924. *Several Quinoxalines of Biological Interest.*

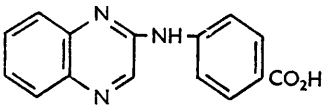
By R. M. Acheson.

Some quinoxaline analogues of pteroic and pteroylglutamic acid have been synthesised. One of these had a small growth-inhibitory effect on *Lactobacillus casei*, prevented by pteroylglutamic acid. 2 : 6 : 7-Trichloroquinoxaline has been prepared and condensed with two amines, but the products had no activity against *Plasmodium gallinaceum*.

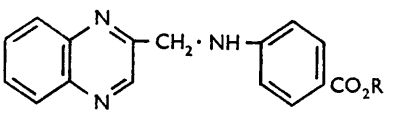
A number of analogues of the growth factors, pteroic and pteroylglutamic acid, have already been prepared [1] and examined biologically. 4-(2-Quinoxalinylcarbonylamino)-benzoylglutamic acid [2] was a pteroylglutamic acid antagonist only with *Lb. casei*. This, the similarity between the quinoxaline and the pteridine ring system, and the report [3] that the growth of *Streptococcus lactis R.*, inhibited by quinoxaline, is restored by excess of pteroylglutamic acid, made it desirable to examine more analogues of pteroic and pteroylglutamic acid.

[1] Acheson, King, and Spensley, *J.*, 1949, 1401, give a summary of earlier literature; see also Fahrenbach, Collins, Hultquist, and Smith, *J. Amer. Chem. Soc.*, 1954, **76**, 4006, and preceding papers.
[2] Woolley and Pringle, *J. Biol. Chem.*, 1948, **174**, 327.
[3] Hall, *Biochem. J.*, 1946, **40**, xlii.

p-2′-Quinoxalinylaminobenzoic acid (I) was obtained in good yield from 2-chloroquinoxaline and *p*-aminobenzoic acid in *n*-propanol; a subsequent note [4] suggests that none of this product could be obtained from the two reactants under a variety of conditions. The compound did not, however, appreciably affect the growth of *S. lactis R.* 2-Chloroquinoxaline also combined with ethyl *p*-aminobenzoyl-(–)-glutamate, but not with the acid, to give the corresponding 2-aminoquinoxaline. Hydrolysis gave *p*-2′-quinoxalinylaminobenzoyl-(–)-glutamic acid which had a small growth-inhibitory effect on *Lb. casei*, prevented by pteroylglutamic acid.



(I)



(II); R = H (III); R = Et

The preparation of *p*-2′-quinoxalinylmethylaminobenzoic acid (II) was next attempted, and for this it was hoped to prepare 2-bromomethylquinoxaline. Although bromination of 2-methylquinoxaline [5] to tribromomethylquinoxaline [6] was easy attempts to reduce this compound or to stop the bromination at the monosubstitution stage were unsuccessful. Hydroxyiminoacetoacetic ester and *o*-phenylenediamine gave a mixture of 2-methylbenziminazole and 2-hydroxy-3-methylquinoxaline. Disodium ditoluene-*p*-sulphonyl-*o*-phenylenediamine and 1 : 2-dibromopropanol gave the expected condensate, hydrolysed to 1 : 2 : 3 : 4-tetrahydro-2-hydroxymethylquinoxaline. The yields obtainable in the last stage were so variable that this approach was abandoned; also oxidation of this quinoxaline with potassium ferricyanide gave only quinoxaline itself.

Quinoxaline-2-aldehyde reacted with *p*-aminobenzoic acid, or its ethyl ester, to give the anils, subsequently prepared [7,8] by less convenient procedures. In spite of Kjaer's failure [7] to reduce these anils that from the ester was hydrogenated over Adams catalyst to ethyl *p*-2′-quinoxalinylmethylaminobenzoate (III); the analogous reduction of the acid anil to the acid (II) has been described.[8] α-Bromo-β-4-ethoxycarbonylanilinoacraldehyde was now obtained from the corresponding 4-ethoxycarbonylanil hydrobromide by hydrolysis, but all attempts to condense it with *o*-phenylenediamine gave black tars. β-Ethoxycarbonylanilino-α-nitroacraldehyde, from ethyl *p*-aminobenzoate and nitrosodiomalondialdehyde, condensed as expected with *o*-phenylenediamine to give 3-nitro-6 : 7-benzo-1 : 5-diazepine, which was also obtained directly from *o*-phenylenediamine and the nitromalondialdehyde.

2-(2-Diethylaminoethyl)-[9] and 2-(3-diethylaminopropyl)-[9] aminoquinoxalines and their 6 : 7-dichloro-derivatives were found inactive against *P. gallinaceum* in chicks. The analytical data given [9] for the first two quinoxalines suggest that they were hemihydrates; the anhydrous compounds are now described. 2 : 6 : 7-Trichloroquinoxaline, which yielded the corresponding 2-aminoquinoxalines from the appropriate amines, was prepared from 1 : 2-diamino-4 : 5-dichlorobenzene by a four-stage synthesis.

Experimental

p-2′-*Quinoxalinylaminobenzoic Acid.*—*p*-Aminobenzoic acid (0·69 g.) and 2-chloroquinoxaline (0·82 g.) were refluxed in *n*-propanol (6 ml.) for 2 hr.; a yellow powder (1·12 g.) then separated and was crystallised from nitrobenzene forming yellow needles. The *acid* was purified by precipitation from aqueous sodium carbonate by dilute hydrochloric acid, and had m. p. 344—345° (decomp.) (Found, after drying at 150° *in vacuo*: C, 66·3, 66·6; H, 4·4, 4·5; N, 15·5.

[4] Drumheller and Schultz, *J. Amer. Chem. Soc.*, 1955, **77**, 6637.
[5] Borsche and Doller, *Annalen*, 1938, **537**, 39.
[6] Bennett and Willis, *J.*, 1928, 1960.
[7] Kjaer, *Acta Chem. Scand.*, 1948, **2**, 455.
[8] Leese and Rydon, *J.*, 1955, 303.
[9] Crowther, Curd, Davey, and Stacey, *J.*, 1949, 1260.

Calc. for $C_{15}H_{11}O_2N_3,\frac{1}{4}H_2O$: C, 66·6; H, 4·3; N, 15·6%). Drumheller and Schultz [4] give m. p. 340° but no analyses.

Ethyl p-2′-*Quinoxalinylaminobenzoyl*-(—)-*glutamate*.—2-Chloroquinoxaline (0·6 g.) and ethyl *p*-aminobenzoyl-(—)-glutamate (1·18 g.) were refluxed in ethanol (5 ml.) for 4 hr. The brown precipitate (1·3 g., 79%) was crystallised from ethanol (charcoal) giving the *quinoxaline* as yellow-brown needles, m. p. 168° (Found, after drying at 116°/0·5 mm.: C, 64·0; H, 5·5; N, 12·2. $C_{24}H_{26}O_5N_4$ requires C, 64·0; N, 5·8; N, 12·4%).

p-2′-Quinoxalinylaminobenzoyl-(—)-*glutamic acid*.—The ester (0·72 g.) in ethanol (12 ml.) was kept with sodium hydroxide (0·24 g.) in water (2 ml.) at 20° for 90 min. The precipitated sodium salt was dissolved in water and acidified, giving the *acid* which was purified by dissolution in aqueous sodium hydrogen carbonate. Treatment with charcoal and precipitation from the boiling solution by dilute hydrochloric acid gave a yellow-brown powder (0·54 g., 86%), m. p. 252° (decomp.) (Found, after drying at 116°/15 mm.: C, 59·6; H, 4·5; N, 14·0. $C_{20}H_{18}O_5N_4,\frac{1}{2}H_2O$ requires C, 59·6; H, 4·7; N, 13·9%).

NN′-*Ditoluene*-p-*sulphonyl*-o-*phenylenediamine*.—A mixture of toluene-*p*-sulphonyl chloride (59 g.), *o*-phenylenediamine (15 g.), and pyridine (75 ml.) was heated on a water-bath for 1 hr. and then poured into water (1 l.), and the precipitate collected. Crystallisation from ethanol gave the derivative as prisms (46·2 g.), m. p. 204° (Lit.[10] gives m. p. 201—202°).

1 : 2 : 3 : 4-*Tetrahydro*-2-*hydroxymethyl*-1 : 4 - *ditoluene* - p - *sulphonylquinoxaline*.—Ditoluene-*p*-sulphonyl-*o*-phenylenediamine (88·2 g.) and 2 : 3-dibromopropanol (46·25 g.) in ethanol (200 ml.) were successively added to a solution from sodium (9·75 g.) and ethanol (1 l.). After refluxing for 6 hr. the solvent was removed and the residual sticky solid washed with water and dried. It was then refluxed with benzene (100 ml.), and after cooling the residue was collected and dissolved in boiling ethanol (1 l.). On cooling the *quinoxaline* (44·5 g.) separated in prisms, m. p. 193° (Found: C, 58·1; H, 5·3; N, 5·7; S, 13·2. $C_{23}H_{24}O_5N_2S_2$ requires C, 58·4; H, 5·1; N, 5·9; S, 13·5%).

1 : 2 : 3 : 4-*Tetrahydro*-2-*hydroxymethylquinoxaline*.—The above derivative (5·08 g.) was dissolved in concentrated sulphuric acid (50 ml.) containing water (0·5 ml.). After 2 days in the warm the solution was poured on ice, basified, and repeatedly extracted with chloroform. Evaporation of the dried extracts gave the *tetrahydroquinoxaline* (1·38 g., 84%), prisms (from ethanol), m. p. 140—141° (Found: C, 65·7; H, 7·3; N, 16·5. $C_9H_{12}ON_2$ requires C, 65·8; H, 7·3; N, 17·1%). The *picrate* separated from water containing a trace of ethanol in yellow prisms, m. p. 179—180° (decomp.) (Found: C, 45·3; H, 4·1. $C_{15}H_{15}O_8N_5$ requires C, 45·6; H, 3·8%). The high yield reported here could never be reproduced. More dilute sulphuric acid failed to produce complete hydrolysis, and increased reaction time gave much lower yields, probably due to sulphonation. Concentrated hydrochloric acid at 170° for 9 hr. gave 46% of the hydroxymethylquinoxaline, m. p. and mixed m. p. 140°.

Potassium ferricyanide (4·8 g.) in water (20 ml.) was added to a solution of the quinoxaline (0·56 g.) and sodium hydroxide (0·7 g.) in water (20 ml.). After 30 min. the solution was filtered and extracted 7 times with chloroform. Evaporation gave a black tar (0·1 g.), from which some quinoxaline, b. p. 130°/10 mm., m. p. 26°, was obtained (Found: C, 73·4; H, 4·8; N, 21·4. Calc. for $C_8H_6N_2$: C, 73·8; H, 4·6; N, 21·5%). Hinsberg [11] gives m. p. 27°.

Methyl Quinoxaline-2-orthocarboxylate.—2-Tribromomethylquinoxaline (5·6 g.) was added to methanolic sodium methoxide [from sodium (1·2 g.) and methanol (30 ml.)] and the mixture refluxed for 4½ hr. The solvent was removed *in vacuo*; the residual *ortho-ester*, which solidified on addition of water, separated from methanol in hair-needles, m. p. 63—65° (Found: C, 61·8; H, 6·0; N, 11·7. $C_{12}H_{14}O_3N_2$ requires C, 61·5; H, 6·0; N, 12·0%).

Reaction of Ethyl Hydroxyiminoacetoacetate with o-*Phenylenediamine*.—(i) The ester (3·2 g.), the diamine (2·16 g.), and acetic acid (1·14 ml.) were refluxed in ethanol (10 ml.) for 5 hr. On cooling, a pale yellow solid (0·25 g., 8%) separated. The filtrate was basified, and the precipitated oil collected with ether and converted into the picrate. 2-Methylbenziminazole picrate (1·8 g., 25%) was obtained, m. p. and mixed [12] m. p. 211—212° (Found: C, 46·2; H, 3·3. Calc. for $C_{14}H_{11}O_7N_5$: C, 46·5; H, 3·0%). The pale yellow solid was soluble in aqueous sodium hydroxide, but not in sodium carbonate solution; crystallisation from ethanol gave 2-hydroxy-3-methylquinoxaline, m. p. 245° (Found: C, 67·2; H, 4·8; N, 17·5. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·0; N, 17·5%). Lit.[13] gives m. p. 245°.

[10] Reverdin and Crepieux, *Ber.*, 1902, **35**, 314.
[11] Hinsberg, *Ber.*, 1884, **17**, 320.
[12] King and Acheson, *J.*, 1949, 1396.
[13] Ruhemann and Stapleton, *J.*, 1900, 249.

(ii) The diamine dihydrochloride (1·81 g.) and the ester (1·59 g.) in ethanol (15 ml.) were refluxed for 3 hr. Very little material was precipitated on neutralisation, but picric acid gave 2-methylbenziminazole picrate (1·4 g., 39%), m. p. and mixed m. p. 211—212°.

(iii) Refluxing the diamine (1·08 g.), the ester (1·59 g.), and ethanol (7 ml.) for 9 hr. gave 2-hydroxy-3-methylquinoxaline (0·5 g., 31%) and 2-methylbenziminazole [isolated as the picrate (1·2 g., 33%)].

Anils from Quinoxaline-2-aldehyde.—(i) The aldehyde (0·46 g.) and *p*-aminobenzoic acid (0·4 g.) were heated at 100° in dioxan (5 ml.) for 1 hr. The anil rapidly separated as yellow needles (0·72 g., 89%), which were crystallised from dioxan; the anil had m. p. 286—287° (decomp.) (Found : C, 69·6; H, 4·2; N, 14·9. Calc. for $C_{16}H_{11}O_2N_3$: C, 69·3; H, 4·0; N, 15·2%). Lit.[7] gives m. p. 285°. It reacted immediately with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, and nothing homogeneous could be isolated from attempts to reduce it with sodium amalgam, or with hydrogen over Raney nickel, or palladised charcoal in alkaline solution; hydrogen over Adams catalyst is successful.[8]

(ii) The aldehyde (1·9 g.) and ethyl *p*-aminobenzoate (2·0 g.) were refluxed in dioxan (10 ml.) for 3 hr., the solution was cooled and water added. The *anil* (3·01 g., 82%) separated from aqueous dioxan in very pale yellow needles, m. p. 139° (Found : C, 71·0; H, 4·8; N, 13·6. Calc. for $C_{18}H_{15}O_2N_3$: C, 70·8; H, 4·9; N, 13·8%). Lit.[7] gives m. p. 139°.

Ethyl p-2-Quinoxalinylmethylaminobenzoate.—The last anil (0·527 g.) in dioxan (15 ml.) was hydrogenated at room temperature and pressure over Adams catalyst until the absorption equivalent to one double bond had taken place. Further absorption occurred if permitted. The dark brown solution was filtered and evaporated to dryness *in vacuo*. Treatment of the residual tar with ethanol gave the secondary *amine* (0·188 g., 35%) which was washed with ethanol; it separated from pyridine in prisms, m. p. 229—232° (slight decomp.) (Found : C, 70·0; H, 5·3; N, 13·3%; *M*, 295. $C_{18}H_{17}O_2N_3$ requires C, 70·4; H, 5·5; N, 13·7%; *M*, 307). It was almost insoluble in boiling ethanol, water, and N-aqueous hydrochloric acid, but dissolved in warm aqueous 3—4N-hydrochloric acid, and did not react with 2 : 4-dinitrophenylhydrazine. It gave a dark blue solid with concentrated hydrochloric acid and a dark purple solution in concentrated sulphuric acid which gave a purple precipitate on dilution with water. The original anil was not affected by hydrogen and palladised charcoal, but with Raney nickel in dioxan at room temperature and pressure absorption ceased when 36% of that required to saturate one double bond had been adsorbed, and a 33% yield of the secondary amine was obtained.

α-*Bromo*-β-4-*ethoxycarbonylanilinoacraldehyde* 4-*Ethoxycarbonylanil.*—Ethyl *p*-aminobenzoate (7·5 g.) and αβ-dibromo-β-formylacrylic acid (5·9 g.) were boiled in ethanol (40 ml.) for 20 min. Next day the orange-red precipitate (7·9 g., 62%) was crystallised from aqueous ethanol, giving the *anil hydrobromide dihydrate* as yellow needles, m. p. 249—250° (decomp.) (Found : C, 44·9; H, 4·5; N, 4·9. $C_{21}H_{21}O_4N_2Br,HBr,2H_2O$ requires C, 44·8; H, 4·6; N, 5·0%).

α-*Bromo*-β-4-*ethoxycarbonylanilinoacraldehyde.*—The hydrobromide (9·7 g.) was refluxed with water (1·5 l.) for 45 min. Next day the yellow precipitate (5·1 g., 99%) was crystallised from ethanol giving the *acraldehyde* in needles, m. p. 159—160° (Found : C, 48·0; H, 3·8. $C_{12}H_{12}O_3NBr$ requires C, 48·3; H, 4·0%). All attempts to condense this compound with *o*-phenylenediamine in boiling ethanol alone, or in the presence of sodium carbonate or one or two mol. of hydrochloric acid, or in ethylene glycol at 140°, gave intractable black tars.

β-4-*Ethoxycarbonylanilino*-α-*nitroacraldehyde.*—A suspension of sodium nitromalondialdehyde (1·39 g.) in water (5 ml.) was added to ethyl *p*-aminobenzoate (1·65 g.) in water (10 ml.) and concentrated hydrochloric acid (1 ml.). After a few minutes on a steam-bath the yellow *acraldehyde* was collected (2·5 g., 95%); it separated from ethanol in needles or prisms, m. p. 158—159° (Found : C, 54·9; H, 4·7; N, 10·4. $C_{12}H_{12}O_5N_2$ requires C, 54·5; H, 4·5; N, 10·6%).

3-*Nitro*-6 : 7-*benzo*-1 : 5-*diazepine.*—(i) The above anil (0·88 g.) and *o*-phenylenediamine (0·36 g.) were refluxed in ethanol (5 ml.). A red solid was precipitated and, after the addition of more ethanol (15 ml.), heating was continued for 1 hr. The red *benzodiazepine* (0·51 g., 81%) was collected and ethyl *p*-aminobenzoate (0·37 g., 67%) recovered from the filtrate. The benzodiazepine was practically insoluble in dilute acids or alkalis and the usual common solvents. It dissolved in concentrated sulphuric acid to a yellow solution which charred when heated and it separated from quinoline, the only effective solvent, in dark red prisms which did not melt nor discolour at 360° (Found, after drying at 144° *in vacuo* over P_2O_5 : C, 57·1; H, 3·5; N, 22·2. $C_9H_7O_2N_3$ requires C, 57·1; H, 3·8; N, 22·2%).

(ii) Sodium nitromalondialdehyde (0·32 g.), *o*-phenylenediamine (0·25 g.), concentrated

hydrochloric acid (0·25 ml.), and water (6 ml.) were heated for 30 min. on a steam-bath. The yellow precipitate rapidly became red (0·31 g., 71%) and had the same properties as the benzodiazepine described above (Found : C, 57·4; H, 3·6%).

Ethyl 6 : 7-*Dichloro*-2-*hydroxyquinoxaline*-3-*carboxylate*.—1 : 2-Dichloro-4 : 5-dinitrobenzene (4·74 g.) was hydrogenated in ethanol (30 ml.) over Raney nickel until the theoretical absorption for two nitro-groups had taken place. The mixture, without filtration as the diamine oxidised very rapidly in air, was poured into boiling ethanol (20 ml.) containing ethyl mesoxalate (3·8 g.) and refluxing was continued for 45 min. The mixture was treated with charcoal and filtered whilst hot. Crystallisation of the product (3·7 g.) from ethyl acetate gave the *ester* as pale green needles, m. p. 230° (Found : C, 46·1; H, 2·9; N, 9·8; Cl, 24·8. $C_{11}H_8O_3N_2Cl_2$ requires C, 46·0; H, 2·8; N, 9·8; Cl, 24·7%).

6 : 7-*Dichloro*-2-*hydroxyquinoxaline*-3-*carboxylic Acid*.—The ester (5·1 g.) was heated on a steam-bath with 2N-sodium hydroxide for 1 hr., water (50 ml.) was added, and the mixture was boiled and filtered into concentrated hydrochloric acid (50 ml.). The *quinoxalinecarboxylic acid* (4·5 g.) separated from ethanol in yellow needles, m. p. 340° (decomp.) (Found : C, 41·9; H, 1·5; Cl, 27·2. $C_9H_4O_3N_2Cl_2$ requires C, 41·7; H, 1·5; Cl, 27·4%).

6 : 7-*Dichloro*-2-*hydroxyquinoxaline*.—The acid (6·1 g.) was refluxed in nitrobenzene (60 ml.) until carbon dioxide was no longer evolved. After cooling light petroleum (200 ml.; b. p. 60—80°) was added and the *quinoxaline* (4·95 g.) then precipitated. It was washed with light petroleum and crystallised from *n*-propanol forming prisms, m. p. 343° (decomp.) (Found : C, 44·5; H, 1·9. $C_8H_4ON_2Cl_2$ requires C, 44·7; H, 1·9%).

2 : 6 : 7-*Trichloroquinoxaline*.—The hydroxyquinoxaline (1·0 g.) was refluxed with phosphoryl chloride (10 ml.) for 45 min. and the resulting dark red solution evaporated to dryness *in vacuo*. Water was added and the residue repeatedly extracted with ether. Evaporation of the dried (Na_2SO_4) extracts gave the *trichloroquinoxaline* (1·0 g.) as pale pink needles (from ethanol), m. p. 147° (Found : C, 40·9; H, 1·4; N, 11·5; Cl, 44·7. $C_8H_3N_2Cl_3$ requires C, 41·1; H, 1·3; N, 12·0; Cl, 45·6%).

6 : 7-*Dichloro* - 2 - 2′ - *diethylaminoethylaminoquinoxaline*.—2 : 6 : 7 - Trichloroquinoxaline (0·35 g.) was heated with 2-diethylaminoethylamine (1 ml.) to 110—140° for 3 hr. and excess of amine was then removed at 100°/14 mm. The residual oil was dissolved in dilute acid, the solution extracted with ether, the aqueous layer basified, and the *quinoxaline* collected with ether. It was a pale yellow oil, b. p. 168—173° (bath temp.)/0·03 mm. (Found : N, 18·7. $C_{14}H_{18}N_4Cl_2$ requires N, 17·9%). The picrate was very difficult to purify, but the highly crystalline *monomethiodide* separated from ethanol in prisms, m. p. 196—197° (Found : C, 39·5; H, 4·7; N, 12·1. $C_{15}H_{21}N_4Cl_2I$ requires C, 39·6; H, 4·6; N, 12·3%).

6 : 7-*Dichloro*-2-3′-*diethylaminopropylaminoquinoxaline*.—This (1·15 g.) was obtained in the same way from 2 : 6 : 7-trichloroquinoxaline (1·2 g.) and 3-diethylaminopropylamine (3·2 ml.), and distilled as a pale yellow oil, b. p. 183—188°(bath. temp.)/0·05 mm. It solidified after the second distillation and crystallised from ether in prisms, m. p. 84—86° (Found : Cl, 20·9. $C_{15}H_{20}N_4Cl_2$ requires Cl, 21·7%). The *picrate* separated from ethanol in orange prisms, m. p. 182° (Found : C, 45·6; H, 4·2; N, 17·2. $C_{21}H_{23}O_7N_7Cl_2$ requires C, 45·3; H, 4·1; N, 17·6%). The *monomethiodide* separated from ethanol in pale brown prisms, m. p. 212° (decomp.) (Found : C, 40·8; H, 5·0; N, 11·4. $C_{16}H_{23}H_4Cl_2I$ requires C, 40·9; H, 4·9; N, 11·9%).

2-2′-*Diethylaminoethylaminoquinoxaline*.—This was obtained (72% yield) similarly and had b. p. 140°/0·02 mm. (Found : C, 69·2; H, 8·6. $C_{14}H_{20}N_4$ requires C, 68·8; H, 8·2%). The dipicrate had m. p. 185° (sinters 183°) (Found : C, 44·4; H, 3·8; N, 19·7. Calc. for $C_{26}H_{26}O_{14}N_{10}$: C, 44·4; H, 3·7; N, 19·9%). Lit.[9] gives b. p. 135°/0·1 mm. and m. p. 183—185°, respectively.

2-3′-*Diethylaminopropylaminoquinoxaline*.—This was also prepared similarly and had b. p. 200—205°/0·1 mm. (Found : C, 69·8; H, 8·8; N, 20·9. $C_{15}H_{22}N_4$ requires C, 69·8; H, 8·5; N, 21·7%). The dipicrate, orange prisms which change to yellow needles, from ethanol, had m. p. 164° (Found : C, 44·8; H, 4·0; N, 18·9. Calc. for $C_{27}H_{28}O_{14}N_{10}$: C, 45·2; H, 3·9; N, 19·5%). Lit.[9] gives b. p. 153°/0·1 mm. and m. p. 127—129° (different crystalline form ?), respectively.

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