Studies on the Synthesis of Anthyridine

S. Carboni, A. Da Settimo, D. Bertini, C. Mori and I. Tonetti

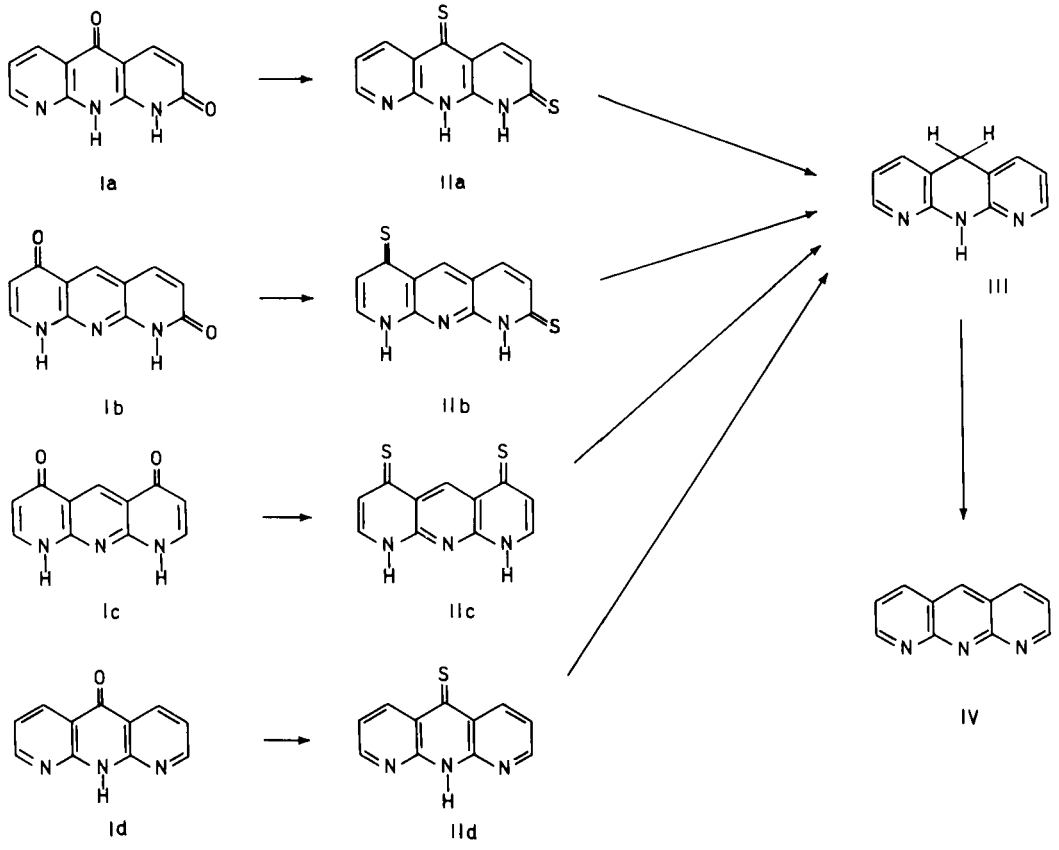
Institute of Pharmaceutical Chemistry, University of Pisa
56100 Pisa, Italy

Received March 8, 1971

The sulfuration of various anthyridones (I) to the corresponding thioderivatives (II) and the desulfuration of these to 5,10-dihydroanthyridine (III) is described. The preparation of anthyridin-5-one (Id) from 6′-methyl-2,2′-dipyridylamino-3-carboxylic acid (V) is also described.

In a previous paper the preparation of anthyridine (IV) by oxidation of 5,10-dihydroanthyridine (III) was described (1). Compound III has been obtained both by catalytic reduction of 4,6-dichloroanthyridine and by reduction with zinc of anthyridin-5-one (Id) (1). The oxidation of compound III above gave over 50% yield, while both of the reduction processes gave only a yield of about 13%; therefore obtaining even modest quantities of anthyridine (IV) presented considerable difficulties. In an attempt to obtain better results the reduction of 2,6-dichloroanthyridine (X), obtained by chlorination of anthyridine-2,6-dione (Ib) (2) with phosphorus oxychloride (Scheme 3) was attempted. However none of the attempts at reduction carried out under varied conditions were success-

SCHEME 1



ful.

However direct substitution of oxygen by sulfur using phosphorus pentasulfide as the thiating agent has been widely applied to heterocyclic systems when the hydroxyl structure is tautomeric with the cyclic amide-like or lactamic structure (3a-d). The reaction presumably proceeds through nucleophilic substitution of thiophosphoryloxy intermediates (4). In addition the replacement of sulfur by hydrogen in sulfurated organic compounds using Raney nickel is well known (5).

In an attempt to overcome the difficulties described above, we have applied this method to various anthyridones previously described (1,2,6). In fact, treatment with phosphorus pentasulfide in pyridine of anthyridine-2,5-dione (Ia), anthyridine-2,6-dione (Ib) and anthyridine-4,6-dione (Ic) (Scheme 1) gave the corresponding dithioderivatives IIa,b,c in fairly satisfactory yield. Also anthyridin-5-one (Id) (6) was converted in very good yield into the corresponding thioderivative IId (Scheme 1). From all four of these sulfurated compounds, 5,10-dihydroanthyridine (III) was obtained by reduction with Raney nickel in yields varying from 23% to 30%.

Therefore, since the starting products are easily obtained, in particular anthyridine-2,6-dione (Ib) and anthyridine-4,6-dione (Ic), and considering the very good yields of the thioderivatives II obtained from all four of the corresponding anthyridones I as well as the satisfactory yields of the dihydroanthyridine by reduction of the thioderivatives, this is a useful method for synthesizing anthyridine (IV).

It may also be pointed out that the formation of III from all four of the thioderivatives II is further proof of the anthyridinic structure of the starting products already described and obtained by different syntheses (1,2,6). The structure of the thioderivatives II is confirmed by their nmr spectra (see Table I).

Anthyridin-5-one (Id) was obtained by decarboxylation of the acid VII (Scheme 2) as well as by the method already described (6). The compound V was prepared by applying Ullmann's reaction to 2-bromonicotinic acid and 2-amino-6-methylpyridine. The cyclization of V to VI required drastic conditions, that is, treatment with concentrated sulfuric acid at 270°. Cyclization did not occur in the absence of the methyl group (7) or other activating groups (*e.g.* amino group) (6), which favour intramolecular electrophilic attack at the 3 positions. Lastly the oxidation of VI with sodium dichromate gave anthyridin-5-one-2-carboxylic acid (VII).

Treatment of V with polyphosphoric acid at 170° gave a product to which the structure VIII is assigned since it hydrolized to V with alkali and underwent methanolysis easily giving the ester IX, which was also obtained by direct esterification of the acid V. In addition compound VIII was transformated into the isomer VI by treatment with concentrated sulfuric acid under the conditions described for the cyclization of V which is analogous to the previously reported behaviour of 7-amino-5*H*-dipyrido-[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (6).

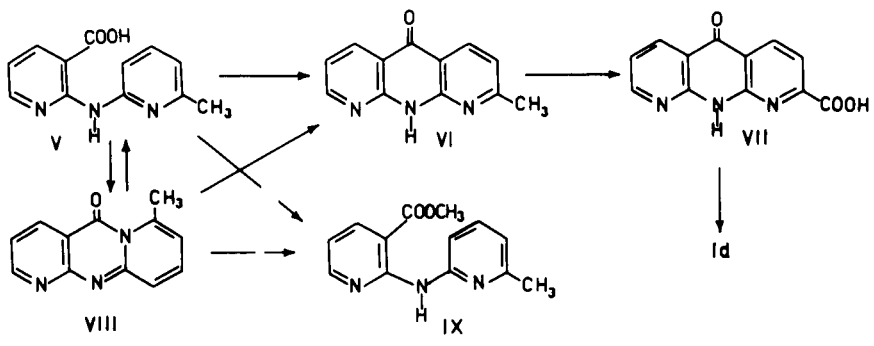
With regard to the 2,6-dichloro derivative X, treatment with dilute sodium hydroxide solution led to the monochloro derivative XII (Scheme 3). The structure of XII was confirmed by its transformation into the azido derivative XIII by reaction with sodium azide. The ir spectrum of the compound XIII in a nujol mull showed the characteristic band at 4.70 μ of the azide group. When the dichloro derivative X was reacted with sodium azide, the azidotetrazole derivative XI was obtained. The ir spectrum of XI showed other bands around 9.25 μ which can be attributed to the tetrazole ring (6), as well as the band at 4.70 μ.

This is in agreement with previous research on azidotetrazoles of 1,8-naphthyridines (8) and anthyridines (6).

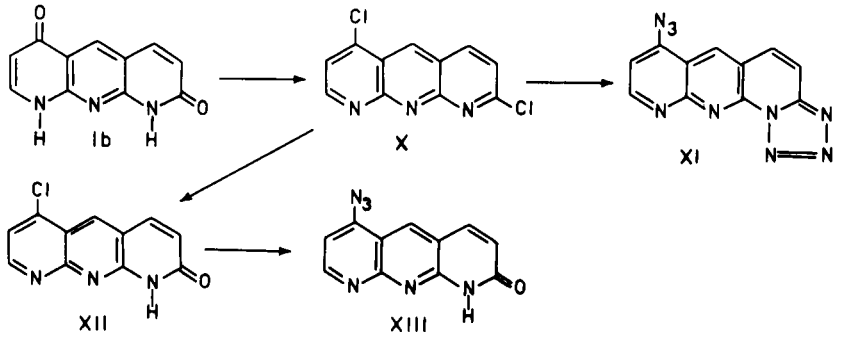
EXPERIMENTAL

All melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer

SCHEME 2



SCHEME 3



Infracord model 137 spectrophotometer in nujol mulls. The proton nmr spectra were obtained on a Jeol Model C 60 HL spectrometer.

Anthyridine-2,6-dithione (IIb).

A mixture of 1.0 g. of anthyridine-2,6-dione (Ib), 2.0 g. of phosphorus pentasulfide and 100 ml. of anhydrous pyridine was refluxed for 20 hours in an oil bath. The resulting warm solution was filtered and diluted with water (300 ml.) to destroy the excess phosphorus pentasulfide. After several hours the solution was evaporated to dryness at reduced pressure, the residue was treated with water (40 ml.), and the solid was collected. The crude product was purified by extraction with boiling carbon disulfide to remove a small quantity of sulfur and crystallized from aqueous dimethylformamide (1.07 g., 93%); dark-red crystals m.p. above 280° with dec.; principal ir peaks: 6.20, 7.52, 7.72, 8.80, 8.92, 9.96, 10.50, 11.60 μ.

Anal. Calcd. for $C_{11}H_7N_3S_2$: C, 53.88; H, 2.88; N, 17.14; S, 26.10. Found: C, 54.10; H, 2.71; N, 17.46; S, 26.40.

Anthyridine-5-thione (IId).

The anthyridone Id (0.20 g.) was heated for 1 hour with phosphorus pentasulfide in pyridine and the reaction mixture was treated in the same way as described above for the preparation of compound IIb.

The corresponding thioderivative IId, obtained in 92% yield, was purified by crystallization from pyridine, dark-brown crystals with m.p. above 320°; principal ir peaks: 6.20, 6.32, 7.10, 7.74, 8.13, 9.56, 9.90, 12.90 μ.

Anal. Calcd. for $C_{11}H_7N_3S$: C, 61.97; H, 3.31; N, 19.71. S, 15.01. Found: C, 62.01; H, 3.36; N, 19.40; S, 15.20.

Anthyridine-2,5-dithione (IIa).

To a boiling solution of 0.5 g. of anthyridine-2,5-dione (Ia) in 60 ml. of anhydrous pyridine was added 1.0 g. of phosphorus pentasulfide. After refluxing for 3 hours, the warm solution was filtered and diluted with water (120 ml.). Successive treatments as described above for anthyridine-2,6-dithione (IIb) afforded anthyridine-2,5-dithione in 53% yield. The product IIa was purified by crystallization from dimethylformamide-acetic acid (2:1); red crystals with m.p. above 320°; principal ir peaks: 6.35, 7.15, 7.75, 8.30, 8.90, 9.20, 10.00, 12.86 μ.

Anal. Calcd. for $C_{11}H_7N_3S_2$: S, 26.10. Found: S, 26.07.

Anthyridine-4,6-dithione (IIc).

This compound was obtained in 60% yield from anthyridine-4,6-dione (Ic) (0.50 g.) in the same way described above for the preparation of the product IIa. The analytical sample was obtained by crystallization from aqueous dimethylformamide, red crystals with m.p. above 320°; principal ir peaks: 6.23, 7.05, 7.25, 8.50, 9.22, 10.00, 12.62 μ.

Anal. Calcd. for $C_{11}H_7N_3S_2$: C, 53.88; H, 2.88; N, 17.14; S, 26.10. Found: C, 53.50; H, 2.63; N, 16.80; S, 25.70.

Reduction of Thioderivatives II to 5,10-Dihydroanthyridine (III).

A suspension of 0.1 g. of the thioderivative and 1.0 g. of Raney nickel in 50 ml. of ethanol was refluxed for 90 minutes (10 hours for IIc). The catalyst was then filtered off and the solution was evaporated to dryness at reduced pressure to give compound III practically pure (1). The yields were 23% for IIa, IId and 30% for IIb, IIc, respectively.

6′-Methyl-2,2′-dipyridylamino-3-carboxylic Acid (V).

A mixture of 2-bromonicotinic acid (3.36 g.), 2-amino-6-methylpyridine (4.0 g.), anhydrous potassium carbonate (2.5 g.), Ullmann copper (0.02 g.) and a trace of potassium iodide was slowly warmed to 170° and kept at this temperature for 5 hours. After cooling the reaction mixture was extracted several times with ethyl ether to remove unreacted 2-amino-6-methylpyridine. The residual solid was extracted with boiling water, the resulting solution was filtered and decolourised with charcoal, and the potassium salt of V was collected after standing overnight (1.6 g.), A further amount of potassium salt was obtained by concentrating the mother liquor (0.35 g., total yield 44%). The analytical sample was purified by crystallization from water m.p. above 320°.

Anal. Calcd. for $C_{12}H_{10}KN_3O_2$: C, 53.91; H, 3.74; N, 15.70. Found: C, 53.58; H, 3.89; N, 15.83.

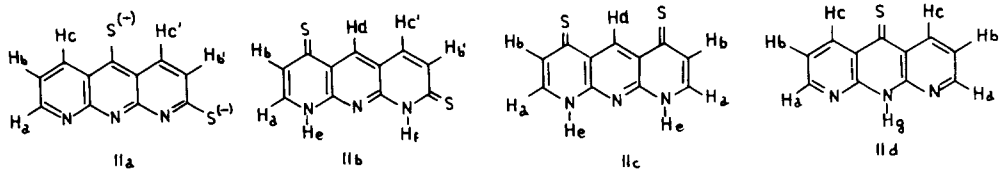
Treatment of the potassium salt with dilute hydrochloric acid gave quantitatively the compound V which was purified by crystallization from ethanol; white crystals m.p. 222-223° dec.

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.22; H, 4.82; N, 18.18.

7-Methyl-5*H*-dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (VIII).

To 7.0 g. of preheated (170°) polyphosphoric acid was added 0.56 g. of V. The resulting mixture was then heated at 200° for 15 minutes. After cooling the reaction mixture was poured onto crushed ice and made alkaline with cold concentrated ammonium hydroxide. The yellow solid was collected by filtration, washed with dilute ammonium hydroxide and crystallized from

TABLE I



	Chemical shifts (δ)							Coupling const. cps							
Compound	Ha	Hb	Hc	Hd	He	Hf	Hg	Hb′	Hc′	Jab	Jbc	Jb′c′	Jac	Solvent	t°C
IIa (a)	3.46	1.96	3.87	–	--	–	–	2.30	3.57	4.4	8.2	9.0	1.9	NaOD-D_2O	22
IIb (b)	7.92	7.30	–	9.37	13.20	14.17	–	7.32	8.18	6.7	–	9.3	–	DMSO-d_6	22
IIb (a)	3.30	2.35	–	4.11	–	–	–	2.35	2.78	5.2	–	9.0	–	NaOD-D_2O	22
IIc (b)	7.97	7.30	–	10.09	13.14	–	–	–	–	7.0	–	–	–	DMSO-d_6	22
IId (a)	4.82	3.32	4.97	–	–	–	(–)(c)	–	–	4.5	8.6	–	1.9	DMSO	100

(a) The chemical shifts (δ) are in ppm from the water signal as internal reference. (b) The broad peaks at δ 13.20, 14.17 and 13.14 show that in neutral media the thioamide-like structure is the predominant one (TMS as internal reference). (c) This signal is dispersed very much.

toluene (0.24 g., 46%); yellow crystals m.p. 195-196°.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.49; H, 4.24; N, 19.55.

The above product VIII, when heated with 2% aqueous potassium hydroxide on a steam bath, gave the potassium salt of V (80%).

Methyl 6'-Methyl-2,2'-dipyridylamino-3-carboxylate (IX).

Method a: from VIII.

A mixture of VIII (0.1 g.) and 10 ml. of anhydrous methanol, was refluxed for 10 hours. There was obtained 0.1 g. (87%) of IX upon concentration of the solution. Recrystallization from methanol gave white needles melting at 128-129°.

Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 63.86; H, 5.63; N, 16.97.

Method b: from V.

Dry hydrogen chloride was passed through a boiling solution of 0.05 g. of V in 10 ml. of anhydrous methanol for 1 hour. Evaporation of the solvent gave a residue which upon neutralization with dilute ammonium hydroxide gave 0.025 g. of IX (47%).

2-Methylanthyridin-5-one (VI).

Method a: from V.

To 7.0 ml. of preheated (220°) concentrated sulfuric acid was added 3.0 g. of V. The reaction mixture was then warmed at 270° for 20 minutes, and, after cooling, poured onto crushed ice. After alkalinization with concentrated ammonium hydroxide the crude precipitate (0.73 g.) was collected, washed with water and extracted several times with boiling ethanol. There was obtained 0.25 g. of VI (9%) upon concentration of the ethanolic solution. The analytical sample was obtained by recrystallization from ethanol, m.p. 296-298° dec.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 67.99; H, 4.12; N, 20.22.

Method b: from VIII.

This compound (0.35 g.) was converted under the conditions described in method a) into compound VI in 28% yield.

Anthyridin-5-one-2-carboxylic Acid (VII).

A solution of 0.25 g. of VI and 0.6 g. of sodium dichromate in 6 ml. of 60% sulfuric acid was heated at 180° for 10 minutes. After cooling the solution was poured into water and the resulting precipitate was collected, washed with water and dried, 0.05 g. of VII (17%). Crystallization from dimethylsulfoxide gave pale yellow crystals with m.p. above 320°; principal ir peaks: 5.84, 6.16, 6.28, 7.02, 7.50, 8.16, 8.80, 12.85 μ.

Anal. Calcd. for $C_{12}H_7N_3O_3$: C, 59.75; H, 2.93; N, 17.42. Found: C, 59.62; H, 3.24; N, 17.45.

Anthyridin-5-one (Id).

Method a.

Fifty mg. of VII was intimately mixed with copper powder and the mixture was heated *in vacuo* (2-3 mm.) at 300°. The resulting sublimate was treated with 10% sodium carbonate solution and the residue collected by filtration; there was obtained a small amount of Id (6).

Method b.

A mixture of 0.1 g. of VII and copper chromite (0.02 g.) in 1.0 ml. of quinoline was refluxed for 30 minutes and after cooling, poured into 5% hydrochloric acid. The solid was collected, washed with water, and treated with 10% sodium carbonate solution and the insoluble residue sublimed *in vacuo* (2-3 mm.) at 250° (0.025 g. of Id; 30%).

2,6-Dichloroanthyridine (X).

A mixture of 1.0 g. of anthyridine-2,6-dione (Ib) (2) and 15 ml. of phosphorus oxychloride was heated at 80° for fifteen hours. The excess phosphorus oxychloride was removed *in vacuo* and the residue poured portionwise onto a well-cooled mixture of ice and ammonium hydroxide. The resulting brown solid was collected and extracted with hot methylene chloride (300 ml.). The extract was dried over anhydrous magnesium sulfate and evaporated to dryness at reduced pressure to give 0.45 g. of X. The alkaline mother-liquors were then extracted with three 200 ml.-portions of methylene chloride and the combined extracts were dried. After evaporation of the solvent there was obtained other 0.25 g. of X (total yield 59%). The analytical sample was obtained by crystallization from toluene; yellow powder with m.p. above 320°; principal ir peaks: 6.24, 6.55, 8.75, 9.12, 10.10, 12.64, 13.82 μ.

Anal. Calcd. for $C_{11}H_5Cl_2N_3$: C, 52.84; H, 2.01; Cl, 28.36. Found: C, 52.70; H, 2.40; Cl, 28.00.

7-Azidotetrazolo[1,5-*a*]anthyridine (XI).

To a solution of 0.2 g. of X in 5 ml. of dimethylformamide was added 0.3 g. of sodium azide and the mixture was stirred at room temperature for 10 hours. The reaction mixture was poured into water and the precipitate was collected, washed with water and dried (0.145 g., 69%). The product was crystallized from dimethylformamide giving brown crystals which decompose explosively at 190° (capillary tube); principal ir peaks: 4.70, 6.22, 6.48, 7.12, 7.43, 7.70, 9.28, 11.72, 12.09, 13.50 μ.

Anal. Calcd. for $C_{11}H_5N_9$: C, 50.23; H, 1.91. Found: C, 50.65; H, 1.59.

6-Chloroanthyridin-2-one (XII).

A suspension of 0.4 g. of 2,6-dichloroanthyridine (X) in 10 ml. of water was made alkaline with a few drops of sodium hydroxide solution and heated on steam bath for one hour. Acidification of the filtered solution gave 0.31 g. (81%) of XII. The analytical sample was purified by crystallization from dimethylformamide. White crystals with m.p. above 320°; principal ir peaks: 5.80, 6.28, 6.48, 7.75, 11.00, 11.75, 12.30, 13.00 μ.

Anal. Calcd. for $C_{11}H_6ClN_3O$: C, 57.03; H, 2.60; Cl, 15.30. Found: C, 57.14; H, 2.81; Cl, 15.70.

6-Azidoanthyridin-2-one (XIII).

To a hot solution of 0.1 g. of XII in 15 ml. of dimethylformamide, was added 0.2 g. of sodium azide. After stirring at room temperature for 15 hours, the reaction product was collected, washed with water and dried (0.1 g., 97% of XIII). The product was purified by crystallization from dimethylsulfoxide; brown crystals with m.p. above 320°; principal ir peaks: 4.70, 6.00, 6.29, 7.76, 10.50, 10.78, 11.39, 12.17 μ.

Anal. Calcd. for $C_{11}H_6N_6O$: C, 55.40; H, 2.52. Found: C, 55.50; H, 2.71.

Acknowledgment.

This work was supported by a grant from the Consiglio Nazionale delle Ricerche. We thank Dr. G. Biagi for the collaboration in the synthesis of 2-methylanthyridin-5-one.

REFERENCES

(1) S. Carboni, A. Da Settimo and I. Tonetti, *J. Heterocyclic*

Chem., 7, 875 (1970).

(2) S. Carboni, A. Da Settimo, P. L. Ferrarini, I. Tonetti and D. Bertini, *Gazz. Chim. Ital.*, **97**, 1274 (1967).

(3) See *e.g.* (a) R. N. Castle and K. Kaji, *Tetrahedron Letters*, 393 (1962); (b) T. Kinoshita and R. N. Castle, *J. Heterocyclic Chem.*, **5**, 845 (1968); (c) S. F. Martin and R. N. Castle, *ibid.*, 6, 93 (1969); (d) T. Nakashima and R. N. Castle, *ibid.*, 7, 209 (1970).

(4) R. G. Shepherd and J. L. Fedrick, "Advances in Heterocyclic Chemistry," (A. R. Katritzky, Ed.), Vol. 4, Academic Press, New York, N. Y., 1965, p. 210.

(5) H. Hauptmann and W. F. Walter, *Chem. Rev.*, **62**, 347 (1962).

(6) S. Carboni, A. Da Settimo and D. Segnini, *J. Heterocyclic Chem.*, **6**, 369 (1969).

(7) S. Carboni and M. Pardi, *Ann. Chim.* (Rome), **49**, 1228 (1959).

(8) S. Carboni, A. Da Settimo, P. L. Ferrarini and P. L. Ciantelli, *J. Heterocyclic Chem.*, 7, 1037 (1970), and references therein.