789. *Pteridine Derivatives. Part IV.* The Formation of 8-Alkyl-2 : 8-dihydro-2-oxopteridines.*

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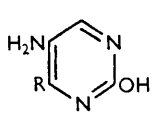
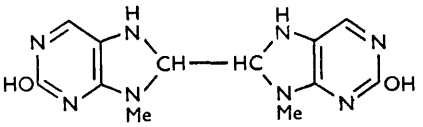
Condensation of 5-amino-2-hydroxy-4-methylaminopyrimidine with 1 : 2-diketones gave 8-alkyl-2 : 8-dihydro-2-oxopteridines. It is concluded that these compounds (which have a strong affinity for one molecule of water) have a *para*-quinonoid type of structure. Condensation of other 4-alkylamino-5-aminopyrimidines with glyoxal and with 1 : 2-diketones has been studied in relation to factors determining the course of the reaction.

It has recently been shown [1] that purines can be converted into pteridines *in vitro* under conditions which might have biological significance. For example, 2-hydroxypurine at 20° and pH 5 gives 4-amino-5-formamido-2-hydroxypyrimidine, which at pH 2 loses the formyl group to give 4 : 5-diamino-2-hydroxypyrimidine (I; R = NH_2). The 4 : 5-diaminopyrimidine formed in this way then reacts almost quantitatively at pH 7 with 1 : 2-dicarbonyl compounds to give pteridines. In Nature, enzymes permit the loss of the formyl group under neutral conditions, *e.g.*, [2-^{14}C]guanine is converted by an amphibian into a pteridine which gives 2-amino-4-hydroxy[2-^{14}C]pteridine-6-carboxylic acid on oxidation.[2]



(I)



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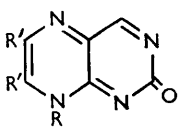

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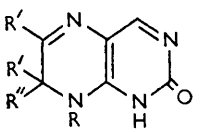

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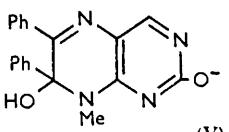


(V)

It has been suggested that, in Nature, the precursors of pteridines are the much more abundant purines.[1] On this hypothesis, the naturally occurring purine glycosides would give pyrimidines with a substituted amino-group at position 4, *e.g.*, (I; R = NHR′). Subsequent condensation with 1 : 2-dicarbonyl compounds would give pteridines with a sugar group attached at $N_{(8)}$. We now describe a preliminary investigation of the condensation of 5-amino-4-alkylaminopyrimidines with 1 : 2-diketones.

It has been shown [3] that condensation of 5-amino-2-hydroxy-4-methylaminopyrimidine (I; R = NHMe) with glyoxal gives a bisdihydropurinyl (II) and not the expected *N*-alkylpteridone (III; R = Me, R′ = H).

* Part III, *J.*, 1956, 3311.

[1] Albert, *Biochem. J.*, 1957, **65**, 124.
[2] Ziegler-Günder, Simon, and Wacker, *Z. Naturforsch.*, 1956, **11**b, 82.
[3] Fidler and Wood, *J.*, 1956, 3311.

Condensation of this pyrimidine (I; R = NHMe) with benzil gave 2 : 8-dihydro-8-methyl-2-oxo-6 : 7-diphenylpteridine (III; R = Me, R′ = Ph). The corresponding trimethyl compound (III; R = R′ = Me) has been prepared by Brown and Mason.[4] These 2-pteridones are soluble in organic solvents and have relatively low melting points, and their absorption spectra are quite distinct from that [3] of the bisdihydropurinyl (II). Both compounds have a strong affinity for 1 molecule of water, which in the case of the diphenyl compound cannot be removed. They are readily soluble in dilute alkali, and in contrast to other *N*-alkylpteridones [5] are not readily degraded by alkali.

Brown and Mason [4] suggest that the strongly bound molecule of water is water of constitution and that the trimethyl compound has structure (IV; R = R′ = Me, R″ = OH) but they admit that the evidence is not conclusive.

The ultraviolet absorption spectra of the hydrated 2 : 8-dihydro-8-methyl-2-oxopteridines (III; R = R′ = Me; and R = Me, R′ = Ph) in ethanol closely resemble that of the anhydrous 8-benzyl-2 : 8-dihydro-6 : 7-dimethyl-2-oxopteridine (III; R = CH_2Ph, R′ = Me) (see Table). Similar absorption is shown by the anhydrous 2 : 8-dihydro-6 : 7 : 8-trimethyl-2-methyliminopteridine (Part V, in the press) either in ethanol or dry dioxan. This strongly suggests that the hydrated pteridones have a *para*-quinonoid type of structure, *e.g.*, (III). In the infrared region, the 8-methylpteridones (III; R = R′ = Me; and R = Me, R′ = Ph) and the 8-benzylpteridones (III; R = CH_2Ph, R′ = H or Me) give a very strong absorption band between **1634** and **1647** cm.$^{-1}$, *i.e.*, close to the region typical of αβ : α′β′-unsaturated ketones.[6,7]

1 : 2 : 7 : 8-Tetrahydro-8-methyl-2-oxo-6 : 7-diphenylpteridine (IV; R = Me, R′ = Ph, R″ = H), prepared by condensation of benzoin with the pyrimidine (I; R = NHMe), has a chromophoric structure very similar to that suggested by Brown and Mason [4] for the hydrated pteridones. While the ultraviolet spectrum of this compound resembles that of (III; R = Me, R′ = Ph) qualitatively, it differs markedly in the intensity of absorption (see Table).

Absorption spectra (in water).

Substance	$\lambda_{max.}$ (mμ)	ε	pH
2 : 8-Dihydro-8-methyl-2-oxo-6 : 7-diphenylpteridine	240; 316 [a]	23,200; 15,600	—
	234; 331	22,400; 12,400	13
2 : 8-Dihydro-6 : 7 : 8-trimethyl-2-oxopteridine [4]	239; 327	21,900; 17,800	7
	240; 344	17,000; 15,500	13
8-Benzyl-2 : 8-dihydro-6 : 7-dimethyl-2-oxopteridine	248; 328 [a]	20,600; 18,200	—
	234; 337	18,100; 14,700	13
8-Benzyl-2 : 8-dihydro-2-oxopteridine	230; 290 [a]	23,800; 8,050	—
	224; 308	23,400; 13,450	13
2 : 8-Dihydro-6 : 7 : 8-trimethyl-2-methyliminopteridine	248; 352 [a]	23,000; 17,400	—
	247; 354 [b]	21,200; 17,300	—
1 : 2 : 7 : 8-Tetrahydro-8-methyl-2-oxo-6 : 7-diphenylpteridine	242; 315 [a]	13,500; 8,500	—
	234; 327	17,200; 9,500	13
8-Benzyl-2-benzylimino-2 : 8-dihydropteridine	232; 325 [a]	15,100; 11,800	—
8-Benzyl-2-benzylimino-2 : 8-dihydro-6 : 7-dimethylpteridine ...	251; 350 [a]	22,800; 16,800	—

[a] In EtOH. [b] In dry dioxan.

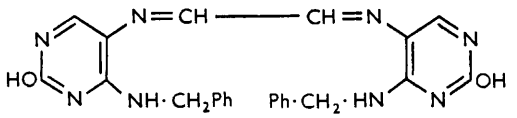
8-Benzyl-2 : 8-dihydro-2-oxopteridine (III; R = CH_2Ph, R′ = H) also has a strong affinity for 1 molecule of water, and a structure (IV; R = CH_2Ph, R′ = H, R″ = OH) is possible. Oxidation of this pteridone was attempted by Brown and Mason's technique [4] but no 8-benzyl-7 : 8-dihydro-2-hydroxy-7-oxopteridine could be detected. The balance of evidence accordingly suggests that the water of hydration is not constitutional (as suggested by Brown and Mason [4]), and that the hydrated pteridones have structure (III).

The solubility in alkali of these pteridones must now be explained. An open-ring

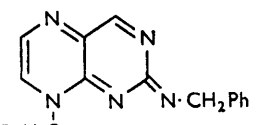
[4] Brown and Mason, *J.*, 1956, 3443.
[5] Albert, Brown, and Wood, *J.*, 1956, 2066.
[6] Cromwell, Miller, Johnson, Frank, and Wallace, *J. Amer. Chem. Soc.*, 1949, **71**, 3337.
[7] Brown, Hoerger, and Mason, *J.*, 1955, 211.

structure is unlikely because the infrared spectrum of the sodium salt of (III; R = Me, R′ = Ph) shows no definite band in the carbonyl stretching region. We suggest that a resonance-stabilised anion (V) is formed by attack of a hydroxyl ion at position 7. This readily explains the resistance to alkaline degradation shown by (III; R = Me, R′ = Ph). Acid hydrolysis readily gives benzil and the pyrimidine (I; R = NHMe) in quantitative yield.

It has been shown [8] that a carbonyl group reacts preferentially with the 5-amino-group of 4 : 5-diaminopyrimidines to give a Schiff's base; with glyoxal this is followed by cyclisation to a pteridine. We suggest that, in a 5-amino-4-methylaminopyrimidine, *e.g.*, (I; R = NHMe), glyoxal reacts preferentially with the methylamino-group to give an aldehyde-ammonia, which then cyclises to give the five-membered ring of the dihydropurinyl (II). In a 5-amino-4-benzylaminopyrimidine, *e.g.*, (I; R = NH·CH_2Ph), the relative nucleophilic reactivity of the 5- and the 4-nitrogen atom should be close to that of a 4 : 5-diaminopyrimidine. Thus condensation of glyoxal with 5-amino-4-benzylamino-2-hydroxypyrimidine (I; R = NH·CH_2Ph) gave 8-benzyl-2 : 8-dihydro-2-oxopteridine (III; R = CH_2Ph, R′ = H), presumably *via* an intermediate Schiff's base. The pteridone was characterised by analysis and by comparison of its spectrum (ultraviolet and infrared) with those of other 8-substituted 2 : 8-dihydro-2-oxopteridines. Some intermolecular condensation also takes place, to give a small quantity of the azomethine (VI), possibly owing to steric causes. Glyoxal reacted similarly with 5-amino-2 : 4-bisbenzylaminopyrimidine, to give the corresponding iminopteridine (VII).



(VI)



(VII)

Diacetyl and benzil react with all the above 4-alkylamino-5-aminopyrimidines (I; R = NHMe, NH_2, or NH·CH_2Ph) to give pteridones (III). As the carbonyl-carbon atoms of diacetyl are less electrophilic, and those of benzil more electrophilic, than those of glyoxal, the governing factor in the above condensations cannot be purely electronic. We suggest that the second factor is steric. Diacetyl and benzil are prevented by steric hindrance from reacting with the 4-methylamino-group in a 5-amino-4-methylaminopyrimidine. This steric hindrance is illustrated by the formation of an azomethine (*i.e.*, initial condensation has taken place at the 5-amino-group) from a 5-amino-4-methylaminopyrimidine and *p*-nitrobenzaldehyde. The diketones and *p*-nitrobenzaldehyde, unlike the small glyoxal molecule, are thus constrained to react first with the 5-amino-group with the formation of a Schiff's base, later cyclising to a pteridine where possible.

Experimental

Yields of substances that have no definite m. p. refer to the stage when they appeared homogeneous in paper chromatography in butanol–5N-acetic acid (7 : 3) on being viewed in ultraviolet light of wavelengths 254 and 365 mμ. Infrared spectra were determined in Nujol mull.

2 : 8-*Dihydro*-8-*methyl*-2-*oxo*-6 : 7-*diphenylpteridine*.—Benzil (1·07 g.) in ethanol (2 c.c.) was added to a solution of 5-amino-2-hydroxy-4-methylaminopyrimidine [9] (0·64 g.) in boiling water (2 c.c.). The solution was heated on the steam-bath for 15 min.; crystals began to separate. The slurry was chilled, and the solid collected and recrystallised from ethanol to give the pale yellow *pteridone* (1·2 g., 79%), m. p. >300° (decomp.) (Found: C, 68·8; H, 4·3; N, 17·2. $C_{19}H_{14}ON_4,H_2O$ requires C, 68·7; H, 4·9; N, 16·9%).

[8] Dick, Wood, and Logan, *J.*, 1956, 2131.
[9] Brown, *J. Appl. Chem.*, 1955, **5**, 358.

The pteridone (0·1 g.) was dissolved in hot 5N-sodium hydroxide (20 c.c.), and the mixture was heated on the steam-bath for 5 min. The solution was filtered and 10N-sodium hydroxide (10 c.c.) added. The sodium salt of the pteridone then rapidly crystallised, was collected, washed with ethanol and acetone, and dried *in vacuo*.

Degradation of 2 : 8-*Dihydro*-8-*methyl*-2-*oxo*-6 : 7-*diphenylpteridine*.—(a) *Acid*. The pteridone (0·5 g.) was refluxed in N-hydrochloric acid (50 c.c.) for 12 hr. The solution was cooled and extracted with chloroform (3 × 25 c.c.), and the extract after drying (Na_2SO_4) was evaporated *in vacuo* to give benzil (0·31 g., 100%), m. p. and mixed m. p. 94—95°. The aqueous layer was diluted to 250 c.c. with 0·1N-hydrochloric acid, and the amount (100%) of 5-amino-2-hydroxy-4-methylaminopyrimidine was estimated by measurement of the intensity of the ultraviolet absorption band at 294 mμ.

(b) *Alkali*. The pteridone (0·2 g.) in 5N-sodium hydroxide was refluxed for 7 hr., then cooled, warm water (200 c.c.) and concentrated hydrochloric acid (19 c.c.) were added, and the benzil (68%) and pyrimidine (66%) were estimated as above.

1 : 2 : 7 : 8-*Tetrahydro*-8-*methyl*-2-*oxo*-6 : 7-*diphenylpteridine*.—To a solution of 5-amino-2-hydroxy-4-methylaminopyrimidine (0·24 g.) and benzoin (0·4 g.) in ethanol (5 c.c.) were added acetic acid (2 c.c.) and boiling water (5 c.c.). The solution was refluxed for 2 hr. and chilled overnight. The solid was collected, extracted with boiling chloroform (50 c.c.; extract excarded), and then treated with hot 5N-sodium hydroxide solution (10 c.c.). The alkaline distract was cooled and neutralised with acetic acid, and after refrigeration 1 : 2 : 7 : 8-*tetrahydro*-8-*methyl*-2-*oxo*-6 : 7-*diphenylpteridine* (0·2 g.) was deposited as colourless needles, m. p. >300° (Found: C, 69·7; H, 4·6; N, 17·7. $C_{19}H_{16}ON_4,\frac{1}{2}H_2O$ requires C, 70·0; H, 5·2; N, 7·3%).

4-*Benzylamino*-2-*hydroxy*-5-*nitropyrimidine*.—2 : 4-Dichloro-5-nitropyrimidine [10] (2 g.) in acetone (10 c.c.) was added dropwise in 10 min. to a stirred mixture of ice and water (200 c.c.). Benzylamine (3 c.c.) in ice-cold water (10 c.c.) was then added during 30 min. The solid was collected, washed with water (50 c.c.), and refluxed with 2N-sodium hydroxide (50 c.c.) for 5 min. Insoluble 2 : 4-bisbenzylamino-5-nitropyrimidine, m. p. 178—180°, was filtered off. The filtrate was cooled and acidified with acetic acid, and 4-*benzylamino*-2-*hydroxy*-5-*nitropyrimidine* was collected and recrystallised from ethanol (150 c.c.), to give pale yellow needles (1·3 g.), m. p. 225—228° (Found: C, 54·0; H, 3·7; N, 23·2. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1; N, 22·8%).

5-*Amino*-4-*benzylamino*-2-*hydroxypyrimidine*.—4-Benzylamino-2-hydroxy-5-nitropyrimidine (1·1 g.) in hot ethanol (200 c.c.) was hydrogenated over Raney nickel at 4 atm. for 3 hr. The solution was boiled, filtered hot, and concentrated to 5 c.c. Refrigeration gave 5-*amino*-4-*benzylamino*-2-*hydroxypyrimidine* which recrystallised from aqueous ethanol as golden prisms, m. p. 218—223° (decomp.) (Found: C, 60·7; H, 4·9; N, 26·1. $C_{11}H_{12}ON_4$ requires C, 61·1; H, 5·5; N, 25·9%).

4-*Benzylamino*-2-*mercaptopyrimidine*.—2 : 4-Dimercaptopyrimidine [11] (10 g.) and benzylamine (50 c.c.) were heated on the steam-bath for 3 days, then the white crystalline product was collected. Recrystallisation from ethanol gave 4-*benzylamino*-2-*mercaptopyrimidine* (13·5 g.) as needles, m. p. 249—253° (decomp.) (Found: C, 60·8; H, 5·3; N, 19·3. $C_{11}H_{11}N_3S$ requires C, 60·8; H, 5·1; N, 19·4%).

4-*Benzylamino*-2-*hydroxypyrimidine*.—4-Benzylamino-2-mercaptopyrimidine (13 g.), chloroacetic acid (10 g.), and water (72 c.c.) were refluxed for 40 min. 10N-Hydrochloric acid (67 c.c.) was added to the solution which was refluxed for a further 3 hr. Evaporation gave a dark brown solid which was dissolved in water (70 c.c.), ammonia was added to pH 8—9, and the mixture was stirred for 30 min. The white precipitate was collected, washed with water and acetone, and recrystallised from ethanol (400 c.c.), to give 4-*benzylamino*-2-*hydroxypyrimidine* as needles, m. p. 213—217° (decomp.) (Found: C, 65·9; H, 5·4; N, 21·1. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9%).

The hydroxypyrimidine could not be coupled with *p*-chlorobenzenediazonium chloride. Nitration gave a mixture of di- and tri-nitro-derivatives.

8-*Benzyl*-2 : 8-*dihydro*-2-*oxopteridine*.—5-Amino-4-benzylamino-2-hydroxypyrimidine (0·2 g.) in hot ethanol (50 c.c.) was added dropwise during 30 min. to polyglyoxal (0·12 g., 2 equivs.) in boiling ethanol (20 c.c.). The mixture was refluxed for a further 30 min., then the yellow

[10] Brown, *J. Appl. Chem.*, 1952, **2**, 239.
[11] *Idem*, *J. Soc. Chem. Ind.*, 1950, **69**, 353.

precipitate was collected. The filtrate was concentrated *in vacuo* to small volume and hot water (4 c.c.) was added. Refrigeration gave 8-*benzyl*-2 : 8-*dihydro*-2-*oxopteridine* (0·06 g.) as pale buff needles, m. p. 240° (decomp.) (Found: C, 60·7; H, 4·8; N, 21·2. $C_{13}H_{10}ON_4,H_2O$ requires C, 60·9; H, 4·7; N, 21·9%). The pteridone dissolved readily in dilute sodium hydroxide solution.

The yellow precipitate (0·03 g.) was dissolved in warm N-ethanolic sodium hydroxide and reprecipitated by careful neutralisation, to give *glyoxylidenebis*-(5-*amino*-4-*benzylamino*-2-*hydroxypyrimidine*) (Found: N, 25·1. $C_{24}H_{22}O_2N_8$ requires N, 24·7%). Treatment of the azomethine with cold dilute hydrochloric acid gave 5-amino-4-benzylamino-2-hydroxypyrimidine.

8-Benzyl-2 : 8-dihydro-2-oxopteridine was treated with aqueous potassium permanganate at 60—70°.[4] No 8-benzyl-7 : 8-dihydro-2-hydroxy-7-oxopteridine could be detected in paper chromatograms of the reaction mixture.

8-*Benzyl*-2 : 8-*dihydro*-6 : 7-*dimethyl*-2-*oxopteridine*.—To a solution of 5-amino-4-benzylamino-2-hydroxypyrimidine (0·1 g.) in hot ethanol (10 c.c.) was added diacetyl (0·1 c.c.). The solution was refluxed for 20 min. and cooled, 8-*benzyl*-2 : 8-*dihydro*-6 : 7-*dimethyl*-2-*oxopteridine* (0·06 g.) separating as golden needles, m. p. 240° (decomp.). This was recrystallised for analysis from ethanol (20 c.c.) (Found: C, 68·0; H, 5·0; N, 21·3. $C_{15}H_{14}ON_4$ requires C, 68·0; H, 5·3; N, 21·1%). The pteridone was soluble in dilute sodium hydroxide.

2 : 4-*Bisbenzylamino*-5-*nitropyrimidine*.—2 : 4-Dichloro-5-nitropyrimidine (0·55 g.) was dissolved in warm benzene (30 c.c.). Benzylamine (2 c.c.) was added dropwise to the stirred solution to give an immediate yellow precipitate. The mixture was stirred for 20 min. and the product (1·55 g.) collected. Recrystallisation from ethanol (200 parts) gave 2 : 4-*bisbenzylamino*-5-*nitropyrimidine* as pale yellow plates, m. p. 179—182° (Found: C, 64·5; H, 4·3; N, 21·0. $C_{18}H_{17}O_2N_3$ requires C, 64·5; H, 5·1; N, 20·9%).

8-*Benzyl*-2-*benzylimino*-2 : 8-*dihydropteridine*.—2 : 4-Bisbenzylamino-5-nitropyrimidine (0·2 g.) in ethanol (70 c.c.) was hydrogenated over Raney nickel as above. To the filtered solution were added acetic acid (0·2 c.c.) and polyglyoxal (0·04 g.) in ethanol (20 c.c.). The solution was refluxed for 10 min., and a saturated solution of potassium hydrogen carbonate (2 c.c.) in water (70 c.c.) was then added. Ethanol (40 c.c.) was distilled *in vacuo* from the solution, and the cooled residual solution was extracted with chloroform (3 × 50 c.c.). The combined chloroform extracts were washed with water (3 × 50 c.c.), dried (Na_2SO_4), and evaporated to dryness *in vacuo*, to give 8-*benzyl*-2-*benzylimino*-2 : 8-*dihydropteridine* as a non-crystallisable, light-brown solid (Found: C, 71·2, 71·1; H, 4·7, 4·6; N, 20·2. $C_{20}H_{17}N_5,\frac{1}{2}H_2O$ requires C, 71·4; H, 5·4; N, 20·9%).

8-*Benzyl*-2-*benzylimino*-2 : 8-*dihydro*-6 : 7-*dimethylpteridine*.—2 : 4-Bisbenzylamino-5-nitropyrimidine (0·3 g.) was reduced as above, and to the filtered solution was added diacetyl (0·2 c.c.). The solution was refluxed for 20 min., then concentrated *in vacuo* to 5 c.c. Refrigeration gave 8-*benzyl*-2-*benzylimino*-2 : 8-*dihydro*-6 : 7-*dimethylpteridine* (0·2 g.) as yellow needles, m. p. 181—185° (decomp.) (Found: C, 74·8; H, 5·8; N, 19·8. $C_{22}H_{21}N_5$ requires C, 74·4; H, 6·0; N, 19·7%).

4-*Chloro*-6-*methylamino*-5-p-*nitrobenzylideneaminopyrimidine*.—To a solution of 5-amino-4-chloro-6-methylaminopyrimidine [12] (0·4 g.) in hot ethanol (20 c.c.) was added *p*-nitrobenzaldehyde (0·44 g.) in hot ethanol (10 c.c.). The solution was refluxed for 30 min. and cooled. The product (0·76 g.) which separated, recrystallised from ethyl acetate (30 c.c.), to give 4-*chloro*-6-*methylamino*-5-p-*nitrobenzylideneaminopyrimidine* as red prisms, m. p. 198—200° (Found: C, 49·2; H, 3·1; N, 24·3. $C_{12}H_{10}O_2N_5Cl$ requires C, 49·4; H, 3·4; N, 24·1%). Treatment of the azomethine with mineral acid effected immediate hydrolysis.

8-*Benzyl*-7 : 8-*dihydro*-2-*hydroxy*-7-*oxopteridine*.—5-Amino-4-benzylamino-2-hydroxypyrimidine (150 mg.) and ethyl glyoxylate hemiacetal (0·2 c.c.) [13] in hot ethanol (15 c.c.) were refluxed for 20 min. The solution was concentrated *in vacuo* to 3 c.c. and hot water (3 c.c.) was added. The pale yellow solid which separated on cooling was collected and recrystallised from ethanol, to give 8-*benzyl*-7 : 8-*dihydro*-2-*hydroxy*-7-*oxopteridine* as white needles, m. p. 238—240° (Found: C, 60·9; H, 3·5. $C_{13}H_{10}O_2N_4$ requires C, 61·4; H, 3·95%).

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[12] Brown, *J. Appl. Chem.*, 1954, **4**, 72.
[13] Rigby, *J.*, 1950, 1912.