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SYNTHESIZING ISOMERIC METHOXY DERIVATIVES OF 6-NITRO-9-CHLOROACRIDINE AND 6-NITROACRIDONE

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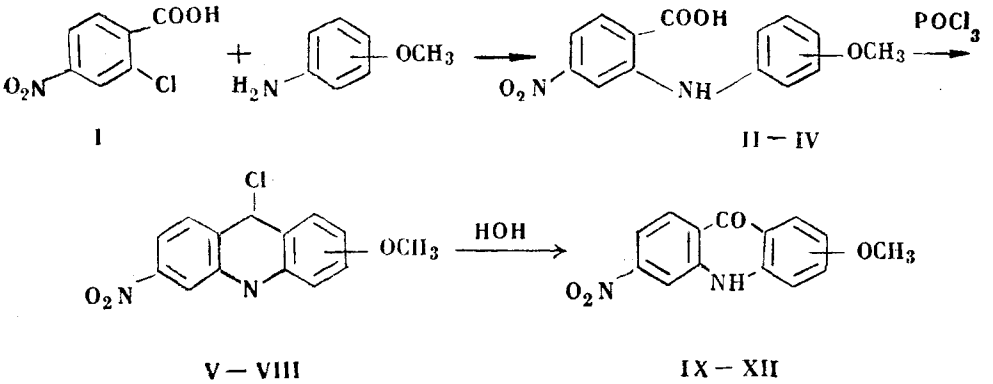
Condensation of 2-chloro-4-nitrobenzoic acid with o, m, and p-anisidines under the conditions of the Ullmann reaction gives the corresponding 2'-, 3'-, or 4'-methoxy derivatives of 5-nitrodiphenylamine-2-carboxylic acid. Phosphorus oxychloride cyclizes the latter to the corresponding methoxy-substituted 6-nitro-9-chloroacridines, and the latter, when treated with dilute hydrochloric acid, give good yields of methoxy derivatives of 6-nitroacridones.

Methoxy and nitro-substituted 9-chloroacridines are intermediates for the synthesis of the corresponding 9-aminoacridine derivatives with high antibacterial activity [1]. A number of 9-dialkylamino-substituted 2-methoxy-6-nitroacridines possess marked trypanocidal action [2]. 2,3-Dimethoxy-6-nitro-9-(γ-diethylamino-β-hydroxypropyl)aminoacridine, prepared first in Germany, then in the USA, displays chemotherapeutic activity in typhoid infection, rickettsiosis, and virus diseases [3]. At the same time, 9-chloroacridine derivatives, containing both the methoxy and the nitro group, have been insufficiently investigated. Thus, only two of the 16 possible isomers of methoxynitro-9-chloroacridine with the methoxy and nitro groups in both benzene rings have been described; they are 2-methoxy-6-nitro-9-chloroacridine [4] and 2-methoxy-7-nitro-9-chloroacridine [5].

To fill this gap 1-, 3-, and 4-methoxyderivatives of 6-nitro-9-chloroacridine have been synthesized, and from these latter and 2-methoxy-6-nitro-9-chloroacridine the corresponding acridones have been obtained. The synthesis is carried out as follows:



The starting materials used were 2'-, 3'-, and 4'-methoxy derivatives of 5-nitrodiphenylamine-2-carboxylic acid (II-IV)* obtained by condensing 2-chloro-4-nitrobenzoic acid (I) with o-, m-, and p-anisidines using the Ullmann reaction [6]. It was shown that the amount of amine taken for the condensation has a considerable effect on the yield of compounds II-IV. The highest yields are obtained with a ratio of one mole of compound I to four moles of amine. 1-, 2-, 3-, and 4-methoxy derivatives of 6-nitro-9-chloroacridine (V-VIII)* were prepared by Magidson and Grigorovskii's method, except that the reaction was effected in chloroform, making it possible to cut the amount of phosphorus oxychloride and eliminate subsequent distilling off of the excess in a vacuum.

Ring closure with 3'-methoxy-5-nitrodiphenylamine-2-carboxylic acid (III) gave a mixture of 1- and 3-methoxy-6-nitro-9-chloroacridines (V and VII), separated by making use of the higher solubility in benzene and lower stability of V as compared with VII. Similar methods for separating 1- and 3-substituted 9-chloroacridines are described by a number of authors [8-10].

Compounds V-VIII gave on boiling with 1 N hydrochloric acid almost quantitative yields of the corresponding acridones (IX-XII). The properties of the compounds are given in the table.

EXPERIMENTAL

Condensation of 2-chloro-4-nitrobenzoic acid (I) with o-, m-, and p-anisidines. 0.25 mole I, 1.0 mole of the anisidine, 0.36 mole potash, and 2 g copper powder are heated together in 300 ml n-amyl alcohol for 3.5-4 hr at

*Compounds IV and VI are described in the patent literature [4], but the methods of synthesizing them are not given.

Properties of the compounds prepared

Compound	Name	M.p., °C*	Nature of crystals	Found, %**				Yield, %
				C	H	Cl	N	
II	2'-Methoxy-5-nitrodiphenylamine-2-carboxylic acid	238—239	Red needles	58.08, 58.23	4.35, 4.27	—	9.86, 9.97	65
III	3'-Methoxy-5-nitrodiphenylamine-2-carboxylic acid	184	Orange needles	58.10, 58.29	4.34, 4.42	—	9.82, 9.78	72
IV	4'-Methoxy-5-nitrodiphenylamine-2-carboxylic acid	235***	Red needles	—	—	—	—	75
V	1-Methoxy-6-nitro-9-chloroacridine	224—225 (decomp.)	Orange plates	57.98, 58.16	3.31, 3.26	12.28, 12.20	9.82, 9.92	15
VI	2-Methoxy-6-nitro-9-chloroacridine	218***	Yellow needles	—	—	—	—	86
VII	3-Methoxy-6-nitro-9-chloroacridine	233—234	Do.	58.02, 57.92	3.41, 3.38	12.32, 12.16	9.76, 9.80	58
VIII	4-Methoxy-6-nitro-9-chloroacridine	223	Do.	57.94, 58.18	3.00, 3.16	12.14, 12.08	9.76, 9.94	
IX	1-Methoxy-6-nitroacridone	Above 360	Yellow needles	61.96, 62.15	3.90, 3.73	—	10.66, 10.58	97
X	2-Methoxy-6-nitroacridone	Above 360	Yellow plates	62.03, 62.28	3.86, 3.82	—	10.64, 10.65	93
XI	3-Methoxy-6-nitroacridone	Above 360	Pale yellow needles	62.10, 61.92	3.64, 3.88	—	10.39, 10.52	96
XII	4-Methoxy-6-nitroacridone	Above 360	Orange needles	61.98, 62.23	3.85, 3.94	—	10.27, 10.20	96

*Solvents for recrystallization: II-IV glacial acetic acid; V absolute alcohol+benzene; VI and VIII chloroform; VII benzene; IX-XII 80% aqueous dimethylformamide.

**For compounds II-IV calculated for $C_{14}H_{12}N_2O_5$: C 58.33; H 4.17; N 9.72%; for V-VIII calculated for $C_{14}H_9ClN_2O_3$:

***Literature data [4]: IV m.p. 235°; VI m.p. 216-218°.

140-150°. Amyl alcohol and excess anisidine are steam-distilled off, the solution is boiled with activated charcoal, filtered, acidified with hydrochloric acid until acid to Congo Red, and the precipitate crystallized.

1- and 3-methoxy-6-nitro-9-chloroacridines (V and VII). 0.1 mole III, 29 ml phosphorus oxychloride and 85 ml chloroform are heated together for 4 hr on a steam bath. The chloroform is taken off under a water pump vacuum, the residue poured into a mixture of crushed ice and ammonia, and the precipitate filtered off and vacuum dried over potassium hydroxide. The product is treated with boiling benzene (thrice with 700 ml), and the insoluble mixed acridones rejected. The precipitate of VII, which separates on cooling the benzene solution, is recrystallized. The benzene filtrate obtained after removing VII is distilled under a water pump vacuum, and the dry residue heated 30 min on a steam bath with 70 ml 1 N hydrochloric acid; the mixture is cooled, made alkaline with ammonia, and the precipitate is filtered off, dried in a vacuum over potassium hydroxide, and extracted with boiling benzene. The undissolved compound IX is converted into V by treatment with phosphorus oxychloride, as indicated above. Compounds VI and VIII are obtained in ways similar to V.

Isomeric methoxy-6-nitroacridones (IX-XII). One part of the appropriate mesochloro derivative (V-VIII) is boiled for 1-2 hrs with 15 vols. 1 N hydrochloric acid. The mixture is then made alkaline with ammonia, and the precipitate is separated off and crystallized. The isomer IX is also obtained by separating compounds V and VII, as indicated above. With compound X it is necessary to boil for 5 hr.

REFERENCES

1. A. Albert, Selective Toxicity [Russian Translation], IL, Moscow, 197, 1953.
2. R. Schnitzer, W. Silberstein, Z. Hyg. Infektkr., 109, 519, 1929.
3. Ch. Miller, Ch. Wagner, J. Org. Chem., 13, 891, 1948.
4. German Patents 364031, 364033, 364037; Swiss Patents 93439, 93752, 93753, 94363, 94625, 94626, 94982, 96608, 96609; C. A., 18, 1131, 1924.
5. N. S. Drozdov, N. S. Leznova, ZhOKh, 5, 690, 1935.
6. F. Ullmann, Lieb. Ann., 355, 312, 1907.
7. O. Yu. Magidson, A. M. Grigorovskii, ZhOKh, 3, 615, 1933.
8. K. Lehmstedt, K. Schrader, Ber., 70, 838, 1937.
9. A. Albert, The Acridines, Lond., 28, 40, 1951.
10. A. F. Bekhli, ZhOKh, Symposium II, 1130, 1953.

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