TABLE XIV

Sulfone %	Th. p., °C.	M. p., °C.	Sulfone, %	Th. p., °C.	M. p., °C.
0.0	111.8	112.4	49.8	98.4	135.0
5.0	98.4	109.1	66.0	98.4	149.8
13.7	98.4	101.4	74.4	98.4	156.2
23.9	98.6	108.3	88.7	98.5	166.3
30.2	98.5	116.1	100.0	171.1	172.1
40.9	98.5	127.1			

Summary

1. The determination of solid–liquid phase diagrams in ten pairs of symmetrically substituted sulfoxides and sulfones showed the formation of continuous series of mixed crystals.

2. Sulfides do not form mixed crystals with sulfoxides or sulfones in the wide ranges studied.

3. These results prove that sulfoxides and sulfones have the same steric configuration. Attributing to the sulfones a tetrahedral configuration the same applies also to the sulfoxides. This confirms the most accepted hypothesis concerning the electronic structure of the sulfoxides.

4. This study is being continued specially in regard to the asymmetrically substituted compounds.

SÃO PAULO, BRAZIL RECEIVED AUGUST 1, 1945

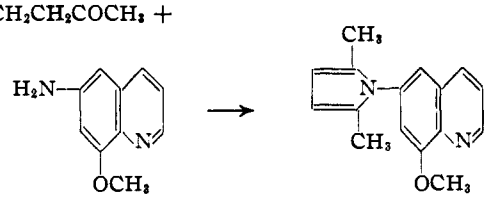
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE[1]]

Some Isomeric (Methoxy)-(2,5-dimethylpyrryl-1)-quinolines

BY HENRY GILMAN AND LAWRENCE FULLHART

In a study[1] of 2,5-dimethylpyrryl-1 derivatives in experimental avian malaria, it was shown that 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline has significant activity. This suggested an examination of some isomers. The following five isomers have been prepared and are now described: 6-methoxy-5-(2,5-dimethylpyrryl-1), 8-methoxy-5-(2,5-dimethylpyrryl-1), 2-methoxy-6-(2,5-dimethylpyrryl-1), 7-methoxy-8-(2,5-dimethylpyrryl-1) and 8-methoxy-6-(2,5-dimethylpyrryl-1). The final step in the synthesis of these compounds was a condensation of a methoxy-amino quinoline with acetonylacetone, and this reaction is represented by the following preparation of 8-methoxy-6-(2,5-dimethylpyrryl-1)-quinoline, an isomer in which the methoxy and basic groups have been transposed with respect to the active type already described.[1,2]

$H_3COCH_2CH_2COCH_3$ +



Of the five isomers prepared, the only one which showed activity was 8-methoxy-6-(2,5-dimethylpyrryl-1)-quinoline. However, the activity of this compound in experimental avian malaria was appreciably less than that of 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline.

Experimental

Synthesis of (Methoxy)-(2,5-dimethylpyrryl-1)-quinolines.—The pyrryl-quinolines were formed, in essential accordance with the general procedure of Hazelwood, Hughes and Lions,[3] by condensing the amino-quinoline with acetonylacetone.

As a rule, a mixture of the aminomethoxyquinoline and the acetonylacetone in 10 cc. of 95% ethanol and 1 cc. of glacial acetic acid was refluxed for three hours. The solution was then poured upon crushed ice, and the solid which precipitated was crystallized from an appropriate solvent. In the condensation of 6-amino-8-methoxyquinoline with acetonylacetone, two drops of 1:1 hydrochloric acid was used in place of the usual 1 cc. of glacial acetic acid. In the preparation of 7-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline, the solution was allowed to stand overnight during which time the compound crystallized out. Table I contains the data on these preparations. Methanol was the solvent.

TABLE I

(METHOXY)-(2,5-DIMETHYLPYRRYL-1)-QUINOLINES

Amino-methoxy-quinoline	Mole × 100	$(CH_3CO-CH_2-)_2$ mole × 100	Product Yield, %	Product M. p., °C.	N Anal., % Found[a]
5-NH_2-6-CH_3O	1.72	2.62	70	125–127	10.93
5-NH_2-8-CH_3O	0.57	1.75	80	155–156	11.14
6-NH_2-2-CH_3O	2.8	4.39	85	88–89	10.96
6-NH_2-8-CH_3O	1.7	5.26	57.5	161–164	11.44
8-NH_2-7-CH_3O[b]	2.87	5.0	96	141–142	11.21

[a] Calcd., N, 11.11.
[b] Ethyl alcohol was the solvent.

Nitro- and Aminoquinolines.—We used concentrated nitric acid in the preparation of 5-nitro-6-methoxyquinoline.[4] To 15.9 g. (0.1 mole) of 6-methoxyquinoline cooled to 0° was added slowly with stirring 50 g. of concentrated sulfuric acid. Then to the solution of the sulfate was added dropwise 50 g. of concd. nitric acid, keeping the solution at 0°. The temperature was allowed to rise to that of the room and then to 40° where it was held for ten hours. After pouring the mixture upon crushed ice, neutralizing with 30% sodium hydroxide, and crystallizing from ethanol there was obtained 19 g. (91%) of compound melting at 104–105°. The nitro compound was reduced to the corresponding amine by the method of Jacobs and Heidelberger.[4b]

(1) Gilman, Stuckwisch and Nobis, THIS JOURNAL, **68**, 326 (1946).

(2) See also, Gilman, Tolman, Yeoman, Woods, Shirley and Avakian, *ibid.*, **68**, 426 (1946), for some types containing the 2,5-dimethylpyrryl and the trifluoromethyl groups.

(3) Hazelwood, Hughes and Lions, *J. Proc. Roy. Soc., N. S. Wales*, **71**, 92 (1937).

(4) (a) Decker and Engler, *Ber.*, **42**, 1739 (1909); (b) Jacobs and Heidelberger, THIS JOURNAL, **42**, 2285 (1920).

5-Nitro-8-methoxyquinoline[5] was prepared by first adding 50 g. of concd. sulfuric acid to 15.9 g. (0.1 mole) of 8-methoxyquinoline[6] at 0°; then the concd. nitric acid was added dropwise, keeping the temperature below 0°. The subsequent operations were like those described for the preparation of 5-nitro-6-methoxyquinoline and the yield of product melting at 151–153° was 16 g. (80%). The reduction was carried out by the procedure of Balaban.[5b]

6-Nitro-2-methoxyquinoline[7] was prepared by adding 5 g. (0.0314 mole) of 2-methoxyquinoline dropwise to 25 cc. of fuming nitric acid cooled to 0°, then 40 g. of concd. sulfuric acid was added at a rate not to increase the temperature above 0°. After stirring for two hours the mixture was poured upon crushed ice, allowed to stand overnight, filtered, and crystallized from benzene to give 6 g. (93%) of product melting at 187°. Koenigs[7] reported a melting point of 181°, but gave no yield. No yield was given by Friedlaender[8] for the preparation of 2-methoxyquinoline. We prepared this ether in 98% yield by adding 30 g. (0.184 mole) of 2-chloroquinoline in 30 cc. of methanol to a solution of sodium methoxide made by dissolving 9 g. (0.391 g. atom) of sodium in 20 cc. of methanol. The solution was refluxed for one hour, and then 15 cc. of 1:1 hydrochloric acid was added, the methanol was removed under reduced pressure, and the residue was extracted with ether and sodium hydroxide solution. The dried ether extracts were distilled to give 28.5 g. (98%) of 2-methoxyquinoline. 6-Nitro-8-methoxyquinoline was prepared in accordance with the procedure of Fourneau and co-workers[9] by a Skraup reaction with 2-amino-5-nitroanisole in a yield of 67.5%. Our melting point agreed with theirs, but they gave no yield. The nitro compound was reduced to the corresponding amine by means of stannous chloride and hydrochloric acid.[5b,9]

8-Nitro-7-methoxyquinoline was prepared by first adding, with cooling, 50 g. of conc. sulfuric acid to 10 g. (0.063 mole) of 7-methoxyquinoline[10]; then 30 g. of concd. nitric acid was added dropwise, keeping the temperature below 0°. The mixture was stirred for one hour, during which time the temperature was allowed to rise to that of the room. The yellow precipitate obtained after pouring upon crushed ice was filtered after first neutralizing with ammonium hydroxide. Crystallization from chloroform gave 8.5 g. (66.2%) of product melting at 177–178°. Balaban[5b] reported a melting point of 178° and a yield of 33%. The reduction of 8-nitro-7-methoxyquinoline was carried out by the procedure of Fieser and Hershberg.[11] A suspension of 8.6 g. (0.042 mole) of the nitro compound and 0.085 g. of Adams catalyst in 50 cc. of ethyl acetate and 10 cc. of absolute ethanol was reduced at a pressure of 43 pounds for three hours at 100°. The yield of 8-amino-7-methoxyquinoline, melting at 118° after recrystallization from ethanol, was 6.3 g. (86.2%). Balaban[5b] reported a yield of 32% using the method of Jacobs and Heidelberger,[4b] and a melting point of 108°. We carried out a reduction of 8.5 g. (0.042 mole) of 8-nitro-7-methoxyquinoline by this[4b] method and obtained 2.5 g. (34%) of 8-amino-7-methoxyquinoline which melted at 108° after recrystallization from 50% ethanol.

Acknowledgment.—The authors are grateful to Drs. R. J. Porter and L. T. Coggeshall, of the University of Michigan, for the antimalarial tests, the results of which will be published elsewhere.

Summary

Five isomers of the known, active 6-methoxy-8-(2,5-dimethylpyrryl-1)-quinoline have been prepared in connection with studies on experimental avian malaria. Only 8-methoxy-6-(2,5-dimethylpyrryl-1)-quinoline was active, but the activity was appreciably less than the isomer in which the two substituents were transposed.

(5) (a) Vis, *J. prakt. Chem.*, [2] **48**, 26 (1893); (b) Balaban, *J. Chem. Soc.*, 2624 (1932).

(6) The 8-methoxyquinoline was prepared by the Skraup [*Monatsh.*, **3**, 544 (1882)] reaction using the modification of Strukov, *Org. Chem. Ind., U. S. S. R.*, **4**, 523 (1937) [*C. A.*, **32**, 4987 (1938)].

(7) Koenigs, *Ber.*, **18**, 2397 (1885). We prepared the corresponding amine in a 66% yield by his procedure.

(8) Friedlaender, *ibid.*, **15**, 336 (1882).

(9) Fourneau and co-workers, *Ann. inst. Pasteur*, **44**, 748 (1930) [C. A., **26**, 1592 (1932)].

(10) Späth and Brumer, *Ber.*, **57**, 1243 (1924).

(11) Fieser and Hershberg, THIS JOURNAL, **62**, 1640 (1940).

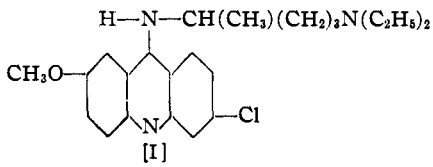
AMES, IOWA RECEIVED JANUARY 22, 1946

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

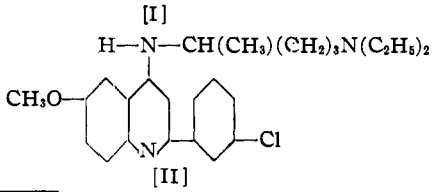
Some Quinolines Patterned as "Open Models" of a Modified Atebrin

BY HENRY GILMAN, ROBERT V. CHRISTIAN AND SYDNEY M. SPATZ[1]

It was shown recently[2] that there was a correlation of some so-called open quinoline models of atebrin [I] with the fundamental acridine type.



[I]



[II]

One of the quinolines then reported which bears a formal relationship to atebrin, and which was active in experimental avian malaria, was 2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methoxyquinoline [II]. This compound has a chlorophenyl group in place of the fused chlorobenzo group in atebrin.

In view of the partial replaceability of the methoxyl group in atebrin by a methyl group,[3] it seemed of interest to prepare some open quinoline models having a methyl group in place of the methoxyl group. One of these is 2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-6-methylquinoline [III] which was prepared by the following sequence of reactions.

(1) Present address: National Aniline Division, Buffalo, N. Y.

(2) Gilman and Spatz, THIS JOURNAL, **66**, 621 (1944).

(3) Magidson and Grigorowsky, *Ber.*, **69**, 396 (1936).