196. *The Synthesis and Properties of* 1 : 7-*Dialkyl Xanthines.*

By Frederick G. Mann and J. W. Geoffrey Porter.

Previous work has shown that although paraxanthine (1 : 7-dimethylxanthine) possesses marked antithyroid activity, this property was not shown by xanthine or by any other methylated xanthine (other than *iso*xanthines) investigated. Since therefore in the normal methylated xanthines this property seemed to be peculiar to the 1 : 7-dimethyl member, the synthesis of other 1 : 7-dialkyl xanthines has been investigated. Two successful methods of preparation have been developed, the first (essentially a Traube synthesis) from the appropriate pyrimidine, and the second from the appropriate iminazole. 1-*Methyl*-7-*ethyl*-, 1-*methyl*-7-n-*propyl*-, 1-*ethyl*-7-*methyl*-, and 1 : 7-*diethyl-xanthine* (and various derivatives) have thus been prepared, and their structure confirmed by their absorption spectra.

Preliminary tests indicate that these dialkyl xanthines, and also 8-*methyl*-1 : 7-*diethylxanthine*, have an antithyroid activity of the same order as that of paraxanthine itself.

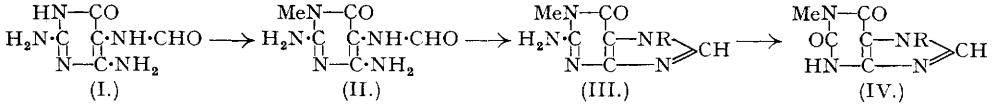
It has been shown by Carter, Mann, Jenkins, and Harley-Mason (*Nature*, 1943, **151**, 728) that both whale liver and human urine contain material which possesses marked antithyroid activity, the latter being determined by (*a*) its property of changing the temperature/heart-rate curve of the summer frog's heart to that typical of the winter frog's heart, *i.e.*, reversing the effect of thyroxine in this respect (Carter, *Brit. J. Exp. Biol.*, 1933, **10**, 256), and (*b*) its effect on the basal metabolic rate of the rat. Furthermore, paraxanthine (1 : 7-dimethylxanthine), isolated from both these sources, possessed high antithyroid activity, being capable of neutralising the action of *ca.* 5000 times its weight of thyroxine in the above tests. The activity of this naturally occurring paraxanthine was found to be identical (within the limits of experimental accuracy) with that of paraxanthine synthesised by a modification of Fischer and Ach's method (*Ber.*, 1898, **31**, 2622; 1906, **39**, 423). Xanthine itself, and 1-methyl-, 7-methyl-, 1 : 3-dimethyl-, 3 : 7-dimethyl-, and 1 : 3 : 7-trimethylxanthine, as well as adenine and guanine, were found to possess negligible antithyroid action (*ca.* 0·001 of that

of paraxanthine). Subsequent tests have shown that 3-methylxanthine, 3 : 9-dimethyl*iso*xanthine and 1 : 3 : 9-trimethyl*iso*xanthine are similarly inert, that 9-methyl*iso*xanthine has only a low activity, but that 1 : 9-dimethyl*iso*xanthine has a high activity, of the same order as that of paraxanthine.

The antithyroid activity of extracts of various mammalian organs shows a very wide range, that of the thyroid glands being particularly high (Carter and Jenkins, *Nature*, 1944, **154**, 639). We have consequently isolated, identified and examined the purine constituents of the ox thyroid gland, and our results (to be published later) show that in this gland compounds other than paraxanthine are apparently responsible for antithyroid activity. Meanwhile, however, since our earlier work showed that of the normal methylated xanthines tested only the 1 : 7-dimethyl derivative possessed this antithyroid activity, we have synthesised various homologues of paraxanthine (hitherto the only known 1 : 7-dialkyl xanthine) in order to determine whether the activity is limited solely to the first member of the homologous series.

A critical examination of the possible synthetic routes has revealed two methods of practical value.

Traube and Dudley (*Ber.*, 1913, **46**, 3839) have shown that 2 : 4-diamino-5-formamido-6-ketodihydropyrimidine (I) is methylated by dimethyl sulphate to the 1-methyl derivative (II), the position of the methyl group being determined by ring closure with formic acid to 1-methylguanine (III, R = H), characterised by conversion to 1-methylxanthine (IV, R = H). The guanine (III, R = H), treated with methyl chloride gave 1 : 7-dimethylguanine (III, R = Me), the position of the second methyl group being determined by a similar conversion to paraxanthine (IV, R = Me). We find that methylation of the formamido-compound (I) to



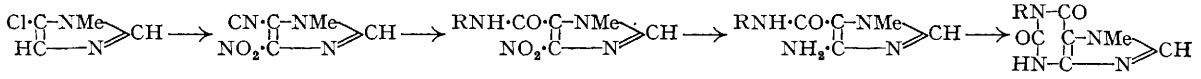
(I.) (II.) (III.) (IV.)

the 1-methyl derivative (II) can be accomplished using methyl iodide, but the yield is lower than when dimethyl sulphate is employed. We have, however, failed to ethylate the compound (I) by the use of diethyl sulphate or ethyl iodide under a variety of conditions and it would appear that the preparation of 1 : 7-dialkyl xanthines by Traube and Dudley's synthesis is limited to the 1-methyl members.

These authors used methyl chloride for the conversion of the guanine (III, R = H) to the 7-methyl derivative (III, R = Me) because methyl iodide gave methiodides of the methylated product. For the introduction of higher alkyl groups, however, we have employed alkyl iodides because of their higher reactivity. An alcoholic solution of the sodium derivative of (III, R = H) when boiled with ethyl iodide gave the crystalline 1-*methyl*-7-*ethylguanine* (III, R = Et), which on treatment with nitrous acid furnished 1-*methyl*-7-*ethylxanthine* (IV, R = Et). The absorption spectra of this and other of the new purines have been measured by Dr. C. B. Allsopp, whose report is given below; the almost complete identity of the spectra of this xanthine and of paraxanthine shows clearly that the ethyl group has also entered the 7-position. It is noteworthy that Traube and Dudley (*loc. cit.*) obtained a 5% yield of paraxanthine, calculated on the guanidine employed for the initial synthesis of the pyrimidine (I) : our yield of the 1-methyl-7-ethyl homologue, similarly calculated, is 2%. The use of *n*-propyl iodide in place of ethyl iodide gave two isomeric propyl derivatives which were isolated as the crystalline sulphates, (*a*) having m. p. 245—247° and (*b*) having m. p. 290—293° : the latter was formed, however, in only very small yield. The compound (*a*) was the *sulphate* of 1-*methyl*-7-n-*propylguanine* (III, R = Pr), since it was converted as usual to 1-*methyl*-7-n-*propylxanthine* (IV, R = Pr) and the spectra of both these compounds were again very closely similar to those of their authentic 1 : 7-dimethyl homologues. The identity of the guanine sulphate (*b*) is, however, uncertain. For structural reasons the guanine is most probably 1-methyl-9-*n*-propyl-*iso*guanine : unfortunately there are no authentic 1 : 9-dialkyl *iso*guanines for direct spectra comparison, and the yield of (*b*) was too small for a pure specimen of the corresponding xanthine to be prepared. Simultaneous alkylation in the 7- and 9-positions is, however, rare, although Fischer (*Ber.*, 1897, **30**, 2220) showed that 2 : 6 : 8-trichloropurine treated with methyl iodide furnished a mixture of the 7- and 9-methyl derivatives, and Baddiley, Lythgoe, and Todd (J., 1944, 318) have shown that 2-methyladenine similarly treated gives a mixture of 2 : 7- and 2 : 9-dimethyladenine. The action of *iso*propyl bromide and of ethylene chlorohydrin (for the ultimate purpose of introducing the vinyl group) on the guanine (III, R = H) gave only one derivative in each case : the yields were exceedingly low and, since it was impossible to determine whether the product isolated corresponded to the (*a*) or (*b*) type, this synthetic approach was not further developed.

Our second method is based essentially on Sarasin and Wegmann's synthesis of 7-methylxanthine (*Helv. Chim. Acta*, 1924, **7**, 713). These authors have shown that 5-chloro-1-methyliminazole (V), prepared by the action of phosphorus pentachloride on *N* : *N'*-dimethyloxamide, can be readily nitrated to the 4-nitro compound which with potassium cyanide affords 4-nitro-5-cyano-1-methyliminazole (VI). They showed that although the nitrile could be readily converted by sulphuric acid to the amide (VII, R = H), its complete hydrolysis to the carboxylic acid was difficult; reduction of the nitro-amide gave, however, the 4-amino-compound (VIII, R = H), which condensed with diethyl carbonate to form 7-methylxanthine (IX, R = H). For our purpose, however, the preparation of substituted amides (VII, where R = an alkyl group) was essential. We have confirmed the great resistance which the nitrile (VI) shows to complete hydrolysis or to alcoholysis; for example, it was recovered unchanged after 6 hours' heating at 130° with concentrated sulphuric acid and much alcohol. Ultimately, however, it was hydrolysed to the 5-*carboxylic acid* (X, R = H) by Bouveault's

method (*Bull. Soc. Chim.*, 1892, **9**, 368; cf. Sudborough, *J.*, 1895, **67**, 602), *i.e.*, by an initial heating with sulphuric acid followed by treatment with one equivalent of sodium nitrite. The acid was readily converted



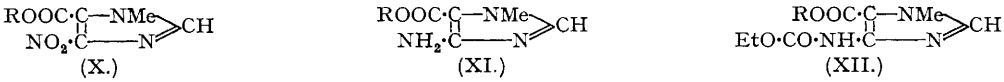
(V.) (VI.) (VII.) (VIII.) (IX.)

by thionyl chloride to the 5-*carboxylic chloride*, which in turn when treated with the appropriate primary amine furnished the 5-*methylamido-*, *ethylamido-* and *phenylamido*-derivatives (VII, R = Me, Et, Ph). The conditions for the reduction of these compounds to the corresponding 4-amino-compounds (as VIII) were controlled chiefly by the fact that the substituent, R, appears to weaken the stability of the ring in (VIII) unless these amines are neutralised by acids: the free amines, and also their salts in the presence of acid, are unstable. Thus the preparation of the amine (VIII, R = Me) by reduction of the nitro-amide (VII, R = Me) with tin and hydrochloric acid (the reagent successfully used by Sarasin and Wegmann on the unsubstituted amide) completely failed; the amine was, however, obtained in moderate yield using ferrous sulphate and ammonia, or aluminium amalgam, and, in 70% yield, using Raney nickel and hydrogen. Even the latter reagent was unsatisfactory for the reduction of the amides (VII, R = Et and Ph); these amides in alcoholic solution were, however, smoothly reduced by palladium and hydrogen provided one equivalent of hydrogen chloride was present for immediate neutralisation.

Similar catalytic reductions performed with the β-*bromoethylamide* (VII, R = $\cdot CH_2CH_2Br$) in the presence of hydrobromic acid, and with the β-*hydroxyethylamide* and the β-*acetoxyethylamide* gave a rapid absorption of hydrogen, but no crystalline product could be isolated.

The presence of the substituent, R, in the amino-amide (VIII) also profoundly affected the ring closure to the xanthine (IX). When the amide (VIII, R = Me) was heated with diethyl carbonate in a sealed tube (Sarasin and Wegmann's conditions), only a minute yield of paraxanthine was obtained, but this yield was increased to 60% when the amide was heated with ethyl chloroformate in dioxan solution in the presence of potassium carbonate. This is, therefore, a new synthesis of paraxanthine. Similar conditions, applied to the amide (VIII, R = Et) successfully gave 7-*methyl*-1-*ethylxanthine* (IX, R = Et), but the ring closure of the phenylamide was not satisfactorily accomplished.

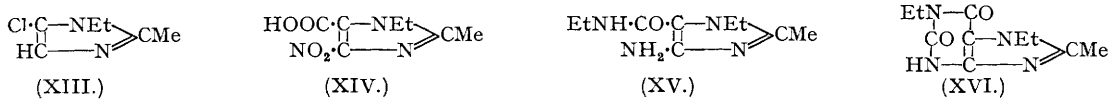
An alternative route from the above 5-carboxylic chloride to the xanthines (IX) was investigated. This chloride when treated with methyl or ethyl alcohol readily furnished the 4-*nitro*-1-*methyliminazole*-5-*carboxylic methyl* and *ethyl esters* (X, R = Me, Et), which were smoothly reduced by hydrogen and palladium in alcoholic solution containing hydrogen chloride to the hydrochlorides of the 4-*amino-esters* (XI, R = Me, Et). All



(X.) (XI.) (XII.)

attempts to convert the latter by the action of ethyl chloroformate to the 4-ethyl-carbamido derivative (XII) failed, however. Had the latter compound been obtained, further reaction with primary amines, involving ring closure, should have furnished the corresponding 1-alkyl-7-methylxanthines (as IX).

All such synthesis starting with the iminazole (V) can however furnish only xanthines having the 7-methyl substituent. To obtain the 7-ethyl homologues, we have converted 5-chloro-2-methyl-1-ethyliminazole (XIII), prepared by the action of phosphorus pentachloride on *N* : *N'*-diethyloxamide (Wallach, *Annalen*, 1882, **214**, 279), to the 4-nitro derivative (Sarasin and Wegmann, *ibid.*, p. 720) and the latter to the 5-cyano derivative (Montequi, *Ann. Soc. Espan. fis. quim.*, 1926, **24**, 731). The nitrile, again hydrolysed by Bouveault's method, furnished 4-*nitro*-2-*methyl*-1-*ethyliminazole*-5-*carboxylic acid* (XIV) which was converted by the consecutive action of thionyl chloride and ethylamine to the 5-carboxylic chloride and then to the 5-*ethylamido-derivative*. The latter was reduced as before to the 4-*amino*-compound (XV), which underwent ring closure by ethyl chloroformate under our previous conditions to 8-*methyl*-1 : 7-*diethylxanthine* (XVI). It is known that the 8-methyl

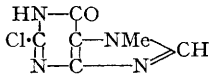


(XIII.) (XIV.) (XV.) (XVI.)

group in xanthines can be readily chlorinated to the corresponding mono-, di-, or tri-chloromethyl group (Boehringer and Sohne, D.R.P. 146,714, 151,133, 153,121). When the compound (XVI) was shaken with a solution of chlorine in phosphorus oxychloride at 40—50° it was smoothly converted to the 8-*trichloromethyl* derivative, and this, on hydrolysis, readily gave 1 : 7-*diethylxanthine*. It should be noted that this iminazole synthesis of the 1 : 7-dialkyl xanthines, unlike the preceding Traube synthesis, leaves no doubt concerning the position of the two alkyl groups: the structure of the 7-methyl-1-ethyl- and 1 : 7-diethyl-xanthines has, however, been independently confirmed by the fact that their absorption spectra are also almost identical with that of paraxanthine (see later).

Two other possible methods deserve brief comment. Fischer (*Ber.*, 1897, **30**, 2400) has shown that theobromine on chlorination gives 2 : 6-dichloro-7-methylpurine which on alkaline hydrolysis furnishes 2-chloro-6-

keto-7-methyl-dihydro-purine (XVII). The potassium salt of the latter, treated with methyl iodide, affords 2-chloro-6-keto-1 : 7-dimethyl-dihydro-purine (XVIII) which on acid hydrolysis gives paraxanthine. Since,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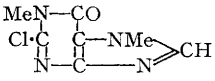
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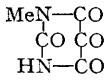
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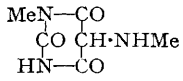

(XX.)

however, the yield of (XVIII) was low, and that obtained with higher alkyl iodides would, in view of the results obtained in our first method, probably be considerably lower, this synthesis was not investigated.

When 1-methylalloxan (XIX) or its reduction product, 1-methyldialuric acid, is treated first with methylamine sulphite and then with acids, 1-methyl-5-methylaminobarbituric acid (XX) is obtained (Fischer and Clemm, *Ber.*, 1897, **30**, 3089; Biltz and Damm, *Ber.*, 1913, **46**, 3662; *Annalen*, 1917, **413**, 137). The latter compound can be readily converted by potassium cyanate to the ψ-uric acid, which with hydrochloric acid furnishes 1 : 7-dimethyluric acid; this compound can be chlorinated to 8-chloro-1 : 7-dimethylxanthine and this, on reduction, furnishes paraxanthine (Fischer, *Ber.*, 1898, **31**, 3550). This synthetic approach is attractive because it would apparently allow a wide variety of alkyl groups to be inserted readily in the 7-position. Its chief disadvantage is the preparation of the initial 1-alkyl alloxan (as XIX). 1-Methylalloxan can be obtained from theobromine (Maly and Andreasch, *Monatsh.*, 1882, **3**, 92; Fischer, *Annalen*, 1882, **215**, 253; *Ber.*, 1882, **15**, 29), and 1-ethylalloxan from 1-ethyluric acid (Biltz and Peukert, *Ber.*, 1925, **58**, 2190), but the yield of both compounds is low. In view of this fact and of the many stages involved, this synthesis was also not investigated.

Table I summarises the yields and some of the physical properties of the 1 : 7-dialkyl xanthines. The yields marked with an asterisk are calculated on the guanidine used initially in the Traube synthesis; the yields not so marked are calculated on the dialkyl oxamide initially used. All these xanthines could be readily recrystallised from hot water; only those dialkyl xanthines having a 7-methyl group separate in the anhydrous condition.

TABLE I.

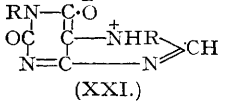
Xanthine.	Yield, %.	M. p.	Water of crystallisation.	Picrate, m. p. (decomp.).
1 : 7-Dimethyl	5*; 12	297—299°	None	247—249°
1-Me-7-Et	2·2 *	225—226	$\frac{1}{2}H_2O$	221—222
1-Me-7-Pr$^{\alpha}$	1·3 *	204—205	$\frac{1}{4}H_2O$	178—179
1-Et-7-Me	9·5	238—239	None	217—218
1 : 7-Diethyl	0·6	191—192	$\frac{1}{2}H_2O$	215—216
1 : 7-Diethyl-8-Me	4	235—236	None	206—207

Dr. C. B. Allsopp has kindly provided the following report on the absorption spectra of the above compounds :

" *Absorption Spectra of* 1 : 7-*Dialkyl-xanthines and -guanines.*—The absorption spectra of the 1 : 7-dialkyl xanthines and guanines were recorded with a Spekker photometer used in conjunction with an intermediate size Hilger quartz spectrograph. The positions of the maxima of intensity could be determined to about 10 A., and their intensities (ε = molecular extinction coefficient) to $0{\cdot}01 \times 10^4$. Beer's law was obeyed at all the concentrations employed, which ranged from M/800 to M/10,000.

" *Xanthines.*—The absorption spectra of xanthine and of its simple derivatives in acid or neutral solution contain one or both of two bands which occur in the regions of the spectrum around 2650 A. and 2400 A., respectively (Gulland and Holiday, *Nature*, 1933, **132**, 782; J., 1934, 1639). In alkaline solutions these bands are displaced by 100 to 200 A. towards longer wave-lengths and, in some cases, *e.g.*, 1-methylxanthine, a derivative showing only one band in acid solution shows both in alkaline solution. Gulland and Holiday observed that the band of shorter wave-length is suppressed by substitution in the 7-position. The spectra of 1 : 7-dimethyl-, 1-methyl-7-ethyl-, 1-methyl-7-*n*-propyl-, 7-methyl-1-ethyl-, 1 : 7-diethyl-, and 8-methyl-1 : 7-diethyl-xanthines now recorded (Tables II and III, and Fig. 1) are in agreement with this observation. They contain only a single band, which occurs at wave-lengths about 2700 A. in neutral and acid solutions, and at about 2900 A. in alkaline solution.

" Examination of the data recorded by Gulland and Holiday reveals no systematic wave-number separation between the maxima of intensity in the two-band spectra, so that the two bands may be assumed to originate from separate electrons. That at shorter wave-lengths might perhaps be attributed to a lone-pair electron on the 7-N atom. It is consistently less intense in acid than in alkaline solution (cf. Baldwin, *Proc. Roy. Soc., A*, 1937, **162**, 228), and is suppressed when this atom is saturated in the manner shown in the structural formulæ for the xanthines proposed by Ogston (J., 1935, 1736) on the basis of dissociation measurements. The disappearance of the band correlates directly with the presence of a positive charge on the 7-N atom in Ogston's formulæ (as XXI).


(XXI.)

" The band at 2700 A. may be attributed to the pyrimidine ring since a band appears at similar wave-lengths in the spectra of all purines (Heyroth and Loofbourow, *J. Amer. Chem. Soc.*, 1934, **56**, 1728). In homologous series the intensity of absorption usually increases with increasing weight of the molecule; but Table II shows that the intensity of the band of the 1 : 7-di-alkyl xanthines decreases with increasing size of the 7-substituent

($\varepsilon_{max.}$ for 1-Me-7-Me = 0·93 × 10^4, for 1-Me-7-Et = 0·77 × 10^4), but increases again if the weight of the 1-substituent is increased ($\varepsilon_{max.}$ for 1-Et-7-Et = 0·83 × 10^4). Such a counterbalancing effect of the two electron-repelling groups shows that the degree of " saturation " of the pyrimidine ring, as measured by the intensity of its absorption band, is very susceptible to slight changes in its electrical symmetry.

" The displacement of the band on passing from acid to alkaline solutions, which might be expected to depend on the degree of dissociation, is approximately constant in the series. Table III shows that when the group substituted in the 1-position is larger than that at the 7-position, the displacement is accompanied by a decrease in intensity which is not observed when the 7-substituent is the larger. The spectrum of 1 : 7-diethyl-8-methylxanthine is also of this type, as might be expected. Increase of pH causes the same displacement of the band and a marked decrease in its intensity.

" *Guanines.*—The absorption spectrum of guanine itself has been measured by Holiday (*Biochem. J.*, 1930, **24**, 619) and by Heyroth and Loofbourow (*loc. cit.*) and those of 7-methylguanine and 9-methyl*iso*guanine by Gulland and Story (*J.*, 1938, 692). Two absorption bands are again involved, but their relationship is simpler

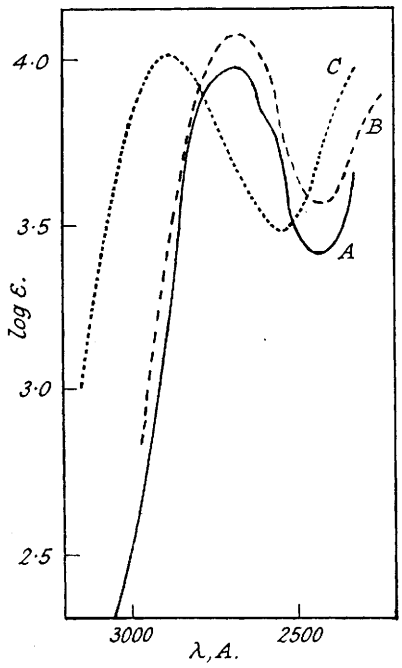


FIG. 1.—*Absorption curves of paraxanthine :*

A, *in neutral solution..*
B, *in acid solution.*
C, *in alkaline solution.*

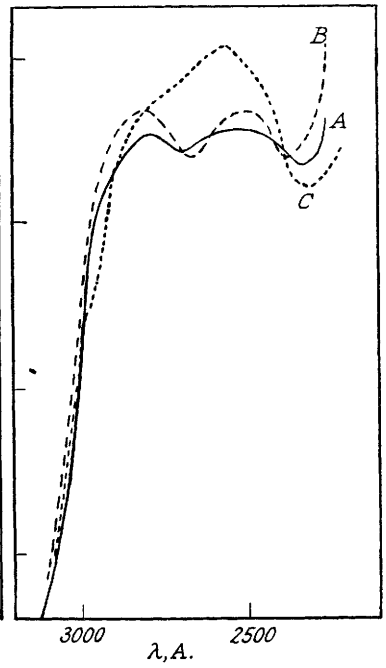


FIG. 2.—*Absorption curves of :*

A, 1 : 7-*Dimethylguanine sulphate.*
B, 1-*Methyl*-7-n-*propylguanine sulphate.*
C, 1-*Methyl*-9(?)-n-*propylguanine sulphate.*

than in the case of the xanthines, since they can be attributed to a lactim–lactam tautomerism. In strong alkaline solution, a band at 2700—2800 A. only is observed : in strong acid (0·05N HCl) the spectrum contains a single band at 2500 A. In aqueous and weakly acid solutions, both bands may be found simultaneously.

" The spectra of 1 : 7-dimethylguanine and of 1-methyl-7-*n*-propylguanine now recorded in aqueous solution accordingly show both bands (Table II and Fig. 2), the spectra of the two compounds being very similar. In contrast, the spectrum of the material believed to be 1-methyl-9-*n*-propyl*iso*guanine contains only one maximum at 2560 A., although there are indications of a possible second band at 2800 A. (Fig. 2). Gulland and Story (*loc. cit.*) record a somewhat similar spectrum for 7-methylguanine in 0·05N-HCl, but with $\varepsilon_{max.}$ at 2500 A. Their 9-methyl*iso*guanine absorbed at shorter wave-lengths than the 7-derivative, so that the 1 : 9-structure attributed to the present material must be tentative. The structure of the 1 : 7-compound, however, was confirmed in that the absorption spectrum of the xanthine derived from it agreed closely with those of the known 1 : 7-dialkylxanthines.

" Fig. 1 shows the absorption curves of paraxanthine in neutral, acid and alkaline solution : those of the new 1 : 7-dialkyl xanthines are so closely similar that they are not included, but the position and intensities of their respective maxima are recorded in the above Tables."

Dr. G. S. Carter has submitted the above synthetic purines and also certain allied derivatives to preliminary tests for antithyroid activity, by determining the concentration needed to abolish the effects of thyroxine in an aqueous solution containing 1 mg. per litre on the temperature/heart-rate curve of the frog's heart (cf. Carter, Mann *et al.*, *loc. cit.*; Carter and Jenkins, *loc. cit.*). The details of these tests and a critical discussion

TABLE II.

Absorption bands of 1 : 7-*dialkyl-xanthines and -guanines in aqueous solution.*

	Position.				
	1.	7.	8.	$\lambda_{max.}$	$\varepsilon_{max.}$
Xanthines	Me	Me	—	2680 A.	$0{\cdot}93 \times 10^4$
	Me	Et	—	2680	0·77
	Me	Pr$^{\alpha}$	—	2690	0·76
	Et	Me	—	2690	0·98
	Et	Et	—	2690	0·83
	Et	Et	Me	2720	1·12
Guanines	Me	Me	—	2790	0·60
				2500	0·62
	Me	Pr$^{\alpha}$	—	2810	0·69
				2500	0·69
	1-Me-9(?)- Pr$^{\alpha}$			2570	1·07

TABLE III.

Influence of pH *on absorption bands of* 1 : 7-*di-alkylxanthines.*

Position.			Acid solution (N/100 HCl).		Alkaline solution (N/100 NaOH).	
1.	7.	8.	$\lambda_{max.}$	$\varepsilon_{max.}$	$\lambda_{max.}$	$\varepsilon_{max.}$
Me	Me	—	2670 A.	$1{\cdot}17 \times 10^4$	2890 A.	$1{\cdot}02 \times 10^4$
Me	Et	—	2670	0·80	2910	0·81
Et	Me	—	2680	1·02	2880	0·78
Et	Et	—	2670	1·00	2900	0·89
Et	Et	Me	2690	1·07	2900	0·91

of their significance will be published elsewhere. They indicate that 1-methyl-7-ethyl-, 1-methyl-7-*n*-propyl-, 7-methyl-1-ethyl-, 1 : 7-diethyl-, 8-methyl-1 : 7-diethylxanthine, and also 1 : 9-dimethyl*iso*xanthine all have an antithyroid activity of the same order as that of paraxanthine. 1 : 7-Dimethylguanine and 9-methyl*iso*-xanthine appear to have definite but markedly lower activities, whilst xanthine, guanine, 3 : 9-dimethyl*iso*-xanthine and 1 : 3 : 9-trimethyl*iso*xanthine have (at the most) exceedingly low activities.

These results if confirmed would indicate that an alkylated xanthine, in order to possess high antithyroid activity, must possess an alkyl group in the 1-position and a second in the 7- or 9-position; the insertion of a third group apparently destroys the activity unless it is in the 8-position. Other minor changes in the main structure also have a marked effect: the considerable loss in activity when paraxanthine is converted into 1 : 7-dimethylguanine is noteworthy.

EXPERIMENTAL.

Solvents used for recrystallisation are named in parenthesis after the compounds concerned. All picrates, unless otherwise stated, were recrystallised from a very dilute aqueous solution of picric acid. The yields given are, unless otherwise stated, those of the pure recrystallised products: the yields of certain of the crude products were much higher.

Alkylation of 2 : 4-*Diamino-5-formamido-6-ketodihydropyrimidine* (I).—(a) The monohydrate of this compound was prepared by Traube and Dudley's method (*loc. cit.*) and when methylated in alkaline solution with dimethyl sulphate as they direct gave the monohydrated 1-methyl derivative (II) in 60% yield. Alternatively, the monohydrated (I) (3 g.) was dissolved in a solution of sodium hydroxide (0·64 g., 1 mol.) in water (10 c.c.), alcohol (30 c.c.) added, the mixture warmed until the precipitated sodium salt dissolved, methyl iodide (3 g., 1·3 mols.) added and the mixture refluxed for 5 hours. The monohydrated 1-methyl derivative (II) separated during the boiling, and a second crop was obtained by evaporation of the filtrate; the united crops after recrystallisation (water) gave the 1-methyl derivative (II) (1·3 g., 40%) identical in properties with that obtained using dimethyl sulphate (Found: for the anhydrous material, C, 36·3; H, 5·8. Calc. for $C_6H_9O_2N_5$: C, 35·8; H, 5·5%). (b) The compound (I) was recovered unchanged after it had been treated in sodium hydroxide solution with diethyl sulphate (1·5 mols.) at 15—16°, at 50—60° or at 100°. Many variations in the order of addition of the hydroxide and sulphate were made but all proved fruitless. The same result was obtained in several experiments in which ethyl iodide was used in place of the methyl iodide described above.

Alkylation of 1-*Methylguanine* (III, R = H).—(a) *Methylation.* Traube and Dudley's methylation with methyl chloride to 1 : 7-dimethyl guanine was confirmed: yield of pure recrystallised product, 31%.

(b) *Ethylation.* A solution of (III, R = H) (2·36 g.) in N-NaOH solution (14·3 c.c., 1 mol. NaOH) was diluted in turn with alcohol (50 c.c.) and ethyl iodide (4·5 g., 2 mols.) and refluxed for 12 hours. The clear solution was evaporated to dryness, and the residue extracted with hot 2% aqueous sodium hydroxide solution (30 c.c.); the filtrate on cooling deposited 1-*methyl-7-ethylguanine* (III, R = Et), colourless needles which after two recrystallisations (water) had m. p. 256—257° (preliminary softening) (Found: C, 49·4; H, 5·7. $C_8H_{11}ON_5$ requires C, 49·7; H, 5·7%); 0·6 g., 22%. When aqueous solutions of this guanine and of picric acid were mixed, the guanine *picrate* was deposited as needles which after recrystallisation had m. p. 266° (decomp.) (Found: C, 40·3; H, 3·5; N, 26·5. $C_8H_{11}ON_5,C_6H_3O_7N_3$ requires C, 39·8; H, 3·3; N, 26·5%).

(c) *Propylation.* *n*-Propyl alcohol (50 c.c.) was added to a solution of 1-methylguanine (2·36 g.) in N-NaOH (14·3 c.c.), which was then refluxed until clear, *n*-propyl iodide (5 g., 2 mols.) added and the refluxing continued for 24 hours. The solution remained clear on cooling, and it was evaporated to dryness, the residue acidified with dilute acetic acid (to decompose any unchanged sodium 1-methylguanine) and again evaporated to dryness. The residue, a mixture of a brown amorphous material and colourless crystals, was extracted with boiling alcohol (50 c.c.) in which only the crystals dissolved. The alcoholic filtrate, when set aside, deposited two distinct crops: (*A*) colourless crystals (0·5 g.) which separated readily and were collected after 4 hours; m. p. 245—247° (decomp.): (*B*) colourless crystals (0·1 g.) which slowly separated during several days; m. p. 290—293° (decomp.).

Crop (*A*), when recrystallised (alcohol) afforded a hydrated *hydriodide* of 1-*methyl*-7-n-*propylguanine* (III, R = Pr$^{\alpha}$), fine needles, m. p. 245—247° (decomp.), which were unstable when exposed to light and air, rapidly becoming brown;

confinement over phosphoric anhydride readily gave the anhydrous *hydriodide*, of unchanged m. p., which was appreciably more stable (Found, for the hydrated salt: C, 38·0; H, 5·2; N, 23·7; I, 22·3. $C_9H_{13}ON_5,\frac{1}{2}HI,H_2O$ requires C, 37·4; H, 5·4; N, 24·3; I, 22·0%. Found for the anhydrous salt: C, 39·6; H, 4·6; N, 26·3; I, 22·9. $C_9H_{13}ON_5,\frac{1}{2}HI$ requires C, 39·8; H, 5·0; N, 25·8; I, 23·4%). The proportion of base to acid in this salt is noteworthy. When a solution of the hydriodide (0·45 g.) in hot alcohol (20 c.c.) was diluted with one of sulphuric acid (0·5 g.) in alcohol (5 c.c.), the mixture became brown and deposited the *sulphate* of the guanine: colourless needles (0·35 g.) (alcohol), m. p. 231—233° (Found: C, 35·4; H, 5·1; N, 22·8. $C_9H_{13}ON_5,H_2SO_4$ requires C, 35·4; H, 4·9; N, 23·0%). This salt in aqueous solution, treated with aqueous sodium picrate, readily gave the *picrate*, yellow needles, m. p. 228—229° (decomp.) (Found: C, 41·0; H, 3·7; N, 25·95. $C_9H_{13}ON_5,C_6H_3O_7N_3$ requires C, 41·3; H, 3·7; N, 25·7%).

Crop (*B*) was also a hydriodide. In view of the small amount, it was converted in alcoholic solution directly to the *sulphate* of [1-methyl-9(?)-*n*-propyl-*iso*guanine] which, although insoluble in boiling alcohol, was recrystallised readily from 50% aqueous alcohol: colourless crystals, m. p. 265° (decomp.) (Found: C, 35·5; H, 4·9; N, 23·4; S, 10·9. $C_9H_{13}ON_5,H_2SO_4$ requires C, 35·4; H, 4·9; N, 23·0; S, 10·5%). The sulphate in turn furnished the *picrate*, yellow needles, m. p. 240—241° (decomp.), depressed by admixture with the 1-methyl-7-*n*-propyl isomeride (Found: C, 41·3; H, 3·7; N, 25·6. $C_9H_{13}ON_5,C_6H_3O_7N_3$ requires C, 41·3; H, 3·7; N, 25·7%).

(d) *iso*Propylation. Preparation (c) was repeated, using *iso*propyl alcohol and iodide, and the refluxing continued for 48 hours. After evaporation to dryness, the residue was extracted with boiling alcohol, which on cooling deposited 1-*methyl*-(7?)-iso*propylguanine hydriodide*, colourless crystals (0·2 g.) (alcohol), m. p. 265—266° (decomp.) (Found: C, 39·9; H, 5·3; N, 25·6; I, 23·3. $C_9H_{13}ON_5,\frac{1}{2}HI$ requires C, 39·8; H, 5·0; N, 25·8; I, 23·4%). Many variations in the conditions of this preparation failed to increase the yield. An alcoholic solution, treated with alcoholic sulphuric acid, deposited the *sulphate*, m. p. 249—250° (Found: C, 42·5; H, 5·2; N, 27·2. $C_9H_{13}ON_5,\frac{1}{2}H_2SO_4$ requires C, 42·1; H, 5·5; N, 27·3%). An aqueous solution of the latter salt afforded the *picrate*, yellow needles, m. p. 239—241° (decomp.) (Found: C, 41·5; H, 3·5. $C_9H_{13}ON_5,C_6H_3O_7N_3$ requires C, 41·3; H, 3·7%).

(e) β-*Hydroxyethylation*. Ethyl alcohol (50 c.c.) was added to a solution of 1-methylguanine (2·5 g.) in N-NaOH (15·25 c.c.), the mixture boiled till clear, ethylene chlorohydrin (4 g., 2 mols.) added and the refluxing continued for 24 hours. The product was taken to dryness, made just acid with acetic acid and extracted with hot water (20 c.c.), which deposited colourless crystals: these after recrystallisation (alcohol) afforded 1-*methyl*-(7?)-β-*hydroxyethylguanine monohydrate* (0·15 g.), m. p. 250—260° with preliminary softening (Found: C, 42·25; H, 5·5. $C_8H_{11}O_2N_5,H_2O$ requires C, 42·3; H, 5·7%); heating at 130°/15 mm. gave the anhydrous *guanine* of unchanged m. p. (Found: C, 45·8; H, 5·5; N, 33·8. $C_8H_{11}O_2N_5$ requires C, 45·9; H, 5·3; N, 33·5%). The aqueous solution gave a *picrate*, m. p. 240° (decomp.) (Found: C, 38·6; H, 3·5; N, 25·9. $C_8H_{11}O_2N_5,C_6H_3O_7N_3$ requires C, 38·3; H, 3·2; N, 25·6%).

Conversion of Above Guanines to Xanthines.—(a) The conversion of 1 : 7-dimethylguanine (III, R = Me) to paraxanthine by Traube and Dudley's directions was confirmed: the paraxanthine, m. p. 296—298°, was obtained in 80% yield. (b) A solution of sodium nitrite (0·5 g., 2 mols.) in water (2 c.c.) was slowly added to a solution of 1-methyl-7-ethylguanine (III, R = Et) (0·7 g.) in N-H_2SO_4 (3·7 c.c., 1 mol. H_2SO_4) kept at 90°. When, towards the end of the addition of the nitrite, a solid product began to separate boiling water was added in just sufficient quantity to maintain a clear solution: finally the latter was refluxed for 0·5 hour, and on cooling deposited the *hemihydrate* of 1-*methyl*-7-*ethylxanthine* (IV, R = Et), long silky needles (0·35 g., 49%) after one crystallisation (water), m. p. 225—226° (with preliminary softening) (Found: C, 47·2; H, 5·4; N, 27·5. $C_8H_{10}O_2N_4,\frac{1}{2}H_2O$ requires C, 47·2; H, 5·4; N, 27·5%). This material, when heated at 130°/15 mm. for 3 hours, gave the anhydrous *xanthine* of unchanged m. p. (Found: C, 49·3; H, 4·9. $C_8H_{10}O_2N_4$ requires C, 49·4; H, 5·15%). The *picrate*, prepared as usual in aqueous solution, separated in fine silky yellow needles, m. p. 221—222° (decomp.) (Found: C, 39·9; H, 3·4; N, 23·5. $C_8H_{10}O_2N_4,C_6H_3O_7N_3$ requires C, 39·7; H, 3·1; N, 23·2%). (c) A solution of sodium nitrite (0·05 g., 2·1 mol.) in water (1 c.c.) was slowly added from a fine capillary dropping-tube to a boiling solution of 1-methyl-7-*n*-propylguanine sulphate (0·2 g.) in water (2 c.c.), and the mixture was refluxed for 15 minutes. On cooling, 1-*methyl*-7-n-*propylxanthine* (IV, R = Pr^n) separated in long needles, which after one crystallisation (water) furnished the *tetartohydrate* (0·03 g., 46%), m. p. 204—205° (Found: C, 50·7; H, 6·3; N, 26·0. $C_9H_{12}O_2N_4,\frac{1}{4}H_2O$ requires C, 50·8; H, 5·9; N, 26·3%). Drying at 130°/0·5 mm. for 3 hours gave the anhydrous *xanthine* of unchanged m. p. (Found: C, 52·3; H, 5·8. $C_9H_{12}O_2N_4$ requires C, 51·9; H, 5·8%). The *picrate*, prepared as usual, crystallised in yellow needles, m. p. 178—179° (decomp.) (Found: C, 41·7; H, 3·4. $C_9H_{12}O_2N_4,C_6H_3O_7N_3$ requires C, 41·2; H, 3·4%).

NN'-Dimethyloxamide was converted to 5-chloro-1-methyliminazole by the method of Wallach and Boehringer (*Annalen*, 1877, **184**, 51; cf. Wallach, *ibid.*, 1882, **214**, 307), and the iminazole, by nitration and subsequent treatment with potassium cyanide was converted to 4-nitro-5-cyano-1-methyliminazole (VI) as described by Sarasin and Wegmann (*loc. cit.*).

4-*Nitro*-1-*methyliminazole*-5-*carboxylic Acid* (X, R = H).—A solution of the 5-cyano-iminazole (VI) (16·5 g.) in concentrated sulphuric acid (175 g., 95 c.c.) was heated at 100° for 2 hours in a flask closed by a calcium chloride tube, and then cooled in ice-water and vigorously agitated whilst a solution of sodium nitrite (9 g., 1·3 mols.) in water (30 c.c.) was slowly added from a dropping funnel, the stem of which, drawn out to a fine capillary tube, dipped below the surface of the acid solution; the addition of the nitrite was adjusted so that the temperature did not rise above 30°. The complete mixture was then heated on a boiling water-bath until effervescence ceased (3—5 hours), the solution cooled, poured on to ice (500 g.) and set aside overnight. The precipitated 5-*carboxylic acid* (X, R = H) was then collected, washed with water, and purified by dissolving in cold 5% aqueous sodium carbonate solution, filtering from a trace of insoluble impurity and reprecipitating with dilute hydrochloric acid. The acid thus obtained (16 g., 92%) had m. p. 161° (effer.) and was sufficiently pure for synthetic purposes; for purification, it was recrystallised (water) and obtained in colourless crystals, m. p. 163° (effer.) (Found: C, 35·2; H, 3·1; N, 25·1. $C_5H_5O_4N_3$ requires C, 35·1; H, 2·9; N, 24·6%). Sarasin and Wegmann give m. p. 160° for the acid obtained from the amide, but give no analytical identification.

The 5-*carboxylic chloride* was prepared by refluxing a solution of the acid (20 g.) in thionyl chloride (50 c.c.) until acid fumes were no longer evolved and a clear solution was obtained. The excess of thionyl chloride was removed (the last traces at 18 mm.), the residual oil dissolved in benzene (60 c.c.) and the crude chloride precipitated by the cautious addition of ligroin (b. p. 60—80°, 200 c.c.) as an oil which on cooling and scratching ultimately crystallised. For purification, it was collected, washed with petrol, dissolved in hot benzene (60 c.c.), and ligroin (*ca.* 120 c.c.) then added to the boiling solution until a faint permanent turbidity appeared: spontaneous cooling caused the chloride to separate in pale yellow plates (21 g., 95%), m. p. 62—62·5° (Found: C, 31·7; H, 2·0; Cl, 18·6. $C_5H_4O_3N_3Cl$ requires C, 31·7; H, 2·1; Cl, 18·7%). The chloride, being rapidly affected by damp air, was stored in an evacuated desiccator.

Methylamide of 4-*nitro*-1-*methyliminazole*-5-*carboxylic acid* (VII, R = Me). A solution of methylamine in benzene was added to a vigorously shaken solution of the chloride (5 g.) also in cold benzene (25 c.c.), until the mixture became permanently basic: much heat was evolved and the methylamide, mixed with methylamine hydrochloride, rapidly crystallised. The complete mixture was then shaken for a further half-hour, the solid material collected, washed with benzene, dried and recrystallised (water); the *methylamide* was obtained in thick colourless needles (4·5 g., 95%), m. p. 191·5—192° (Found: N, 30·5. $C_6H_8O_3N_4$ requires N, 30·4%).

The *ethylamide* (VII, R = Et) was prepared in 95% yield and purified precisely similarly; colourless needles, m. p. 145—146° (Found: C, 42·6; H, 4·9. $C_7H_{10}O_3N_4$ requires C, 42·2; H, 5·0%). The *phenylamide* (VII, R = Ph) was similarly prepared (75% yield) and recrystallised from much water; colourless crystals, m. p. 191—192° (Found: C, 53·8; H, 4·5. $C_{11}H_{10}O_3N_4$ requires C, 53·7; H, 4·1%). The *β-bromoethylamide* (VII, R = CH_2·CH_2Br) was similarly obtained using a benzene solution of freshly prepared β-bromoethylamine: colourless crystals, m. p. 154—155° (Found: N, 20·5. $C_7H_9O_3N_4Br$ requires N, 20·3%). The *β-hydroxyethylamide* (VII, R = CH_2·CH_2OH) was similarly prepared using monoethanolamine, and recrystallised from alcohol: hard colourless crystals, m. p. 148—149° (Found: C, 39·5; H, 4·7. $C_7H_{10}O_4N_4$ requires C, 39·25; H, 4·7%). This amide was further characterised by refluxing with acetic anhydride for 1 hour, and evaporating to dryness: recrystallisation (benzene) of the residue gave the *β-acetoxyethylamide* (VII, R = CH_2·CH_2OAc), needles, m. p. 109—110° (Found: C, 42·1; H, 4·8. $C_9H_{12}O_5N_4$ requires C, 42·2; H, 4·7%).

Reduction of the 4-Nitro-methylamide (VII, R = Me) *to the 4-Amino-compound* (VIII, R = Me).—The first of the following three methods is the most satisfactory and is that used in the complete purine synthesis; only brief details of the other methods are given. (i) Raney nickel (0·3 g.) was added to a solution of the methylamide (1·65 g.) in warm alcohol (100 c.c.) in a hydrogenation apparatus, the air was removed, and hydrogen passed in at *ca.* 800 mm. whilst the solution was vigorously agitated. Absorption of hydrogen was rapid during the first hour and was complete after three hours, when the total absorption (600 c.c., N.T.P.) was that theoretically required for 3 mols. The solution, repeatedly filtered to remove nickel and then evaporated in a vacuum at room temperature, gave a crystalline residue (1·35 g.) of the *4-amino* compound (VIII, R = Me), which twice crystallised (acetone–ether, 1 : 1), had m. p. 149—150° (decomp.) (Found: C, 47·1; H, 6·5. $C_6H_{10}ON_4$ requires C, 46·8; H, 6·5%): 0·95 g., 70%. The amine is freely soluble in cold water and in methyl and ethyl alcohols, moderately soluble in cold acetone, and almost insoluble in ether, benzene and ligroin. It was further characterised by adding concentrated hydrochloric acid (3 drops) to a solution of the amine (0·2 g.) in hot acetone (10 c.c.), when on cooling and scratching the *hydrochloride* separated; colourless plates (alcohol–ether, equal vols.), m. p. 213° with preliminary darkening (Found: C, 37·7; H, 5·5; Cl. 18·8. $C_6H_{10}ON_4$,HCl requires C, 37·8; H, 5·8; Cl, 18·8%).

(ii) Aluminium groats (8 g.) were converted to the amalgam by Mann and Pope's method (*Proc. Roy. Soc., A.*, 1925, **107**, 86) and immediately covered with a solution of the methylamide (4·5 g.) in warm 95% alcohol (150 c.c.). The mixture was then gently refluxed for 8 hours, small additions of 95% alcohol being occasionally made to keep the mixture mobile. The copious deposit of aluminium hydroxide was then collected, and thrice extracted with hot acetone (150 c.c. in all): the filtrate and the extracts were united and evaporated, and the crude crystalline residue (3 g.) after recrystallisation (acetone) furnished the 4-amino compound (1·5 g.), m. p. 149—150° (decomp.), unchanged by admixture with that prepared by method (i).

(iii) A solution of the methylamide (2·7 g.) in hot water (50 c.c.) was added to one of hydrated ferrous sulphate (30 g.) also in water (60 c.c.), and aqueous ammonia (*d*, 0·88, *ca.* 15 c.c.) then slowly added until the vigorously agitated mixture had a permanent odour of ammonia. The complete mixture was boiled for 5 minutes, filtered and the filtrate evaporated in a desiccator. The red crystalline residue, after two crystallisations (alcohol) gave a colourless product (0·5 g.), m. p. 188° (decomp.): this product contained sulphate ions, which were not removed by further crystallisations. It was therefore treated in alcoholic solution with picric acid, which precipitated the 4-amino methylamide *picrate*, needles, m. p. 201° (decomp.) (Found: C, 37·8; H, 3·8. $C_6H_{10}ON_4$,$C_6H_3O_7N_3$ requires C, 37·6; H, 3·4%).

Reduction of the 4-Nitro-ethylamide (VII, R = Et).—(i) *In the absence of acids.* A solution of the ethylamide (4 g.) in hot alcohol (100 c.c.) was reduced precisely as in Expt. (i) above, the theoretical quantity of hydrogen (1360 c.c., N.T.P.) being absorbed. The crude crystalline residue, after recrystallisation (acetone), afforded the *4-amino ethylamide* (VIII, R = Et), colourless needles (2·3 g., 69%), m. p. 137—138° (decomp.) (Found: C, 50·5; H, 6·95. $C_7H_{12}ON_4$ requires C, 50·0; H, 7·1%). The pure amine rapidly darkened after crystallisation, and in subsequent preparations the base was dissolved in warm acetone, and converted by the method described above to the *hydrochloride*, colourless crystals (alcohol–ether), m. p. 189—190° (decomp.) (Found: Cl, 17·5. $C_7H_{12}ON_4$,HCl requires Cl, 17·4%). (ii) *In the presence of hydrogen chloride.* Preparation of the catalyst: animal charcoal (3 g.), previously purified by extraction first with hot hydrochloric acid and then repeatedly with boiling water, was added to a solution of potassium palladochloride (0·8 g.), and the mixture shaken in a hydrogen atmosphere until absorption (*ca.* 170 c.c., N.T.P.) ceased. The catalyst was collected, washed with water and dried in a vacuum: it could be used for 3—4 consecutive reductions before its activity appreciably diminished. For the reduction, this catalyst and concentrated hydrochloric acid (2·2 c.c., 1 mol.) were added in this order to a solution of the ethylamide (4 g.) in hot alcohol (100 c.c.), and the agitated mixture hydrogenated as usual: absorption, 1350 c.c. (N.T.P.). The filtered solution, evaporated in a desiccator, gave the crystalline 4-amino hydrochloride, which after recrystallisation (alcohol–ether) had m. p. as above: 3·0 g., 73%. This salt in alcoholic solution readily gave the *picrate*, feathery orange needles, m. p. 182° (decomp.) (Found: C, 39·5; H, 3·7. $C_7H_{12}ON_4$,$C_6H_3O_7N_3$ requires C, 39·3; H, 3·8%).

Reduction of the 4-Nitro-phenylamide (VII, R = Ph).—A mixture of the catalyst, hydrochloric acid (2·6 c.c., 1 mol.) and a solution of the phenylamide (5·4 g.) in hot alcohol (150 c.c.) was hydrogenated as in the last experiment: absorption, 1480 c.c. (theoretical). The oily residue from the evaporation, when triturated with acetone, gave the crystalline *hydrochloride* of the *4-amino compound* (VIII, R = Ph), colourless crystals (2·25 g., 41%) (acetone) which on heating slowly darkened and decomposed above 130° without melting (Found: Cl, 13·1. $C_{11}H_{12}ON_4$,HCl requires Cl, 12·6%).

When similar experiments were performed with the 4-nitro β-bromethylamide (VII, R = ·CH_2·CH_2Br) in the presence of hydrobromic acid, or with the β-hydroxyethylamide (VII, R = ·CH_2CH_2OH) or β-acetoxyethylamide (VII, R = ·CH_2CH_2OAc), absorption of hydrogen readily occurred but no crystalline product could be isolated.

Paraxanthine from the Amino-methylamide (VIII, R = Me).—A solution of the methylamide (0·7 g.) in warm dioxan (15 c.c.), to which ethyl chloroformate (2·1 g., 4 mols.) and anhydrous potassium carbonate (2 g., 3·1 mols.) had been added, was heated under reflux in a bath at 105° for 4 hours. After cooling, the solid material was collected, extracted with boiling alcohol (5 c.c.) to remove any hydrochloride of the unchanged amine, mixed thoroughly with cold water (10 c.c.) and made just acid (litmus) with 20% aqueous acetic acid. The undissolved paraxanthine was collected, washed with ice-water (2 c.c.) and recrystallised (water, 10 c.c.): fine needles (0·5 g., 61%), m. p. 297—299°, unaffected by admixture with an authentic sample (Found: C, 46·9; H, 4·6; N, 30·9. Calc. for $C_7H_8O_2N_4$: C, 46·7; H, 4·4; N, 31·1%). The yield could be increased by heating the above mixture for much longer periods (*ca.* 24 hours): the hydrogen chloride, liberated by the initial action of the ethyl chloroformate, precipitated some of the unchanged amine as its hydrochloride, which being almost insoluble in dioxan reacted only very slowly with the potassium carbonate. The conditions cited above are therefore preferable, the unchanged amine being recovered as follows. The alcoholic extract was evaporated to dryness, and the residual hydrochloride then ground to a thick paste with an excess of potassium carbonate moistened with water, and finally extracted with boiling acetone. The filtered extract on evaporation gave the crystalline amino methylamide which after one recrystallisation (acetone–ether) was pure: m. p. 149—150° (decomp.). The paraxanthine was further characterised by conversion to the picrate, m. p. 247—249° (decomp.) (Found: N, 24·2. Calc. for $C_7H_8O_2N_4$,$C_6H_3O_7N_3$: N, 24·0%).

7-Methyl-1-ethylxanthine.—A solution of the hydrochloride of the 4-amino ethylamide (VIII, R = Et) (2·5 g.) in a

mixture of dioxan (15 c.c.) and alcohol (2 c.c.), to which potassium carbonate (2·5 g., 1·8 mols.) had been added, was heated at 105° for 0·5 hour with shaking. Ethyl chloroformate (3·3 g., 2·9 mols.) was then added, and the heating continued for a further 15 hours, with additions of the carbonate (0·5 g.) and the chloroformate (0·5 g.) at 2-hourly intervals. The product was then evaporated on a water-bath to dryness, and the crystalline residue extracted with boiling alcohol (5 c.c.) to remove any unchanged hydrochloride of the amine. The final residue, after acidification with acetic acid as before, followed by two crystallisations (water) gave 7-*methyl*-1-*ethylxanthine*, long colourless needles, m. p. 238—239° (Found : C, 49·8; H, 5·2; N, 28·5. $C_8H_{10}O_2N_4$ requires C, 49·5; H, 5·15; N, 28·8%) : 0·8 g., 47% yield, allowing for recovered hydrochloride. The xanthine in aqueous solution gave a *picrate*, m. p. 217—218° (decomp.) (Found : N, 23·0. $C_8H_{10}O_2N_4,C_6H_3O_7N_3$ requires N, 23·2%).

4-*Nitro*-1-*methyliminazole*-5-*carboxylic Esters.*—A mixture of the 5-carboxylic chloride (3 g.) and methanol (6 c.c.) was boiled for 2 minutes, diluted with water (20 c.c.) and cooled; the *methyl ester* (X, R = Me) rapidly separated, and after recrystallisation (aqueous methanol) gave colourless crystals, m. p. 127—128° (Found : C, 39·0; H, 3·9. $C_6H_7O_4N_3$ requires C, 38·9; H, 3·8%) : 2·6 g., 96%. The *ethyl ester* (X, R = Et), similarly prepared and recrystallised (aqueous alcohol), formed long needles, m. p. 100—101° (Found : N, 21·4. $C_7H_9O_4N_3$ requires N, 21·1%) : yield, almost quantitative.

Reduction of the 4-*nitro*-5-*carboxylic esters.* (i) Raney nickel (*ca.* 0·2 g.) was added to a solution of the 4-nitro methyl ester (X, R = Me) (1·5 g.) in methanol (50 c.c.), which was hydrogenated as usual, the theoretical absorption (545 c.c., N.T.P.) being complete in 3 hours. Evaporation of the filtered solution gave a crystalline residue of the 4-*amino*-5-*carboxylic methyl ester* (XI, R = Me), colourless crystals (1 g.) (benzene), m. p. 126—127° (Found : C, 46·6; H, 5·7. $C_6H_9O_2N_3$ requires C, 46·4; H, 5·8%). The amine readily formed a *picrate*, m. p. 236° (decomp.) (Found : C, 37·9; H, 3·3. $C_6H_9O_2N_3,C_6H_3O_7N_3$ requires C, 37·5; H, 3·1%). When concentrated hydrochloric acid was cautiously added to an acetone solution of the amine, the *hydrochloride* readily crystallised : colourless crystals (alcohol–ether), m. p. 183° (decomp.) (Found : Cl, 19·0. $C_6H_9O_2N_3$,HCl requires Cl, 18·6%).

The hydrochloride was also prepared by direct reduction. The palladium catalyst (described above) and concentrated hydrochloric acid (2·3 c.c., 1 mol. acid) were added to a solution of the 4-nitro methyl ester (X, R = Me) (3·7 g.), which on hydrogenation absorbed the theoretical amount of hydrogen (1345 c.c., N.T.P.) in 3 hours. The filtered solution was evaporated to dryness in a vacuum, and the crystalline residue extracted with warm alcohol; the alcoholic extract on dilution with ether deposited the pure hydrochloride (3 g., 79%), m. p. 183° (decomp.). (ii) Repetition of the last experiment, using the palladium catalyst and a solution of the 4-nitro ethyl ester (X, R = Et) gave the *hydrochloride* of the 4-*amino*-1-*methyliminazole*-5-*carboxylic ethyl ester* (XI, R = Et), colourless crystals (alcohol–ether), m. p. 190° (decomp.) (Found : Cl, 17·6. $C_7H_{11}O_2N_3$,HCl requires Cl, 17·3%).

Many attempts were made to condense the above amino-esters with ethyl chloroformate to form the 4-ethylcarbamido derivatives; in spite of a wide variety of conditions employed, however, all attempts failed, only the unchanged amines (or their hydrochlorides) being subsequently isolated.

4-*Nitro*-5-*cyano*-2-*methyl*-1-*ethyliminazole.*—A solution of the 5-chloro-iminazole (38 g.) in absolute ethyl alcohol (200 c.c.), to which potassium cyanide (26·5 g., 2 mols.) and potassium iodide (1·1 g., 0·32 mol.) had been added, was refluxed for 6 hours and the solvent removed. The dark brown residue was extracted with water (200 c.c.), and the insoluble oil thrice extracted with chloroform (300 c.c. in all). The united chloroform extracts were dried (sodium sulphate) and distilled, the 5-cyano-iminazole being obtained as a colourless liquid, b. p. 170—172°/0·05 mm., which crystallised after several days and then had m. p. 70—71° (Found : C, 46·6; H, 4·5. Calc. for $C_7H_8O_2N_4$: C, 46·7; H, 4·4%) : 30 g., 84%.

4-*Nitro*-2-*methyl*-1-*ethyliminazole*-5-*carboxylic Acid* (XIV).—This was obtained precisely as the 1-methyl acid (X, R = H), using the above cyanide (25 g.), concentrated sulphuric acid (280 g., 152 c.c.), and sodium nitrite (11·5 g., 1·1 mols.) in water (50 c.c.). The 5-*carboxylic acid* (XIV), worked up as before, separated in colourless crystals (23 g., 95%), m. p. 139—141° (effer.), almost unaffected by recrystallisation (water) (Found : C, 42·5; H, 4·2; N, 21·3. $C_7H_9O_4N_3$ requires C, 42·2; H, 4·5; N, 21·1%).

A suspension of this acid (20 g.) in thionyl chloride (55 c.c.) was refluxed until clear (*ca.* 2 hours), and the excess of thionyl chloride removed. The oily residue was dissolved in benzene (15 c.c.) and the liquid carboxylic chloride cautiously precipitated by the addition of ligroin (b. p. 60—80°); all attempts to induce it to crystallise failed and it decomposed when heated even at 0·05 mm. pressure. To remove traces of thionyl chloride, therefore, a current of dry air was drawn through the carboxylic chloride at 10 mm. pressure, and the chloride was then dissolved in dry benzene and treated with a benzene solution of ethylamine as previously described. The crude solid product when recrystallised (water) afforded the pure 5-*carboxylic ethylamide*, colourless needles, m. p. 85—86° (Found : C, 47·8; H, 6·1; N, 25·0. $C_9H_{14}O_3N_4$ requires C, 47·8; H, 6·2; N, 24·8%) : 20 g. (90% yield calculated on the acid).

Ethylamide of 4-*Amino*-2-*methyl*-1-*ethyliminazole*-5-*carboxylic Acid* (XV).—(i) A solution of the 4-nitro ethylamide (3 g.) in cold alcohol (60 c.c.), to which Raney nickel (0·5 g.) had been added, on hydrogenation rapidly absorbed the theoretical volume of hydrogen (890 c.c., N.T.P.). Evaporation of the filtered solution in a vacuum gave a viscous green oil which could not be crystallised. A small portion of this oil in alcoholic solution readily gave the *picrate* of the 4-*amino* compound (XV), yellow needles, m. p. 176° (Found : C, 42·4; H, 4·5. $C_9H_{16}ON_4,C_6H_3O_7N_3$ requires C, 42·4; H, 4·5%). The remainder of the oil, in warm acetone solution, was precipitated as the *hydrochloride* by the usual method : colourless crystals (alcohol–acetone), m. p. 169° (decomp.) (Found : C, 46·4; H, 7·3; Cl, 15·2. $C_9H_{16}ON_4$,HCl requires C, 46·4; H, 7·3; Cl, 15·3%) : yield, *ca.* 30%.

(ii) A solution of the 4-nitro compound (8·7 g.) in alcohol (120 c.c.) to which the palladium catalyst and concentrated hydrochloric acid (4·5 c.c., 1 mol. acid) had been added readily absorbed the theoretical quantity of hydrogen (2585 c.c., N.T.P.). The filtered solution, when taken to dryness in a vacuum gave a partially crystalline residue, from which on recrystallisation the pure hydrochloride, m. p. 169° (decomp.), was obtained : 4 g., 45%.

The low yields in these two reductions are apparently due to decomposition during the evaporation in the vacuum : in each case the initial filtrate was colourless, but evaporation of the first solution caused a green coloration, and that of the second solution a deep yellow coloration, to develop. More rapid evaporation by distillation under reduced pressure accelerated the decomposition without increasing the yield.

8-*Methyl*-1 : 7-*diethylxanthine* (XVI).—A mixture of the above hydrochloride (1 g.), dioxan (5 c.c.) and potassium carbonate (1·5 g., 2·5 mols.) was heated under reflux at 105° for 0·5 hour. Ethyl chloroformate (2·1 g., 4·2 mols.) was then added, and the heating continued for 6 hours with alternate additions of carbonate (0·5 g.) and chloroformate (0·5 g.) at hourly intervals. The product, worked up as previously described, afforded the *xanthine* (XVI), colourless crystals (water), m. p. 235—236° (Found : C, 54·2; H, 6·6; N, 25·7. $C_{10}H_{14}O_2N_4$ requires C, 54·0; H, 6·3; N, 25·2%) : 0·3 g., 36%. The xanthine is only sparingly soluble in hot water, and almost insoluble in cold water and the usual organic solvents. In aqueous solution it readily afforded a *picrate*, yellow needles, m. p. 206—207° (decomp.) (Found : C, 42·8; H, 3·6; N, 22·0. $C_{10}H_{14}O_2N_4,C_6H_3O_7N_3$ requires C, 42·6; H, 3·8; N, 21·7%).

1 : 7-*Diethylxanthine.*—Chlorination of the 8-methyl group in the xanthine (XVI) proceeds readily, but care is necessary to obtain the pure trichloro compound. For this purpose, the powdered xanthine (XVI, 0·9 g.) was dissolved in a solu-

tion of chlorine (2·3 g., 3·5 mols.) in phosphorus oxychloride (15 c.c.), and the clear product heated at 50° for 1·5 hours. Removal of the oxychloride at 18 mm. left an oil which rapidly crystallised when triturated with water (1 drop) and, when dried and recrystallised (*cyclo*hexane), furnished *8-trichloromethyl-*1 : 7-*diethylxanthine*, colourless needles, m. p. 149—150° (Found : C, 37·5; H, 3·5; N, 17·5. $C_{10}H_{11}O_2N_4Cl_3$ requires C, 36·9; H, 3·4; N, 17·2%) : 0·6 g., 18%.

A suspension of this trichloro compound (0·35 g.) in water (30 c.c.) was refluxed for 1 hour, when a clear solution had formed and carbon dioxide evolution had ceased. The solution, concentrated to 10 c.c. and cooled, deposited 1 : 7-*diethylxanthine hemihydrate*, colourless needles (water), m. p. 191—192° (Found : C, 50·0; H, 6·3; N, 25·4. $C_9H_{12}O_2N_4,\frac{1}{2}H_2O$ requires C, 49·8; H, 6·0; N, 25·8%) : the hydrate, heated at 130°/15 mm. for 3 hours, gave the anhydrous *xanthine* of unchanged m. p. (Found : C, 51·8; H, 5·8. $C_9H_{12}O_2N_4$ requires C, 51·9; H, 5·8%) : 0·15 g., 75%. The xanthine in aqueous solution gave a *picrate*, m. p. 215—216° (decomp.) (Found : C, 41·3; H, 3·7. $C_9H_{12}O_2N_4,C_6H_3O_7N_3$ requires C, 41·2; H, 3·4%).

Paraxanthine from Caffeine.—(The following experimental work was carried out by Mr. J. Harley-Mason, for whose collaboration we are greatly indebted.) The most ready preparation of paraxanthine has hitherto been Fischer and Ach's method (*loc. cit.*) whereby caffeine is converted to 8-chlorocaffeine which is then further chlorinated at 170° without a solvent to 3-chloromethyl-8-chloro-paraxanthine which on hydrolysis and reduction furnishes paraxanthine. The yield is low, however, largely owing to the difficulty in controlling the second chlorination. We have improved the method considerably by using *o*-dichlorobenzene as a solvent, and have also modified it for the preparation of 1-methylxanthine : the yield of the latter is low, but the accessibility of the starting materials makes it a valuable preparative method.

A mixture of 8-chlorocaffeine (40 g.) and *o*-dichlorobenzene (redistilled, b. p. 165—175°) (80 c.c.) containing a small crystal of iodine was boiled under reflux whilst chlorine was passed through sufficiently rapidly for an excess to escape throughout the operation. After 1·5 hours, the mixture was steam-distilled (for *ca.* 2 hours), the residual solution (*ca.* 500 c.c.) slowly evaporated to 150 c.c., and set aside overnight. The solid which had separated was collected, dissolved in hot dilute sodium hydroxide solution, and the sodium salt of the 8-chloroparaxanthine then precipitated by the addition of 30% sodium hydroxide solution. The dissolution and precipitation of the sodium salt were repeated, and the purified salt was then dissolved in hot water and decomposed with acetic acid. 8-Chloroparaxanthine (12 g.) was thus precipitated, and another crop (2 g.) separated from the steam distillate during 2—3 days : reduction using hydriodic acid and phosphonium iodide (Fischer and Clemm, *Ber.*, 1898, **31**, 2622) gave paraxanthine, which was purified by recrystallisation from hot water.

To prepare 1-methylxanthine, the above chlorination was continued for 3·5 hours, and the dichlorobenzene mixture then set aside for 3 days. The considerable crystalline deposit (mainly trichlorocaffeine) was then collected, dissolved in boiling acetic acid (50 c.c.), boiling water (200 c.c.) added, and the mixture boiled for 6 hours, during which period formaldehyde was evolved and the volume reduced to *ca.* 100 c.c. The solution, when set aside for 2 days, deposited 8-chloro-1-methylxanthine, which was purified via the sodium salt as described above, and then reduced by Fischer and Clemm's method to 1-methylxanthine (Found : C, 43·0; H, 4·3; N, 33·2. Calc. for $C_6H_6O_2N_4$: C, 43·4; H, 3·6; N, 33·7%) : 6 g. The success of this preparation depends on the extent of the chlorination, which however can be judged only by experience with the particular apparatus employed.

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