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CHEMOTHERAPEUTIC DYES. PART II

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Several 1-amino- and 3-aminophenoxazines containing alkyl and/or ester groupings have been synthesised with a view to studying their tuberculostatic activity.

In continuation of our previous work on chemotherapeutic dyes (this *Journal*, 1956, 33, 671) several more substituted aminophenoxazines have been synthesised with a view to studying the effect of various substituents on tuberculostatic activity (cf. Bootlroyd *et al.*, *J. Chem. Soc.*, 1953, 1504). For this purpose nitrophenoxazines were prepared by the ring-closure of the corresponding diphenylamines with sodium hydroxide, following the method of Ullmann and Sane (*Ber.*, 1911, 44, 3735); the nitrophenoxazines were then catalytically reduced to the corresponding aminophenoxazines. In two cases, however, the nitrophenoxazines were directly obtained by the condensation of 2-aminophenol and 4-methyl-2-aminophenol with 4-chloro-3 : 5-dinitro-1-*tert.*-amylbenzene and 1 chloro-4 : 6-dinitro-3-ethylbenzene respectively, in alkaline medium.

The required diphenylamines were obtained from methyl 2-chloro-3 : 5-dinitrobenzoate, ethyl 2-chloro-3 : 5-dinitrobenzoate, ethyl 4-chloro-3 : 5-dinitrobenzoate and 1-chloro-4 : 6-dinitro-3-ethylbenzene by condensing with 2-aminophenol and 4-methyl-2-aminophenol. Two of these chloro compounds, viz., 1-chloro-4 : 6-dinitro-3-ethylbenzene and 4-chloro-3 : 5 dinitro-1-*tert.*-amylbenzene, as well as 4 : 6-dinitro-3-ethyl-phenol, have been prepared for the first time. *m*-Ethylphenol was nitrated by a special technique detailed in the Experimental. The replacement of hydroxy group by chlorine in the dinitrophenols was achieved by the action of phosphorus oxychloride in the presence of diethylaniline. 4-Methyl-2-aminophenol required in the above condensations was obtained by the reduction of 2-nitro-*p*-cresol in dioxane medium using Raney nickel as catalyst (Freeman and White, *J. Org. Chem.*, 1956, 21, 379).

Reduction of the nitrophenoxazines was carried out in acetic acid medium with hydrogen in the presence of Adams' catalyst and the bases were isolated in their oxidised form as imine hydrochlorides. As the hydrochlorides did not show satisfactory melting points due to the presence of some water-insoluble impurities, the bases were characterised through their picrates.

Experimental

4 : 6-Dinitro-3-ethylphenol (I).—*m*-Ethylphenol (16 g.) was added to H_2SO_4 (40 c.c., cold conc., A.R.). The resulting phenolsulphonic acid was then added dropwise into 30 c.c. nitric acid (*d* 1.5) under stirring, the temperature being maintained between 0° and 5°. The mixture was left overnight, allowing the temperature to rise very slowly to the room temperature. Fine-yellow needles separated out. To ensure complete nitra

tion, however, the product was heated over a boiling water-bath for 5 minutes and then poured over crushed ice. The precipitated dinitrophenol was filtered and recrystallised from ethanol, yield 26 g., m.p. 85°. (Found: N, 13.01. $C_8H_8O_5N_2$ requires N, 13.21%).

1-Chloro-3-ethyl-4 : 6 - dinitrobenzene (II).—The above compound (I, 25 g.) was dissolved in cold $POCl_3$ (125 c.c.) and the mixture cooled externally by ice, and to it diethylaniline (40 c.c.) was gradually added dropwise under stirring. The mixture which turned red was heated in the steam-bath for 2 hours. After cooling, it was poured over crushed ice (1 kg.). The solid separating out was filtered, washed with excess of water and then dried. Recrystallisation from ethanol gave shining flakes with brownish tinge, yield 25 g., m.p. 90°. (Found : C, 41.08 ; H, 2.85 ; N, 11.99. $C_8H_7O_4N_2Cl$ requires C, 41.64 ; H, 3.03 ; N, 12.15%).

4-Chloro-3 : 5-dinitro 1-tert.- amylbenzene (III). — 3 : 5-Dinitro-1 - *tert.*-amylphenol (15 g.), obtained by the nitration of *p-tert.*-amylphenol in acetic acid medium (Anschutz and Rauff, *Annalen*, 1903, **327**, 211), was treated with $POCl_3$ (80 c.c.) and diethylaniline (24 c.c.) as in the preceding case. A gummy mass was obtained after decomposition, which after dissolving in methanol was left overnight. The crystalline product (cream coloured flakes) obtained was recrystallised from methanol once more, yield 9 g., m.p. 90-91°. (Found : C, 48.02 ; H, 4.35 ; N, 10.33. $C_{11}H_{13}O_4N_2Cl$ requires C, 48.44 ; H, 4.77 ; N, 10 28%).

In a similar way, the following chloro compounds were obtained from the corresponding dinitrophenols. Their melting points were found to be in accordance to the figures recorded in the literature.

TABLE I

Compounds.	M.P.
(IV) Methyl 2-chloro-3 : 5-dinitrobenzoate	90°
(V) Ethyl 2-chloro-3 :5-dinitrobenzoate	54-55°
(VI) Ethyl-4-chloro-3 :5-dinitrobenzoate	83°

2'-Hydroxy-2 : 4-dinitro-5-ethyldiphenylamine (VII).—To a suspension of 1-chloro-3-ethyl-4 : 6-dinitrobenzene (4.6 g., 0.02 *M*) and *o*-aminophenol (2.2 g., 0.02 *M*) in ethanol (20 c.c.) sodium acetate solution (12 c.c., *ca.* 2*N*) was added under stirring. A reddish brown product separated out on refluxing for 2 hours in a steam-bath, under stirring. After cooling, the diphenylamine was filtered and recrystallised from ethanol in shining small crystals, yield 5.5 g., m.p. 180°. (Found : C, 55.10 ; H, 3.92 ; N, 14.01. $C_{14}H_{13}O_5N_3$ requires C, 55.45 ; H, 4.29 ; N, 13.86%).

In a similar way, the following diphenylamines were prepared (Table II).

TABLE II

	Diphenylamine. (A = 2′-hydroxy).	M.P.	Yield.	Crystalline form.	Nitrogen. Found.	Nitrogen. Calc.
(VIII)	A-2 : 4-dinitro-5-carbomethoxy	190°	96.0%	Orange flakes	12.57	12.61
(IX)	A-5′-methyl-2 : 4-dinitro-6-carbomethoxy-	207°	92.3	Bright orange tiny crystals	12.25	12.10
(X)	A-2 : 4-dinitro-6-carbethoxy-	167°	84.0	Reddish orange needles	11.95	12.10
(XI)	A-5′-methyl-2 : 4-dinitro-6-carbethoxy-	190°	70.0	Reddish brown shining crystals	11.82	11.61
(XII)	A-2 : 6 dinitro-4-carbethoxy-	128°	86.5	Orange shining flakes	11.89	12.10
(XIII)	A-5′-methyl-2 : 6-dinitro-6-carbethoxy-	178°	86.0	Brown small shining crystals	11.56	11.63

2-Ethyl-3-nitrophenoxazine (XIV).—2′- Hydroxy-2 : 4-dinitro-5-ethyldiphenylamine (5 g.) was suspended in ethanol (20 c.c.) and about 15 c.c. of 2*N* sodium hydroxide solution was added under stirring. Colour of the reaction mixture instantaneously darkened on the addition of alkali solution after which the mixture was refluxed for half an hour. On cooling in a freezing mixture, dark reddish brown nitrophenoxazine separated out. It was filtered, washed with dilute caustic soda solution followed by a little ethanol, and recrystallised from acetic acid, m.p. 208°, yield 3.8 g. (89%). (Found: C, 65.14 ; H, 4.09 ; N, 10.86. $C_{14}H_{11}O_5N_3$ requires C, 65.62 ; H, 4.69 ; N, 10.94%).

The following nitrophenoxazines (Table III) were prepared in a similar way by the ring-closure of the corresponding diphenylamines. The nitrophenoxazines were recrystallised from *o*-xylene or acetic acid and were, in general, dark red or dark reddish brown crystalline solids.

TABLE III

	Phenoxazine.	M.P.	Yield.	Mol. formula.	% Nitrogen. Found.	% Nitrogen. Calc.
(XV)	1-Carbomethoxy-3-nitro-	225°	97.0%	$C_{14}H_{10}O_5N_2$	9.99%	9.97%
(XVI)	1-Carbomethoxy-8-methyl-3-nitro-	265°	97.0	$C_{15}H_{12}O_5N_2$	9.23	9.33
(XVII)	1-Carbethoxy-3-nitro-	250°	84.6	$C_{15}H_{12}O_5N_2$	9.46	9.33
(XVIII)	1-Carbethoxy-8-methyl-3-nitro-	228°	88.4	$C_{16}H_{14}O_5N_2$	9.18	8.92
(XIX)	3-Carbethoxy-1-nitro-	192°	90.0	$C_{15}H_{12}O_5N_2$	9.40	9.33
(XX)	3-Carbethoxy-8-methyl-1-nitro-	220°	96.0	$C_{16}H_{14}O_5N_2$	9.04	8.92

2-Ethyl-8-methyl-3-nitrophenoxazine (XXI).—1-Chloro-4 : 6-dinitro-3-ethylbenzene (3.3 g.) and 4-methyl-2-aminophenol (1.8 g.) were suspended in 20 c.c. ethanol and 9 c.c. of approximately 2*N* sodium acetate solution was added. After refluxing the mixture over steam-bath for an hour and a half under stirring, a 10% NaOH solution (12 c.c.) was added. The mixture was refluxed for 40 minutes more. On cooling in ice, a dark brown product separated out which was filtered and then washed with dilute NaOH and ethanol. The nitrophenoxazine was purified by recrystallisation from *o*-xylene, m.p. 236°, yield 3.5 g. (90.6%). (Found : C, 66.20 ; H, 4.82 ; N, 10.51. $C_{15}H_{14}O_3N_2$ requires C, 66.6 ; H, 5.18 ; N, 10.37%).

3-tert.-*Amyl-1-nitrophenoxazine* (XXII).—3-*tert.*-Amyl-1-nitrophenoxazine was also directly obtained from *o*-aminophenol (0.02*M*) and 4-chloro-3:5-dinitro-1-*tert.*-amylbenzene (0.02*M*) as in the previous case and was recrystallised from methanol in dark reddish brown crystals, m.p. 148°, yield 44%. (Found: N, 9.58. $C_{17}H_{18}O_3N_2$ requires N, 9.40%).

Aminophenoxazines

3-*Imino-2-ethylphenoxazine* (XXIII).—2-Ethyl-3-nitrophenoxazine (1 g.), suspended in glacial acetic acid (30 c.c.), was reduced at the room temperature (25°) by shaking in an atmosphere of hydrogen (60 lbs. pressure) for 12 hours, using Adams' catalyst (60 mg.). A light red solution was obtained which turned dark brown (with a greenish tinge) on exposure to air. It was quickly filtered and concentrated in vacuo to about 10 c.c. The free base was then obtained by neutralising with concentrated ammonium hydroxide. The crude base was filtered, dried and dissolved in anhydrous benzene. On passing dry HCl gas through the benzene solution, the imine hydrochloride (1 g.) separated out as a brown product.

The *hydrochloride* gave a red solution in water but contained some insoluble impurity.

The *picrate* was obtained as a red precipitate by adding a saturated aqueous picric acid solution to the filtered aqueous solution of the imine hydrochloride and was recrystallised from ethanol, m.p. 230-32° (decomp.). (Found: C, 52.37; H, 3.00; N, 15.58. $C_{14}H_{12}ON_2.C_6H_3O_7N_3$ requires C, 52.9; H, 3.31; N, 15.45%).

3-*Imino-2-ethyl-8-methylphenoxazine* (XXIV).—The nitrophenoxazine (XVIII, 1g.) was reduced catalytically as in the previous case, yielding a brown solution which darkened on exposure. The base which separated after neutralising with concentrated ammonium hydroxide was directly converted into the picrate by adding a dry ethereal solution of picric acid to the dry ethereal extract of the base. The picrate (1 g.) was filtered and washed with ethanol; m.p. 220-22° (decomp.). (Found: N, 15.26. $C_{15}H_{14}ON_2.C_6H_3O_7N_3$ requires N, 14.99%).

3-*Imino-1-carbomethoxyphenoxazine* (XXV).—1-Carbomethoxy-3-nitrophenoxazine (1 g.) on catalytic reduction yielded a green solution which turned blue on exposure to air. The base obtained was converted into its hydrochloride (0.9 g.) and finally into the picrate. The imine hydrochloride and the picrate were both of green colour, of which the latter was purified by recrystallisation from ethanol; m.p. of the picrate, 170°. (Found: N, 14.28. $C_{14}H_{10}O_3N_2.C_6H_3O_7N_3$ requires N, 14.49%).

3-*Imino-1-carbomethoxy-8-methylphenoxazine* (XXVI).—In the reduction of 1-carbomethoxy-8-methyl-3-nitrophenoxazine (1 g.), some unusual colour changes were observed. The acetic acid solution was green on reduction but turned scarlet-red after exposure. During the removal of acetic acid by reduced pressure distillation, the red solution became violet. The base obtained in the oxidised form after neutralising the acidic solution with concentrated ammonium hydroxide was violet-black in colour. On passing dry HCl gas in the dry benzene extract of the base, the imine hydrochloride (1 g.) separated out as a 'green' product. Aqueous solution of the hydrochloride was reddish

violet in colour and on treatment with a saturated picric acid solution, a yellow precipitate of the picrate was obtained. The precipitate was filtered and washed with a little ethanol, m.p. 162°. (Found: N, 13.94. $C_{15}H_{12}O_3N_2.C_6H_3O_7N_3$ requires N, 14.08%).

3 *Imino*-1-*carbethoxyphenoxazine* (XXVII).—Reduction of 1-carbethoxy-3-nitrophenoxazine (1 g.) was carried out for 12 hours at 60 lbs. initial hydrogen pressure. The light brown solution turned red on exposure. The free base was converted into the imine hydrochloride which separated out as a green compound (1 g.). The picrate was obtained in the usual way as a yellowish green precipitate which was recrystallised from ethanol, m.p. 168° (decomp.). (Found: N, 14.34. $C_{15}H_{12}O_3N_2.C_6H_3O_7N_3$ requires N, 14.08%).

3-*Imino*-1-*carbethoxy*-8-*methylphenoxazine* (XXVIII) was obtained by the reduction of 1-carbethoxy-8-methyl-3-nitrophenoxazine (1 g.) in acetic acid medium. The reduced solution was reddish brown which darkened on exposure and ultimately turned reddish violet. The imine hydrochloride (1 g.) prepared was of bright green colour but gave a red solution in water. The *hydrochloride* was finally converted into the picrate which separated out as a dirty green precipitate and was recrystallised from ethanol, m.p. 167°. (Found: N, 13.51. $C_{16}H_{14}O_3N_2$. $C_6H_3O_7N_3$ requires N, 13.70%).

1-*Imino*-3-*carbethoxyphenoxazine* (XXIX).—3-Carbethoxy-1-nitrophenoxazine (1 g.) was reduced to the corresponding aminophenoxazine and isolated as imine hydrochloride (1.05 g.), a green compound, in the usual way. The hydrochloride was not completely soluble in water as usual. The *picrate* was therefore prepared which separated as a yellow precipitate and was recrystallised from a mixture of ethanol and aqueous picric acid, m.p. 132° (decomp.). (Found: N, 14.22. $C_{15}H_{12}O_3N_2.C_6H_3O_7N_3$ requires N, 14.08%).

1-*Imino*-3-*carbethoxy*-8-*methylphenoxazine* (XXX).—Reduction of 3-carbethoxy-8-methyl-1-nitrophenoxazine (1 g.) was carried out in the usual way. The reduced solution turned reddish violet on exposure. The imine hydrochloride (0.9 g.) obtained from the base was a green compound and was converted into the picrate which separated as a dark green precipitate. The picrate was purified by recrystallisation from ethanol, m.p. 146° (decomp.). (Found: N, 13.83. $C_{16}H_{14}O_3N_2.C_6H_3O_7N_3$ requires N, 13.70%).

1-*Imino*-3-tert.-*amylphenoxazine* (XXXI).—The suspension of 3-*tert*.-amyl-1-nitrophenoxazine (1 g.) in acetic acid (30 c.c.) on reduction gave an almost colorless solution which soon turned blue on exposure. The imine hydrochloride was obtained from the base as usual but it contained about 50% material insoluble in water. The *picrate* was therefore prepared directly from the base by adding a dry ethereal solution of picric acid to the dry ethereal extract of the base and was obtained as a reddish brown precipitate. It was filtered and washed with ethanol, m.p. 138-40° (decomp.). (Found: N, 14.28. $C_{17}H_{18}ON_2.C_6H_3O_7N_3$ requires N, 14.14%).

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