650. *The Oxidation of Derivatives of* o-*Phenylenediamine. Part IV.* A New Series of Glyoxalinophenazines derived from Anilino*apo*safranines and their Behaviour on Hydrogenation.*

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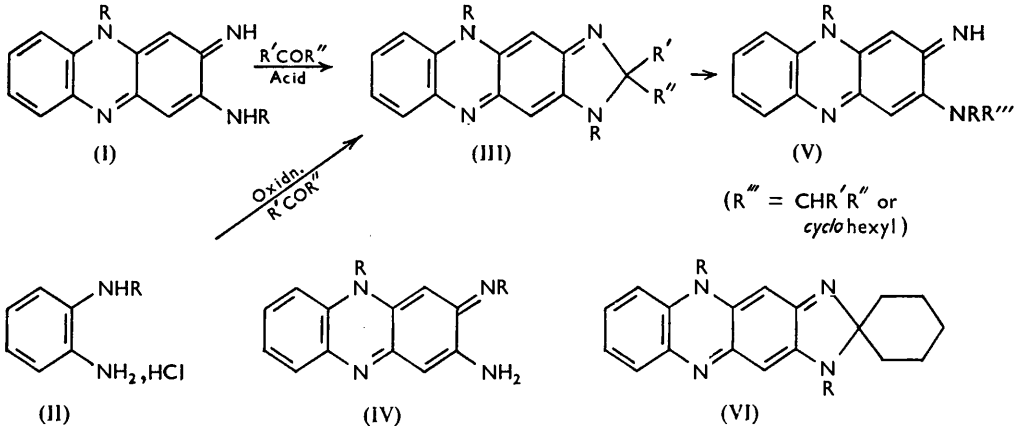
Certain ketones condense with anilino*apo*safranine derivatives to give glyoxalinophenazines. The same products are formed from suitable *o*-phenylenediamine derivatives by oxidation in the presence of the ketone. Catalytic hydrogenation of the glyoxalinophenazines yields in most cases substituted anilino*apo*safranines containing a further substituent in the N^2-position. The latter derivatives are extremely potent substances in combating experimental tuberculosis in mice.

IN Part I [1] the formation of glyoxalinophenazine derivatives from anilino*apo*safranine was mentioned as a confirmation of the structure of the latter. The present paper describes the synthesis of a number of these compounds, the evidence on which their structure is based, and their behaviour on hydrogenation.

Glyoxalinophenazines may be formed by condensation of certain ketones with the anilino*apo*safranine derivatives in acid solution, preferably in syrupy phosphoric or polyphosphoric acid, or by oxidation of the corresponding 2-aminodiphenylamine salt with ferric chloride or *p*-benzoquinone in the presence of excess of ketone. With *cyclo*hexanone, acetone, and derivatives of the latter, yields were of the order of 50%, while with acetophenone and 4-acetylpyridine they were below 20%. No glyoxalinophenazine could be isolated with benzophenone, 4 : 4′-dihydroxybenzophenone, or deoxybenzoin in either synthetic method. The glyoxalinophenazines (III) are yellow to orange-red compounds which exhibit a greenish-yellow fluorescence in solution and they are formed as shown.



It is unlikely that the anilino*apo*safranines (I; R = Ph) are intermediates in the formation of the glyoxalinophenazines (III) from the *o*-phenylenediamine derivatives (II), as the glyoxalinophenazines may be obtained from compounds of type (II) in cases where oxidation of the latter in the absence of the ketone does not yield anilino*apo*safranine derivatives.[2] Further, the glyoxalinophenazines (III) are much more readily formed by the oxidation process than they are by condensation of the ketone with the anilino*apo*safranines (I). In all cases where glyoxalinophenazines (III) were obtained by oxidation of *o*-phenylenediamine derivatives, compounds of type (IV) were also produced.

The structure of the glyoxalinophenazines is based on the following facts. During the

* Part III, *J.*, 1956, 896.

[1] Barry, Belton, O'Sullivan, and Twomey, *J.*, 1956, 888.
[2] *Idem*, *J.*, 1956, 893.

condensation of anilino*apo*safranine derivatives (I) with a ketone, a molecule of water is eliminated without the production of an olefinic bond. A molecular-weight determination gave a value of 420 for the glyoxalinophenazine (III; R = Ph, R′ = R″ = Me): the calculated value is 402. Compounds of type (IV) do not yield glyoxalinophenazines on treatment with a ketone in the presence of acid. The formation of a tribromo-derivative of compound (I; R = Ph) was used as evidence for the presence of the =NH group in anilino*apo*safranine since the isomer (IV; R = Ph) yielded only a dibromo-derivative.[1] We have now shown that the glyoxalinophenazine (III) yields a dibromo-derivative, the bromine atoms occupying the 1 : 4-positions of the phenazine nucleus. Further evidence for the absence of the =NH group in the glyoxalinophenazines is the stability of these compounds in boiling acetic anhydride.[1] In the degradation of anilino*apo*safranine (I; R = Ph) anilino*apo*safranone was isolated; the same product was obtained when the glyoxalinophenazine (III; R = Ph, R′ = R″ = Me) was degraded, the alkyl substituent being eliminated. It is therefore clear that only the nitrogen atoms at the 2- and the 3-position of the phenazine nucleus can be involved in the condensation. The presence of a glyoxaline ring in the compounds (III) is supported by the formation of ring compounds by the condensation of acetone with anthranilamide derivatives in the presence of hydrochloric acid.[3] Hydrogenation, in alcohol, at room temperature and pressure with Adams catalyst, resulted in the uptake by the glyoxalinophenazines of two molar equivalents of hydrogen to give colourless or nearly colourless solutions. On exposure to the air the solutions rapidly became dark-red and compounds of structure (V) separated. It is presumed that the quinonoid system in the compounds (III) is first reduced and then hydrogenolysis of the 2′ : 3′-bond of the glyoxaline ring occurs. This recalls the hydrogenolysis of quaternary salts of Schiff's bases recorded by Forbes.[4] The compounds (V) are unstable in boiling acetic anhydride. They give tribromo- in contrast to the dibromo-derivatives obtained from the glyoxalinophenazines. The compounds (V) do not fluoresce in solution and the close resemblance of their properties to those of anilino*apo*safranine derivatives (I) strongly supports the structure assigned.

The compounds (III; R = Ph, R′ = R″ = Me) and (V; R = Ph, R‴ = Pr^i) were examined spectrophotometrically in the infrared region by Mr. E. R. Stuart of the Chemical Laboratory. The samples were submitted under code numbers, B.621 and B.670 respectively. He reports as follows: " B.670 shows sharp absorption in the region of 3300 $cm.^{-1}$ characteristic of the =NH group.[5] This absorption is not shown by B.621. In addition an extra band at 2880 $cm.^{-1}$ in B.670 appears to indicate a tertiary carbon–hydrogen bond in this compound. This band is also absent from the spectrum of B.621.

" In both cases, the spectrum in the 1400—1600 $cm.^{-1}$ region is complex owing to phenyl residues and C=N bonds, but the spectra show considerable similarities. In B.670 a well-defined doublet at 1160—1120 $cm.^{-1}$ is taken as being indicative of an *iso*propyl group absent in B.621."

In the ultraviolet region these compounds have light absorption maxima at 280 and 475 mμ (B.670) and 270 and 465 mμ (B.621). For the hydrochlorides the maxima were observed at 280 and 490 mμ (B.670, HCl) and 270, 475, and 500 mμ (B.621,2HCl).

The use of *cyclo*alkyl ketones in the glyoxalinophenazine synthesis results in the formation of *spiro*-compounds of type (VI) which also undergo hydrogenolysis, giving N^2-*cyclo*alkylanilino*apo*safranine derivatives (V; R‴ = *cyclo*hexyl). The hydrogenation appears to be somewhat temperamental, as we have found that ring opening did not take place under experimental conditions apparently identical with those which we had already shown to be satisfactory for the hydrogenolysis. However, frequent repetition of the hydrogenation under varied conditions always has failed to open the glyoxaline ring in compounds (III) where R′ or R″ = aryl or where R = *cyclo*hexyl or benzyl. Hydrogenation of compound (III; R = Ph; R′ = Me, R″ = CH_2Cl) resulted in the loss of the chlorine atom, the product being the hydrochloride of the imine (V; R = Ph, R‴ = Pr^i). Again hydrogenation of the glyoxalino-compound (III; R = Ph, R = Me,

[3] Carrington, *J.*, 1955, 2527.
[4] Forbes, *J.*, 1955, 3926.
[5] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.

R″ = CH_2·CO_2Et) resulted in considerable decomposition and no identifiable material was isolated; however, this compound was readily reduced in ether by lithium aluminium hydride to the corresponding alcohol (III; R = Ph, R′ = Me, R″ = CH_2·CH_2·OH), and the latter was then hydrogenated to yield the ring-opened compound (V; R = Ph, R′ = Me, R″ = CH_2·CH_2·OH).

When tested in experimental tuberculosis in mice, some of the compounds of type (V) have shown greater protective activity than we have encountered so far with any other type of compound. The biological details will be published elsewhere.

Experimental

Glyoxalinophenazines (III) *from* (a) o-*Phenylenediamines and* (b) *Anilino*apo*safranines.*—The following are typical preparations:

5 : 1′-*Di*-(p-*chlorophenyl*)cyclo*hexane*spiro-2′-*glyoxalino*(5′ : 4′-2 : 3)*phenazine* (VI; R = *p*-C_6H_4Cl). Method (a): 2-Amino-4′-chlorodiphenylamine hydrochloride (2·2 g.) and *cyclo*hexanone (2 c.c.) in ethanol (60 c.c.) were treated with *p*-benzoquinone (2 g.) in aqueous ethanol (2 : 1; 70 c.c.) at 30°. After 30 min. the solution was made alkaline with aqueous sodium hydroxide (10%), and the precipitate collected, dried, and chromatographed in benzene on alumina. The first material eluted exhibited a strong green-yellow fluorescence in solution and was obtained as orange crystals (1·3 g.), m. p. 299—301° (from benzene–ligroin) (Found: C, 70·9; H, 5·0; N, 10·5; Cl, 13·4. $C_{30}H_{24}N_4Cl_2$ requires C, 70·5; H, 4·7; N, 11·0; Cl, 13·9%).

In general the yields were about 50%, except in the case of *N-cyclo*hexyl-*o*-phenylenediamine where it was 10%. The compounds are stable in boiling acetic anhydride.

5 : 2′-*Dihydro*-2′ : 2′-*dimethyl*-5 : 1′-*diphenylglyoxalino*(5′ : 4′-2 : 3)*phenazine* (III; R = Ph, R′ = R″ = Me). Method (b): Anilino*apo*safranine (2 g.), acetone (50 c.c.), ethanol (40 c.c.), and polyphosphoric acid (7 g.) were heated under reflux for 5 hr. The mixture was made alkaline and the product purified as in the previous preparation. The *compound* was obtained as orange crystals (1·0 g.), m. p. 230—232° (from benzene–ligroin), identical with the product obtained from 2-aminodiphenylamine hydrochloride and acetone by method (a).

The other *compounds* in this series have been tabulated (Table 1).

Table 1. 2′ : 2′-*Substituted* 5 : 2′-*dihydro*-5 : 1′-*diphenylglyoxalino*-(5′ : 4′-2 : 3)*phenazines.*

(III; R = Ph)			Found (%)				Required (%)		
R′	R″	M. p.	C	H	N	Formula	C	H	N
Me	Me [a]	230—232°	81·3	6·2	12·7	$C_{27}H_{22}N_4,\frac{1}{2}C_6H_6$	81·8	5·6	12·7
Me	Et	173—176	80·5	6·0	13·1	$C_{28}H_{24}N_4$	80·8	5·8	13·5
Et	Et [b]	216—218	80·0	6·3	13·0	$C_{29}H_{26}N_4$	80·9	6·0	13·0
Me	Bu^s	182—183	80·5	6·4	12·5	$C_{30}H_{28}N_4$	81·1	6·3	12·6
Me	CH_2·CO_2Et	151—152	75·7	6·0	11·5	$C_{30}H_{26}O_2N_4$	76·0	5·5	11·8
Me	CH_2·CH_2·OH	197—200	77·2	5·7	12·4	$C_{28}H_{24}ON_4$	77·8	5·6	13·0
Me	CH_2Cl [c]	187—190	73·8	5·5	12·4	$C_{27}H_{21}N_4Cl$	74·2	4·8	12·8
Me	Ph	223—225	83·7	5·5	10·7	$C_{32}H_{24}N_4,\frac{1}{2}C_6H_6$	83·5	5·4	11·1
Me	4-Pyridyl	265—266	80·3	5·1	14·7	$C_{31}H_{23}N_5$	80·0	5·0	15·1

5 : 1′-*Substituted* 5 : 2′-*dihydro*-2′ : 2′-*dimethylglyoxalino*(5′ : 4′-2 : 3)*phenazines.*

(III; R′ = R″ = Me) R								
p-C_6H_4Cl [d]	.....	246—247	68·8	4·5	11·4	$C_{27}H_{20}N_4Cl_2$	68·8	4·3	11·9
p-C_6H_4Me		211—213	80·1	6·2	13·0	$C_{29}H_{26}N_4$	80·9	6·0	13·0
*cyclo*Hexyl		257—258	78·6	8·2	13·5	$C_{27}H_{34}N_4$	78·3	8·2	13·5
CH_2Ph		224—225	80·5	6·3	13·0	$C_{29}H_{26}N_4$	80·9	6·0	13·0

5 : 1′-*Substituted* 5 : 2′-*dihydro*cyclo*hexane*spiro-2′-*glyoxalino*(5′ : 4′-2 : 3)-*phenazines.*

(VI) R =								
Ph		292—294	81·7	6·5	12·1	$C_{30}H_{26}N_4$	81·4	5·9	12·7
p-C_6H_4Cl [e]		299 [f]	70·9	5·0	10·5	$C_{30}H_{24}N_4Cl_2$	70·5	4·7	11·0
p-C_6H_4·OPr^i		289	76·9	6·8	9·4	$C_{36}H_{38}O_2N_4$	77·4	6·8	10·0

All compounds recrystallised from benzene–ligroin. [a] *M* (Rast), 420. $C_{27}H_{22}N_4$ requires *M*, 402. *Hydrochloride*, red crystals, m. p. 245° (decomp.) (Found: N, 11·5; Cl, 14·4. $C_{27}H_{22}N_4$,2HCl requires N, 11·8; Cl, 15·0%); *methosulphate*, red-brown, m. p. 265° (decomp.) [Found: N, 8·5; S, 9·5. $C_{27}H_{22}N_4$,2$(CH_3)_2SO_4$ requires N, 8·6; S, 9·8%]. [b] Also m. p. 145—147°. [c] Found: Cl, 8·1. $C_{27}H_{21}N_4Cl$ requires Cl, 8·1%. [d] Found: Cl, 14·8. $C_{27}H_{20}N_4Cl_2$ requires Cl, 15·1%. [e] Found: Cl, 13·3. $C_{30}H_{24}N_4Cl_2$ requires Cl, 13·9%. [f] With decomp.

2-N-iso*Propylanilino*apo*safranine* (3 : 5-*Dihydro*-3-*imino*-5-*phenyl*-2-N-iso*propylanilino*-*phenazine*).—The following is a typical hydrogenation: 5 : 2′-Dihydro-2′ : 2′-dimethyl-5 : 1′-diphenylglyoxalino(5′ : 4′-2 : 3)phenazine (1·5 g.), ethanol (80 c.c.), and Adams catalyst (0·1 g.) were shaken in an atmosphere of hydrogen at room temperature and pressure until an almost colourless solution was obtained; two mols. were consumed. The solution was filtered and became deep red on exposure to the air, and dark red crystals (1·2 g.) separated, having m. p. 198—199° (Found: C, 79·9; H, 6·0; N, 13·7. $C_{27}H_{24}N_4$ requires C, 80·2; H, 5·9; N, 13·9%).

The other *compounds* in this series have been tabulated (Table 2).

TABLE 2. N^2-*Substituted anilino*apo*safranine derivatives.*

(V; R = Ph; R‴ = CHR′R″)			Found (%)				Required (%)		
R′	R″	M. p.	C	H	N	Formula	C	H	N
Me	Me [a]	198—199°	79·9	6·0	13·7	$C_{27}H_{24}N_4$	80·2	5·9	13·9
Me	Et	174	80·1	6·2	13·5	$C_{28}H_{26}N_4$	80·4	6·2	13·4
Me	CH_2·CH_2·OH	212—214	77·2	6·1	12·9	$C_{28}H_{26}ON_4$	77·4	6·0	12·9
Et	Et	167—168	80·3	6·6	13·1	$C_{29}H_{28}N_4$	80·6	6·5	13·0
Me	Bu[a]	164	80·8	6·9	12·5	$C_{30}H_{30}N_4$	80·7	6·7	12·6
(V; R‴ = Pr[i]) R									
p-C_6H_4Cl [b]	.....	211—213	68·3	4·7	11·5	$C_{27}H_{22}N_4Cl_2$	68·5	4·7	11·8
p-C_6H_4Me		202—204	80·2	6·5	13·1	$C_{29}H_{28}N_4$	80·6	6·5	13·0
(V; R‴ = *cyclo*hexyl) R									
Ph		160—162	81·0	6·7	12·5	$C_{30}H_{28}N_4$	81·1	6·3	12·6
p-C_6H_4Cl [c]		248—250	70·1	5·0	11·0	$C_{30}H_{26}N_4Cl_2$	70·2	5·1	10·9
p-C_6H_4·OPr[i]	.....	200	77·7	7·1	—	$C_{36}H_{40}O_2N_4$	77·1	7·1	—

All the compounds in this Table were recrystallised from ethanol. [a] *Hydrochloride*, green crystals, m. p. 250° (decomp.) (Found: N, 12·7; Cl, 7·8. $C_{27}H_{24}N_4$,HCl requires N, 12·7; Cl, 8·1%); *methosulphate*, green crystals, m. p. 218° (decomp.) [Found: N, 10·4; S, 5·2. $C_{27}H_{24}N_4$,$(CH_3)_2SO_4$ requires N, 10·6; S, 6·0%]. [b] Found: Cl, 15·2. $C_{27}H_{22}N_4Cl_2$ requires Cl, 15·0%. [c] Found: Cl 13·9. $C_{30}H_{26}N_4Cl_2$ requires Cl, 13·8%.

Bromination of 5 : 2′-*Dihydro*-2′ : 2′-*dimethyl*-5 : 1′-*diphenylglyoxalino*(5′ : 4′-2 : 3)*phenazine*.—The base in carbon tetrachloride was stirred with excess of bromine in the same solvent. The precipitated hydrobromide was converted into the 1 : 4-*dibromo-base* with alcoholic sodium hydroxide and recrystallised from benzene–light petroleum. It was an orange powder, m. p. 245° (decomp.) (Found: Br, 24·8. $C_{27}H_{20}N_4Br_2,C_6H_6$ requires Br, 25·1%). Identical material was obtained when the glyoxalinophenazine was heated under reflux in chloroform with *N*-bromosuccinimide, and the product recrystallised from benzene–light petroleum.

Bromination of N^2-iso*Propylanilino*apo*safranine*.—By using the methods described the 1 : 4 : N^3-*tribromo-base* was obtained as a dark brown powder, m. p. 310° (Found: Br, 36·6. $C_{27}H_{21}N_4Br_3$ requires Br, 37·4%).

5 : 2′-*Dihydro*-5 : 1′-*diphenyl*-2′-(2-*hydroxyethyl*)-2′-*methylglyoxalino*(5′ : 4′-2 : 3)*phenazine*.—2′-Ethoxycarbonylmethyl-5 : 2′-dihydro-5 : 1′-diphenyl-2′-methylglyoxalino(5′ : 4′-2 : 3)phenazine (1·1 g.) in dry ether (250 c.c.) was added to a suspension of lithium aluminium hydride (1·5 g.) in dry ether (100 c.c.). After 3 hr. water was added and then dilute sulphuric acid. The acid layer was separated and made alkaline with aqueous sodium hydroxide. The precipitate was dried and extracted with benzene, and the extract chromatographed on alumina. The *glyoxalinophenazine* was obtained as a yellow powder (0·2 g.), m. p. 197—200° (Found: C, 77·3; H, 5·7; N, 12·4. $C_{28}H_{24}ON_4$ requires C, 77·8; H, 5·6; N, 13·0%).

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