903. *Polyazanaphthalenes. Part VIII.*[1] *Further Derivatives of Quinoxaline.*

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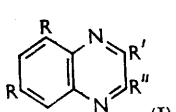
Syntheses of some quinoxaline derivatives from benzene-1,2,3,5-tetra-amine and from 3,5-dinitro-1,2-phenylenediamine are described and the orientation of the products is discussed. Analysis of the infrared spectra of a series of quinoxaline derivatives leads to the assignment of four ring-stretching vibration frequencies characteristic of this ring system.

The synthesis of two pteroic acid analogues containing the quinoxaline ring system was described in Part I of this series.[2] These compounds, however, lacked the 5- and 7-substituents (corresponding to the 2- and 4-substituents present in pteroic acid) which appear to be essential for biological activity; accordingly, we sought, in the present work, for methods which would lead to analogues containing such substituents.

Suitable starting materials for this purpose were benzene-1,2,3,5-tetra-amine[3] and 3,5-dinitro-1,2-phenylenediamine,[4] both of which are readily prepared from picramide;[5] both compounds condensed readily with biacetyl to give the quinoxaline (I; R = NH_2 or NO_2, R′ = R″ = Me) in good yield.



(I)

Condensation with αβ-dicarbonyl compounds may give rise to two isomeric products. Earlier work in the pteridine[6] and 1,4,5-triaza-naphthalene[2] series has shown that the product formed in neutral or weakly acid solution is that resulting from cyclisation of an intermediate derived by condensation of the β-carbonyl group with the most basic amino-group, the isomeride being formed in strongly acid solution. Since the 2-amino-group is likely to be the strongest in benzene-1,2,3,5-tetra-amine, the compound formed from this and pyruvaldehyde at pH 6·5 is regarded as 5,7-diamino-3-methylquinoxaline (I; R = NH_2, R′ = Me, R″ = H); only intractable products resulted from condensations with

[1] Part VII, preceding paper.
[2] Leese and Rydon, *J.*, 1955, 303.
[3] Nietzki and Hagenbach, *Ber.*, 1897, **30**, 539.
[4] Horner, Schwenk, and Junghanns, *Annalen*, 1953, **579**, 212.
[5] Holleman, *Rec. Trav. chim.*, 1930, **49**, 112.
[6] Elion, Hitchings, and Russell, *J. Amer. Chem. Soc.*, 1950, **72**, 78.

ethyl sodio-oxaloacetate, with dihydroxyacetone,[7] and with 1,2-dibromopropionaldehyde and *p*-aminobenzoic acid.[8] Similarly, the product obtained from 3,5-dinitro-1,2-phenylenediamine, in which the 1-amino-group is the stronger, and pyruvaldehyde in strongly acid solution is formulated as 5,7-dinitro-3-methylquinoxaline (I; R = NO_2, R′ = Me, R″ = H); no reaction occurred with dihydroxyacetone and only an intractable amorphous product resulted from the reaction with 1,2-dibromopropionaldehyde and *p*-aminobenzoic acid. Condensation of 3,5-dinitro-1,2-phenylenediamine with ethyl sodio-oxaloacetate in acetic acid afforded a product formulated, on similar grounds, as the 3-hydroxy-2-acetate (I; R = NO_2, R′ = OH, R″ = CH_2·CO_2Et), which could not be satisfactorily decarboxylated in aqueous alkali [2] owing to extensive decomposition; when the condensation was carried out in ethanolic sulphuric acid this compound was accompanied by the isomeride (I; R = NO_2, R′ = CH_2·CO_2Et, R″ = OH), which was hydrogenated to the corresponding diamine (I; R = NH_2, R′ = CH_2·CO_2Et, R″ = OH).

A more promising, and unambiguous, route to the required 3-methylquinoxalines appeared to be by the reductive cyclisation of the appropriate *N*-*o*-nitrophenylalanines [9] and a satisfactory yield of 5,7-diamino-2-hydroxy-3-methylquinoxaline (I; R = NH_2, R′ = Me, R″ = OH) was indeed obtained by catalytic hydrogenation of *N*-picrylalanine. At this stage in the work, however, the insignificant biological activity of the diamino-dimethyl compound (I; R = NH_2, R′ = R″ = Me) became known to us and further work in the quinoxaline series was abandoned.

It is well known [10] that the infrared spectra of benzene derivatives show four bands, near 1600, 1580, 1500, and 1450 cm.$^{-1}$, which arise from skeletal stretching modes of the ring carbon–carbon bonds, the intensity of the second band being markedly enhanced when the benzene ring is conjugated with a double bond. We have examined the infrared spectra of twelve quinoxaline derivatives, prepared in the course of the present and earlier [2] work, and the Table shows the bands which may be assigned to the stretching vibrations of the ring carbon–carbon or carbon–nitrogen bonds in these compounds, the means of the observed frequencies being 1608, 1552, 1505, and 1477 cm.$^{-1}$. Cheeseman,

Ring stretching vibrations of some substituted quinoxalines.

Substituents				Frequencies (cm.$^{-1}$)			
2-	3-	5-	7-	I	II	III	IV
Me	Me	H	H	1605w	1570m	1492s	1468m
H	H	NH_2	NH_2	1605s	1530m	1511s	1473m
H	Me	NH_2	NH_2	1607s	1544s	1511m	1475s
Me	Me	NH_2	NH_2	1618s	1552m	1500m	1476m
OH	Me	H	H	1611m	1568s	1505w	1487w
OMe	Me	H	H	1600s	—	1497w	1473s
OH	CH_2·CO_2Et	H	H	1620s	—	1506m	1487m
OH	Me	NH_2	NH_2	1594s	1528m	—	—
OH	CH_2·CO_2Et	NH_2	NH_2	1590s	—	1519w	—
OH	CH_2·CO_2Et	NO_2	NO_2	1613s	—	—	—
Me	Me	NO_2	NO_2	1618w	1576m	—	—
CH_2·CO_2Et	OH	NO_2	NO_2	1609s	1547s	—	—
			Mean ± S.E.	1608 ± 3	1552 ± 6	1505 ± 3	1477 ± 3

(Spectra measured in KBr discs. Intensities designated in the conventional manner.)

Katritzky, and Øksne [11] measured the infrared spectra of six quinoxaline derivatives and ascribed frequencies of about 1615 and 1590 cm.$^{-1}$ to ring stretching vibrations; their tabulated results also show bands at about 1505 and 1470 cm.$^{-1}$ which appear to correspond to our third and fourth bands. Our bands I—III appear to correspond to the three

[7] Forrest and Walker, *J.*, 1949, 2077.
[8] Waller *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 19.
[9] Plöchl, *Ber.*, 1886, **19**, 6; Leuckart and Hermann, *ibid.*, 1887, **20**, 24; Hinsberg, *Annalen*, 1888, **248**, 71.
[10] Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 2nd edn., 1958, p. 69.
[11] Cheeseman, Katritzky, and Øksne, *J.*, 1961, 3983.

similar bands (mean frequencies 1620, 1571, and 1498 cm.$^{-1}$) observed by Culbertson, Decius, and Christensen [12] in the infrared spectra of a series of quinazoline derivatives.

Experimental

Conventions used in reporting spectroscopic results are as in Part VII.[1]

Derivatives of Benzene-1,2,3,5-tetra-amine.—The trihydrochloride, prepared in 89% yield by the method of Nietzki and Hagenbach,[3] was used in the following condensations:

(*a*) Condensation with biacetyl gave 5,7-diamino-2,3-dimethylquinoxaline (I; R = NH_2, R′ = R″ = Me) (84% yield) as yellow needles, m. p. 227° (lit.,[3] m. p. 228°), $\nu_{max.}$ 3368, 3255, and 3076 (NH stretching), 3024 (aromatic CH stretching), 2952 and 2882 (methyl CH stretching), 1618 (aromatic CC or CN), 1590 (NH deformation), 1552, 1500, and 1476 (aromatic CC or CN), 1443 (methyl CH deformation), 1420 (not assigned), 1377 (methyl CH deformation) cm.$^{-1}$.

(*b*) Sodium carbonate (1·8 g.), in water (10 ml.), was added to a solution of the trihydrochloride (5·3 g.) and sodium sulphite (0·5 g.) in water (80 ml.), previously saturated with nitrogen. The solution was warmed to 40° and treated dropwise with a solution of glyoxal sodium bisulphite (5·97 g.) in water (60 ml.). After 20 min. at 60°, the mixture was cooled and the reddish-brown precipitate (2·8 g.) collected by filtration; it rapidly changed into a black, amorphous, infusible solid, insoluble in all the common organic solvents. The filtrate was basified with 40% aqueous sodium hydroxide and extracted with chloroform (8 × 100 ml.). The dried extract was concentrated to 10 ml. and treated with light petroleum (b. p. 60—80°); the precipitated 5,7-*diaminoquinoxaline* (I; R = NH_2, R′ = R″ = H) (0·28 g., 9%) crystallised from benzene in yellow needles, m. p. 170° (Found: C, 60·4; H, 5·7; N, 35·0. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%), $\nu_{max.}$ 3385, 3311, and 3192 (NH stretching), 3049 (aromatic CH stretching), 2765 and 2331 (not assigned), 1636 (NH deformation), 1605 (aromatic CC or CN), 1581 (NH deformation), 1530, 1511, and 1473 (aromatic CC or CN), 1449, 1433, and 1381 (not assigned) cm.$^{-1}$.

(*c*) A stirred solution of the trihydrochloride (2·65 g.) and sodium sulphite (0·25 g.) in water (100 ml.) was saturated with nitrogen and brought to pH 6·5 with N-sodium hydroxide; a mixture of 30% aqueous pyruvaldehyde (2·7 ml.), aqueous sodium hydrogen sulphite (*d* 1·34; 6·8 ml.) and water (7 ml.) was added immediately and the pH re-adjusted to 6·5 with more N-sodium hydroxide. Next day, dark material was removed and the filtrate basified with N-sodium hydroxide and extracted continuously with ether for 12 hr. Evaporation of the dried extract and crystallisation of the residue from a large volume of light petroleum (b. p. 100—120°), followed by recrystallisation from a small volume of benzene, gave 5,7-*diamino-3-methylquinoxaline* (I; R = NH_2, R′ = Me, R″ = H) (0·15 g., 9%) as pale green crystals, m. p. 225—227° (Found: N, 32·3. $C_9H_{10}N_4$ requires N, 32·2%), $\nu_{max.}$ 3381, 3306, and 3189 (NH stretching), 3042 (aromatic CH stretching), 2911 and 2849 (methyl CH stretching), 2754 (not assigned), 1634 (NH deformation), 1607 (aromatic CC or CN), 1573 (NH deformation), 1544, 1511, and 1475 (aromatic CC or CN), 1426 and 1374 (methyl CH deformation) cm.$^{-1}$.

Derivatives of 3,5-Dinitro-1,2-phenylenediamine.—Material, m. p. 215°, prepared according to Horner, Schwenk, and Junghanns,[4] was used in the following condensations:

(*a*) The diamine (500 mg.) and biacetyl (0·25 ml.) were heated for 90 min. in refluxing ethanol (15 ml.) containing 0·2N-hydrochloric acid (5 ml.). Next day, the precipitated 2,3-*dimethyl-5,7-dinitroquinoxaline* (I; R = NO_2, R′ = R″ = Me) (550 mg., 88%) was collected; recrystallisation from ethanol gave needles, m. p. 150° (Found: C, 48·1; H, 3·6; N, 22·3. $C_{10}H_8N_4O_4$ requires C, 48·4; H, 3·3; N, 22·6%), $\nu_{max.}$ 2939 (methyl CH stretching), 1618 and 1576 (aromatic CC or CN), 1528 (NO_2), 1448 (methyl CH deformation), 1401 (not assigned), 1359 (methyl CH deformation), 1340 (NO_2) cm.$^{-1}$.

(*b*) The diamine (400 mg.), suspended in ethanol (10 ml.) containing N-hydrochloric acid (1 ml.), was heated on the water-bath for 2 hr. with 30% aqueous pyruvaldehyde (0·6 ml.) in water (4 ml.). After having been kept overnight at 0°, the pale brown precipitate was extracted with hot water (10 ml.). Recrystallisation of the residue from ethanol gave 5,7-*dinitro-3-methylquinoxaline* (I; R = NO_2, R′ = Me, R″ = H) (110 mg., 23%), m. p. 166—168° (Found: C, 46·3; H, 2·7; N, 24·2. $C_9H_6N_4O_4$ requires C, 46·2; H, 2·6; N, 23·9%).

(*c*) The diamine (4 g.) and ethyl sodio-oxaloacetate (5·5 g.) were heated on the water-bath for 4 hr. in acetic acid (120 ml.). The solution was then concentrated under reduced pressure

[12] Culbertson, Decius, and Christensen, *J. Amer. Chem. Soc.*, 1952, **74**, 4834.

until solid began to separate. The crystals (4·08 g., 63%) which were deposited on cooling were collected and recrystallised from ethanol, yielding *ethyl 5,7-dinitro-3-hydroxyquinoxalin-2-ylacetate* (II; R = NO_2, R′ = OH, R″ = CH_2·CO_2Et) as orange needles, m. p. 214° (decomp.) (Found: C, 44·9; H, 3·0; N, 17·4. $C_{12}H_{10}N_4O_7$ requires C, 44·7; H, 3·1; N, 17·4%), $\nu_{max.}$ 3307, 3236, and 3085 (NH stretching), 2991 (not assigned), 2887 (methylene CH stretching), 1703 (ester C=O), 1641 (amide C=O), 1609 and 1547 (aromatic CC or CN), 1533 (NO_2), 1434 (methyl CH deformation), 1396 (not assigned), 1363 (methyl CH deformation), 1340 (NO_2) cm.$^{-1}$.

(*d*) A solution of ethyl sodio-oxaloacetate (4 g.) in ethanol (50 ml.) was added, during 30 min., to a refluxing, stirred suspension of the diamine (3 g.) in ethanol (30 ml.) and 2N-sulphuric acid (100 ml.). When the addition was half complete the reflux condenser was removed to allow ethanol to boil off. Heating was continued for 90 min. after the completion of the addition. The product, collected by filtration from the cooled mixture, was fractionally crystallised from acetic acid. The more soluble portion was the 3-hydroxy-2-acetate described in (*c*) above (1·9 g., 39%), identified by m. p. and mixed m. p. 214° (decomp.) and by the infrared spectrum. The less soluble fraction (1·08 g., 24%) crystallised from ethanol in golden-yellow needles, m. p. 265°, and is regarded as *ethyl 5,7-dinitro-2-hydroxyquinoxalin-3-ylacetate* (I; R = NO_2, R′ = CH_2·CO_2Et, R″ = OH) (Found: C, 44·7; H, 3·0; N, 18·3; O, 34·1. $C_{12}H_{10}N_4O_7$ requires C, 44·7; H, 3·1; N, 17·4; O, 34·8%); it has $\nu_{max.}$ 3184 and 3097 (NH stretching), 2953 and 2877 (methyl or methylene CH stretching), 2297 (not assigned), 1689 (ester C=O), 1665 (amide C=O), 1613 (aromatic CC or CN), 1528 (NO_2), 1439 and 1373 (methyl CH deformation), 1335 (NO_2) cm.$^{-1}$. Hydrogenation over Adams platinum oxide catalyst in ethanol at 40°/10—20 atm. yielded *ethyl 5,7-diamino-2-hydroxyquinoxalin-3-ylacetate* (I; R = NH_2, R′ = CH_2·CO_2Et, R″ = OH), m. p. 251° (decomp.) (from ethanol) (Found: C, 55·2; H, 5·2; N, 20·7. $C_{12}H_{14}N_4O_3$ requires C, 55·0; H, 5·4; N, 21·4%), $\nu_{max.}$ 3359 (NH stretching), 2995 (not assigned), 2929 and 2840 (methyl or methylene CH stretching), 1731 (ester C=O), 1646 (amide C=O), 1637 (NH stretching), 1590 and 1519 (aromatic CC or CN), 1424 and 1387 (methyl CH deformation) cm.$^{-1}$.

5,7-Diamino-2-hydroxy-3-methylquinoxaline (I; R = NH_2, R′ = Me, R″ = OH).—Picryl chloride (29·7 g.) in ethanol (450 ml.) was added to a warm solution of DL-alanine (10·7 g.) in water (120 ml.) containing sodium hydrogen carbonate (20·2 g.). When the reaction had subsided, the solution was heated under reflux for 2 hr., the ethanol removed under reduced pressure, and the residual solution diluted with water to 250 ml. After treatment with charcoal, the filtrate was made just acid with concentrated hydrochloric acid and extracted with ether (8 × 250 ml.). Evaporation of the dried extract left a semi-solid mass which was dissolved in a mixture of anhydrous benzene (200 ml.) and anhydrous ether (200 ml.), treated with charcoal, and filtered through kieselguhr. Diethylamine (1·5 ml.) was added to the filtrate and the gummy precipitate removed by filtration through kieselguhr. Addition of more diethylamine (10 ml.) precipitated the *diethylamine salt* of *N-picryl-DL-alanine* (24 g., 54%), which crystallised from ethanol in bright yellow needles, m. p. 177° (Found: N, 18·2. $C_{13}H_{19}N_5O_8$ requires N, 18·8%); esterification, by the usual Fischer–Speier procedure, gave the *ethyl ester* of *N-picryl-DL-alanine* (92%), which crystallised from ethanol in pale yellow needles, m. p. 93° (Found: C, 40·5; H, 3·7; N, 17·3. $C_{11}H_{12}N_4O_8$ requires C, 40·3; H, 3·7; N, 17·1%).

The above diethylamine salt (21 g.) was hydrogenated over Adams platinum oxide (0·6 g.) in ethanol (100 ml.) at 100°/70 atm. for 8 hr. The insoluble portion of the product was extracted with 2N-hydrochloric acid (200 ml.), and the extract filtered to remove spent catalyst. Addition of solid sodium hydrogen carbonate to the filtrate precipitated the *diamine* (6·0 g., 56%), which crystallised from water in needles, m. p. 314° (decomp.) (Found: N, 29·2. $C_9H_{10}N_4O$ requires N, 29·5%), $\nu_{max.}$ 3348, 3245, and 3127 (NH stretching), 2925 and 2845 (methyl CH stretching), 1656 (amide C=O), 1632 (NH deformation), 1594 and 1528 (aromatic CC or CN), 1429 (methyl CH deformation), 1396 (not assigned), 1373 (methyl CH deformation) cm.$^{-1}$.

Infrared Spectra of Other Quinoxaline Derivatives.—The spectra of the following compounds, prepared in earlier work,[2,13] were measured in potassium bromide discs.

2,3-Dimethylquinoxaline. 3001 (aromatic CH stretching), 2912 (methyl CH stretching), 2356, 2331, and 1652 (not assigned), 1605, 1570, 1492, and 1468 (aromatic CC or CN), 1437 methyl CH deformation), 1402 (not assigned), 1369 (methyl CH deformation) cm.$^{-1}$.

[13] Leese, Ph.D. Thesis, London, 1951.

2-*Hydroxy*-3-*methylquinoxaline*. 3303, 3198, and 3097 (NH stretching), 3008 (aromatic CH stretching), 2967 and 2893 (methyl CH stretching), 2841, 2784, and 2711 (not assigned), 1664 (amide C=O), 1611, 1568, 1505, and 1487 (aromatic CC or CN), 1438 and 1384 (methyl CH deformation) cm.$^{-1}$.

2-*Methoxy*-3-*methylquinoxaline*. 3032 (aromatic CH stretching), 2994 (not assigned), 2937 and 2888 (methyl CH stretching), 2355 and 1646 (not assigned), 1600, 1497, and 1473 (aromatic CC or CN), 1433 (methyl CH deformation), 1414 (not assigned), 1379 (methyl CH deformation) cm.$^{-1}$.

Ethyl 2-*hydroxyquinoxalin*-3-*ylacetate*. 3161 (NH stretching), 3011 (aromatic CH stretching), 2901 (methyl or methylene CH stretching), 1687 (ester C=O), 1642 (amide C=O), 1620, 1506, and 1487 (aromatic CC or CN), 1468 (not assigned), 1438 and 1383 (methyl CH deformation) cm.$^{-1}$.

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