their effects upon the electrical forces in and around the molecule, a number of halogen-substituted compounds have been included. A further reason for including the benzoquinoline compounds is the fact that I and its methiodide have been found to be more active against Lymphoma 8 than are

(1) This research was supported by grants from the American Cancer Society, the Research Corporation and the Medical Research Foundation. The Cancer Chemotherapy National Service Center supplied *p*-dimethylaminobenzaldehyde.

(2) C. T. Bahner, *Cancer Research*, **15**, 588 (1955).

(3) C. T. Bahner, *Cancer Research Supplement No.* 4.

(4) M. R. Lewis, B. Hughes, C. T. Bahner, and Bates, *Growth*, **19**, 1 (1955).

(5) M. R. Lewis, B. Hughes, and Bates, *Growth*, **19**, 323 (1955).

(6) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(7) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

(8) C. H. Browning, J. B. Cohen, S. Ellingworth, and H. Gulbransen, *Proc. Royal Soc., B.*, **100**, 293 (1926); C. H. Browning, J. B. Cohen, S. Ellingworth, and H. Gulbransen, *Proc. Royal Soc., B.*, **105**, 99 (1929).

(9) A. Haddow, R. J. C. Harris, G. A. R. Kon, and E. M. I. Roe, *Phil. Trans. Royal Soc. London*, **241**, 147 (1948).

the corresponding pyridine compounds. It might be that the third ring of the benzoquinolines would make them even more active. Haddow, Harris, Kon, and Roe[9] reported that 5-(*p*-dimethylaminostyryl)acridine, which may be thought of as 4-(*p*-dimethylaminostyryl)-2,3-benzoquinoline, had a slight but significant inhibitory effect on the growth of Walker 256 tumor in rats. When we attempted the synthesis of this compound, we obtained a product having the correct composition, but melting at 256° instead of 237–239°, the melting point reported by Porai-Koschitz[10] for his product.

All three benzoquinolines and most of the other compounds listed appeared active when tested against Lymphoma 8. There was a wide range, however, between 4-(*p*-dimethylaminostyryl)-3-methylquinoline and the relatively inactive 4-(*p*-dimethylaminostyryl)-6-iodoquinoline. Details of these tests, carried out at the Wistar Institute of Anatomy and Biology through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey Bates, and with the financial assistance of a grant from the National Cancer Institute, are to be reported elsewhere.

EXPERIMENTAL

The substituted lepidines used were prepared by reaction of substituted anilines with methyl vinyl ketone by the method of Campbell and Schaffner.[11] Methyl isopropenyl ketone furnished by the Celanese Corporation of America was used in place of methyl vinyl ketone to obtain lepidines containing a 3-methyl group.

The following method of preparing the styrylquinolines produced substantially improved yields with less inconvenience than the method we had used previously. Anhydrous zinc chloride, the lepidine, and *p*-dimethylaminobenzaldehyde were mixed in the proportion of 1 mole:2 moles:4 moles and heated 16 to 24 hr. at 110–120°. Water vapor was permitted to escape and the mixture was stirred at intervals. Chloroform, about 4 ml. per gram of starting materials, was added cautiously to the hot mass and boiled under a reflux condenser. The undissolved zinc salt was recovered by filtration, washed with more chloroform or ether, and dried. This dark red solid was triturated with excess 8*N* ammonium hydroxide and allowed to stand 1 hr. The yellow styrylquinoline liberated was washed with water and recrystallized from methanol, isopropanol, or ethyl acetate. Commercial methylpentanes were used in a Soxhlet extractor to separate the product from zinc salts and other insoluble impurities. An additional quantity of product was recovered from the chloroform solution by washing it with 8*N* sodium hydroxide until basic, then with water, drying over sodium sulfate, distilling off the solvent and excess aldehyde under vacuum, and recrystallizing the residue. The 3-methyl compounds were recovered solely from the chloroform solution, since they did not form insoluble zinc salts under the conditions employed.

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(10) A. Porai-Koschitz, *Centr.*, *II*, 1528 (1907).

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

Isoquinoline Analogs of 4-(*p*-Dimethylaminostyryl)quinoline[1]

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Received November 26, 1956

Studies[2,3] at the Wistar Institute of Anatomy and Biology and the Oak Ridge Institute of Nuclear Studies have shown that 4-(*p*-dimethylaminostyryl)quinoline (Ia)[4,5] and its methiodide (Ib)[6] administered in the diet of rats bearing Lymphoma 8 tumors brought about regression of the tumors, and that a number of related compounds showed different potencies in this respect. In order to learn the significance of structural relations, isoquinoline isomers of Ia and Ib, and other closely related isoquinoline derivatives were prepared for testing.

4-(*p*-Dimethylaminostyryl)quinazoline (III) combines structural features of Ia and IIa. Siegle and Christensen[7] were unable to isolate any 4-styrylquinazoline from the tar obtained by reaction of benzaldehyde with 4-methylquinazoline, but III was prepared readily by the method described below.

It has been reported that Ia was more effective than the corresponding 2-(*p*-dimethylaminostyryl)-quinoline compound, Ic, and Ib was more active than Id. The isoquinoline compound IIa resembles Ia in having the styryl group attached to the heterocyclic ring at a position adjacent to the benzene ring, but resembles Ic in having the styryl group attached to a carbon atom adjacent to the ring nitrogen. On the other hand IIc resembles Ic both in the fact the styryl group is attached to a carbon farther from the benzene ring and the fact that the styryl group is attached to a carbon adjacent to the ring nitrogen. Observations at the Wistar Institute of Anatomy and Biology,[8] to be

(1) The organic syntheses reported here were supported in part by grants from the American Cancer Society, the Medical Research Foundation, and a Frederick Gardner Cottrell Grant from the Research Corporation to Carson-Newman College.

(2) B. Hughes, A. L. Bates, C. T. Bahner, and M. R. Lewis, *Proc. Soc. Exptl. Biol. Med.*, **88**, 230 (1955); M. R. Lewis, B. Hughes, C. T. Bahner, and A. L. Bates, *Growth*, **19**, 1 (1955); M. R. Lewis, B. Hughes, and A. L. Bates, *Growth*, **19**, 323 (1955).

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(4) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(5) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

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(7) J. Siegle and B. E. Christensen, *J. Am. Chem. Soc.*, **73**, 5777 (1951).

(8) These observations were made possible through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey Bates, and a grant from the National Cancer Institute.