ATTEMPTED SYNTHESIS OF THE 1,6-DIHYDROPURINE SYSTEM*

By R. M. Hoskinson†

The 1,6-dihydropurines are little known substances which have been obtained from certain purines by chemical[1] and electrochemical[2–8] reduction and by catalytic hydrogenation.[9,10]‡

One example[11] has been obtained synthetically but, otherwise, no general method of preparation is available. This note describes attempts to form these compounds from appropriate imidazoles and indicates that the 4-amino-5-aminomethylimidazoles, which could yield 1,6-dihydropurines by cyclization, are unstable and unsuited for use in synthesis.

Base-promoted displacement of halogen from 5-chloro-1-methyl-4-nitroimidazole with diethyl malonate afforded 5-diethoxycarbonylmethyl-1-methyl-4-nitroimidazole as its red sodium salt which, on careful acidification, was converted into the colourless carbon acid (II). Hydrolysis and decarboxylation of (II) in 10N HCl furnished 5-carboxymethyl-1-methyl-4-nitroimidazole (III) and, in lower yield, its monoester (IV). The acid, (III), could not be converted into an acid chloride owing to the ease with which it underwent a further decarboxylation forming (V). However, by esterification and treatment with hydrazine, the hydrazide (VI) was obtained. After Curtius rearrangement[12] of (VI), in ethanol with amyl nitrite, and catalytic hydrogenation of the resulting urethane (VII), the amine (VIII) was isolated as the picrate. Owing to its

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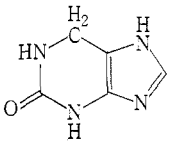
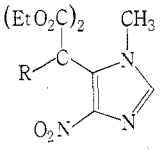
‡ Bendich first demonstrated that purine and 2-hydroxypurine could undergo catalytic hydrogenation. The reduced products were not isolated, and it was inferred from spectroscopic data that they were 1,6-dihydropurines. Re-examination of these reactions has now established that dihydro-2-hydroxypurine can be readily obtained and is identical with 1,6-dihydro-2-hydroxypurine (I) prepared independently from xanthine by electrochemical reduction.[5,8] In contrast, the parent dihydropurine is unstable and could not be isolated.

[1] Fichter, Fr., and Kern, W., *Helv. chim. Acta*, 1926, **9**, 380.
[2] Baillie, T. B., and Tafel, J., *Ber. dt. chem. Ges.*, 1899, **32**, 68.
[3] Tafel, J., *Ber. dt. chem. Ges.*, 1899, **32**, 3194.
[4] Tafel, J., and Weinschenk, A., *Ber. dt. chem. Ges.*, 1900, **33**, 3369.
[5] Tafel, J., and Ach, B., *Ber. dt. chem. Ges.*, 1901, **34**, 1165.
[6] Tafel, J., and Ach, B., *Ber. dt. chem. Ges.*, 1901, **34**, 1170.
[7] Tafel, J., and Dodt, J., *Ber. dt. chem. Ges.*, 1907, **40**, 3752.
[8] Tafel, J., and Mayer, R., *Ber. dt. chem. Ges.*, 1908, **41**, 2546.
[9] Bendich, A., Russell, P. J., and Fox, J. J., *J. Am. chem. Soc.*, 1954, **76**, 6073.
[10] Bendich, A., "Ciba Foundation Symposium on Chemistry and Biology of Purines." p. 308. (Churchill: London 1957.)
[11] Mitter, P. C., and Chatterjee, N., *J. Indian chem. Soc.*, 1934, **11**, 867.
[12] Smith, P. A., *Org. React.*, 1947, **3**, 337.

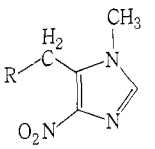
thermal instability and ease of resinification the free amine could not be obtained. No products of intramolecular cyclization of (VIII) could be detected. Attempts to form other solid derivatives of (VIII) either by formylation with acetic formic anhydride or chloral[13] or by reaction with phenyl chlorothiolformate[14] were unsuccessful.



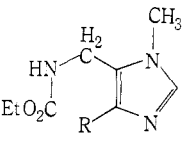
(I)



(II) R = H
(IX) R = NO_2

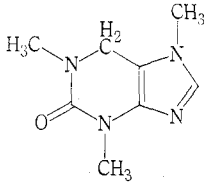


(III) R = CO_2H
(IV) R = CO_2Et
(V) R = H
(VI) R = NH_2NHCO
(X) R = NO_2

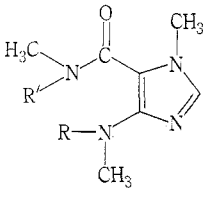


(VII) R = NO_2
(VIII) R = NH_2

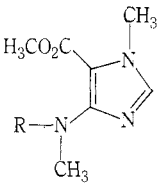
An alternative synthetic route to 4-amino-5-aminomethyl-1-methylimidazole, based on the diester (II), was then studied. Reaction of (II) with fuming nitric acid furnished (IX), which after hydrolysis and decarboxylation produced 1-methyl-4-nitro-5-nitromethylimidazole (X). This dinitro compound was also formed in low yield by reaction of 5-chloro-1-methyl-4-nitroimidazole with nitromethane. Catalytic hydrogenation of (X) occurred readily (e.g. with platinum–ethanol) but gave an unstable oil from which the expected diamine could not be isolated. Some 4-amino-imidazoles are unstable substances;[15] the hydrogenation products of (VII) and (X) appear to be further examples.



(XI)



	R	R′
(XII)	H	H
(XIII)	CHO	H
(XIV)	CHO	NO
(XVIII)	CH_3CO	H



(XV) R = CHO
(XVI) R = H
(XVII) R = CH_3NHCO

[13] Blicke, F. F., and Chi-Jung Lu, *J. Am. chem. Soc.*, 1952, **74**, 3933.

[14] Rivier, M. H., *Bull. Soc. chim. Fr.*, 1907, 733; Cook, A. H., and Smith, E., *J. chem. Soc.*, 1949, 2329.

[15] Hofmann, K., "Imidazole and its Derivatives." Part 1, p. 142. (Interscience: New York 1953.)

In a third sequence the synthesis of deoxycaffeine (XI),[2,3] from the readily obtainable base caffeidin[16] (XII), appeared feasible. Formylation of caffeidin with acetic formic anhydride gave the *N*-formyl derivative (XIII) which, after reaction in

TABLE 1

IONIZATION CONSTANTS AND ULTRAVIOLET SPECTRA

Compound		pK_a*	λ_{max} (log ϵ)†	pH or H_0
(II)		−1·52±0·02 (310) 6·80±0·01 (259)	306 (3·79)	4·0
(II),	anion		260 (4·37), 304 (3·73) 431 (3·47)	9·0
(III)		−0·88±0·01 (310) 3·03±0·05 (320)	*220 (3·61)*, 308 (3·85)	1·0
(III),	cation		278 (3·86)	−3·0
(III),	anion		*230 (3·65)*, 313 (3·90)	7·0
(IV)		−0·82±0·01 (320)	*222 (3·62)*, 307 (3·86)	7·0
(IV),	cation		*221 (3·61)*, 276 (3·86)	−3·0
(VI)		−1·01±0·04 (316)	*226 (3·65)*, 308 (3·82)	7·0
(VI),	cation		275 (3·81)	−3·0
(VII)		−0·66±0·04 (315)	*227 (3·58)*, 307 (3·85)	7·0
(VII),	cation		277 (3·83)	−3·0
(IX)		‡	294 (3·63)	E
(X)		−1·74±0·02 (305), 6·42±0·02 (260)	300 (3·77)	4·0
(X),	anion		259 (4·03), 377 (3·71)	9·0
(XII)		4·57±0·02 (310)	284 (3·96)	7·0
(XII),	cation		248 (3·82), 282 (3·95)	2·0
(XIII)		‡	*251 (3·80)*	E
(XIV)		‡	*235 (4·05)*, *304 (3·22)*	E
(XV)		‡	251 (3·90)	E
(XVI)		4·21±0·01 (310)	230 (3·57), 291 (4·07)	7·0
(XVI),	cation		244 (3·86), 284 (4·11)	2·0
(XVII)		2·02±0·03 (250)	238 (3·91)	7·0
(XVII),	cation		*255 (3·58)*	−0·2

* Measured spectrometrically by methods of Albert and Serjeant ("Ionization Constants of Acids and Bases." (Methuen: London 1962.)); analytical wavelength (mμ) in parentheses.

† In aqueous buffer of given pH or H_0 or in ethanol (E). Inflexions in italics.

‡ Substances are too unstable in acid solution to permit pK_a determination.

acetic acid with sodium nitrite, provided the nitrosoamide (XIV). Rearrangement of (XIV) to the ester (XV) occurred, on heating in refluxing benzene, in the manner of *N*-alkyl-*N*-nitrosoamides.[17] Deformylation of (XV) with methanolic hydrogen chloride and reaction of the derived amino ester (XVI) with methyl isocyanate afforded

[16] Biltz, H., and Rakett, H., *Ber. dt. chem. Ges.*, 1928, **61**, 1409.

[17] White, E. H., *J. Am. chem. Soc.*, 1955, **77**, 6011.

the substituted urea (XVII). It was expected that reduction of (XVII) with lithium aluminium hydride might introduce an hydroxymethyl function at C 5 which, by cyclization, could yield deoxycaffeine (XI). In fact treatment of (XVII) in tetrahydrofuran at 0° with the hydride resulted in smooth intramolecular displacement of the methoxyl group and the regeneration of caffeine.

Relevant ionization and spectral data for new substances reported here are given in Tables 1 and 2.

TABLE 2

PROTON MAGNETIC RESONANCE SPECTRA

τ values quoted to nearest 0·05 p.p.m.; J values in c/s

Compound	Medium	N 1–CH_3	H 2	Other
(II)	$CDCl_3$	6·2	2·4	CH_2: q 5·65 (J 7); Me: t 8·7 (J 7); malonyl CH: s 3·8
(III)	D_2O	6·25	2·15	CH_2: s 5·75
(IV)	$CDCl_3$	6·25	2·4	C 5–CH_2: s 5·8; ester CH_2: q 5·7 (J 7); ester Me: t 8·7 (J 7)
(VI)	$(CD_3)_2SO$	6·3	2·3	C 5–CH_2: s 6·1; NH(br) 0·7,* 5·7,* 6·7*
(VII)	$CDCl_3$	6·0	2·5	C 5–CH_2: d 5·25† (J 6); ester CH_2: q 5·9 (J 7); ester Me: t 8·75 (J 7); NH(br) 4·2*
(IX)	$CDCl_3$	6·25	2·3	CH_2: q 5·5 (J 7); Me: t 8·6 (J 7)
(X)	$(CD_3)_2SO$	6·15	1·9	CH_2: s 3·75
(XII)	$CDCl_3$	6·1	2·75	4-NMe: s 7·1;‡ NH(br) 5·75;* 5-NMe: d 7·1‡ (J 4); NH(br) 2·85*
(XIII)	$(CD_3)_2SO$	6·4	2·45	4-NMe: s 7·0; 5-NMe: d 7·4† (J 4); CHO: s 1·9; NH(br) 2·2*
(XIII)	$CDCl_3$	d§6·1, 6·2	2·6	4-NMe: d§ 6·65, 6·8; 5·NMe: d 7·1† (J 5); CHO: s 1·75; NH(br) 3·5*
(XIV)	$CDCl_3$	6·0	d§2·2, 2·3	4-NMe: d§ 6·6, 6·85; 5-NMe: s 6·75; CHO: d§ 1·75, 1·95
(XV)	$CDCl_3$	6·0‡	2·45	4-NMe: s 6·7; OMe: s 6·1;‡ CHO: s 1·6
(XVI)	$CDCl_3$	6·2‡	2·7	4-NMe: d 6·9† (J 5); OMe: s 6·1‡; NH(br) 4·6*
(XVII)	$CDCl_3$	6·1‡	2·55	4-NMe: s 6·85; Me of MeNHCO: d 7·25† (J 5); OMe: s 6·15;‡ NH(br) 4·8*
(XVIII)	$CDCl_3$	6·0	2·45	4-NMe: s 6·7; 5-NMe: d 7·0† (J 5); Ac: s 8·0; NH(br) 3·2*

* Signals collapse with D_2O.

† Signals collapse to a singlet with D_2O.

‡ These assignments are uncertain and may be the reverse of those made in the Table.

§ Signals described as doublets are twin peaks probably arising from restricted internal rotation of the type observed elsewhere for carbonyl–nitrogen bonds (Paulsen, H., and Todt, K., *Angew. Chem. int. Edn*, 1966, 5, 899; see also references therein; Stabb, H. A., and Lauer, D., *Tetrahedron Lett.*, 1966, 4593) and carbon–carbonyl bonds (Sidall, T. H., and Garner, R. H., *Tetrahedron Lett.*, 1966, 3513) of amides.

Experimental

Analyses are by Dr J. E. Fildes and her staff. pK_a values were measured by Mr A. Juodvalkis; ultraviolet spectra are by Mr I. Pavelić; p.m.r. spectra taken on a Perkin–Elmer R10 spectrometer with tetramethylsilane as internal standard (τ 10·0) are by Mr S. E. Brown.

5-Chloro-1-methylimidazole and 5-chloro-1-methyl-4-nitroimidazole were prepared by published procedures.[18,19] Light petroleum had b.p. 60–80°.

5-Diethoxycarbonylmethyl-1-methyl-4-nitroimidazole (*II*)

To a stirred, refluxing solution of 5-chloro-1-methyl-4-nitroimidazole (1·64 g) and diethyl malonate (4 ml) in dry benzene (30 ml) was added (over 1 hr) a solution of sodium ethoxide (0·46 g sodium) in dry ethanol (10 ml). Stirring and refluxing were continued for 1 hr and the precipitated red salt collected. This was dissolved in water (20 ml) forming an intense red solution which was layered over chloroform; the aqueous phase was titrated with 5N hydrochloric acid till the coloration was removed. Evaporation of the chloroform and crystallization of the oil (benzene) afforded *5-diethoxycarbonylmethyl-1-methyl-4-nitroimidazole* (1·5 g), m.p. 66–68° (Found: C, 46·3; H, 5·3; N, 14·7. $C_{11}H_{15}N_3O_6$ requires C, 46·0; H, 5·2; N, 14·6%).

5-Carboxymethyl-1-methyl-4-nitroimidazole (*III*)

A rapidly stirred suspension of 5-diethoxycarbonylmethyl-1-methyl-4-nitroimidazole (25 g) in 10N hydrochloric acid (75 ml) was heated in an oil-bath at 100° for 2 hr. The resulting solution was concentrated and was repeatedly co-evaporated with ethanol till a crystalline solid remained. The solid was extracted with boiling acetone and, after crystallization (ethanol) of the acetone-insoluble residue, the *acid* (7 g), m.p. 157° (froths), was obtained (Found: C, 38·7; H, 3·9; N, 22·5. $C_6H_7N_3O_4$ requires C, 38·9; H, 3·8; N, 22·7%).

5-Ethoxycarbonylmethyl-1-methyl-4-nitroimidazole (*IV*)

Evaporation of the acetone-soluble extract from above and crystallization of the residue (ethanol) provided the *monoester* (3 g), m.p. 106–107° (Found: C, 45·3; H, 5·1; N, 19·7. $C_8H_{11}N_3O_4$ requires C, 45·1; H, 5·2; N, 19·7%).

1,5-Dimethyl-4-nitroimidazole (*V*)

5-Carboxymethyl-1-methyl-4-nitroimidazole (0·1 g) suspended in dry diethyleneglycol dimethyl ether (3 ml) was heated in an oil-bath (150°) for 20 min. Evaporation of the solvent and crystallization of the residue (water) yielded the dimethylnitroimidazole (45 mg), m.p. 160–161° (lit.[20] 160°) (Found: C, 42·8; H, 5·1; N, 29·6. $C_5H_7N_3O_2$ requires C, 42·6; H, 5·0; N, 29·8%).

5-Hydrazinocarbonylmethyl-1-methyl-4-nitroimidazole (*VI*)

5-Carboxymethyl-1-methyl-4-nitroimidazole (3·1 g) suspended in a solution of methanol (1·6 ml) and 1,2-dichloroethylene (4·8 ml) was treated with 36N sulphuric acid (0·05 ml) and the suspension heated under reflux for 16 hr. Hydrazine (99%, 2 ml) was then added and the volatile solvent evaporated. The residual oil was dissolved in ethanol (15 ml) and the solution heated under reflux during 4 hr. On cooling, the *acid hydrazide* (2·5 g), m.p. 186–189°, was obtained (Found: C, 36·4; H, 4·8; N, 34·8. $C_6H_9N_5O_3$ requires C, 36·2; H, 4·6; N, 35·2%).

5-N-Ethoxycarbonylaminomethyl-1-methyl-4-nitroimidazole (*VII*)

To 5-hydrazinocarbonylmethyl-1-methyl-4-nitroimidazole (7 g), suspended in refluxing 5% ethanolic hydrogen chloride (50 ml), was added freshly prepared amyl nitrite (7 ml) over 30 min. Heating under reflux was continued for 5 hr after which the ethanol was evaporated and the residual oil dissolved in water (20 ml). Neutralization of the solution (Dowex 1, carbonate form) and repeated concentration with water (3 × 20 ml) gave the *urethane* (3·5 g), m.p. 106–108°, which crystallized after refrigeration (benzene–light petroleum) (Found: C, 42·0; H, 5·4; N, 24·4. $C_8H_{12}N_4O_4$ requires C, 42·1; H, 5·3; N, 24·6%).

[18] Blicke, F. F., and Godt, H. C., *J. Am. chem. Soc.*, 1954, **76**, 3653.
[19] Sarasin, J., and Wegmann, E., *Helv. chim. Acta*, 1924, **7**, 713.
[20] Pyman, F. L., *J. chem. Soc.*, 1922, 2616.

4-Amino-5-N-ethoxycarbonylaminomethyl-1-methylimidazole (VIII) (as Picrate)

The urethane described above (0·1 g), Raney nickel (0·3 g), and ethanol (5 ml) were shaken together under hydrogen (1 atm). After 30 min hydrogen consumption had ceased and the catalyst was removed; the solution was concentrated to 1 ml and treated with saturated aqueous picric acid (5 ml). Cooling in ice provided the *picrate* (0·15 g), m.p. 148° (dec.) (Found: C, 39·4; H, 4·0; N, 22·6. $C_{14}H_{17}N_7O_9$ requires C, 39·4; H, 4·0; N, 23·0%).

5-Diethoxycarbonylnitromethyl-1-methyl-4-nitroimidazole (IX)

5-Diethoxycarbonylmethyl-1-methyl-4-nitroimidazole (2·1 g) was cooled in ice and treated with fuming nitric acid (8 ml) over 10 min. The solution was kept 4 hr at 25° and then poured onto ice. The oil formed was solidified by trituration. Crystallization (benzene) yielded the *nitromalonyl ester* (1·5 g), m.p. 94–96° (Found: C, 40·0; H, 4·3; N, 16·7. $C_{11}H_{14}N_4O_8$ requires C, 40·0; H, 4·3; N, 17·0%).

1-Methyl-4-nitro-5-nitromethylimidazole (X)

(i) 5-Diethoxycarbonylnitromethyl-1-methyl-4-nitroimidazole (5·3 g), dissolved in methanol (15 ml) containing potassium hydroxide (4 g) and water (20 ml), was heated under reflux for 70 min. The solution was cooled in ice and adjusted to pH 2 with 5N hydrochloric acid (dropwise). Concentration caused rapid precipitation of the *dinitroimidazole* and recrystallization (ethanol) gave 2·2 g, m.p. 125–127° (Found: C, 32·2; H, 3·4; N, 30·0. $C_5H_6N_4O_4$ requires C, 32·3; H, 3·3; N, 30·1%).

(ii) 5-Chloro-1-methyl-4-nitroimidazole (0·32 g), in a solution of dimethyl sulphoxide (1 ml) and nitromethane (0·4 ml), was treated portionwise (over 15 min) with dry potassium t-butoxide (0·45 g) dissolved in dimethyl sulphoxide (7 ml). The resulting red solution was kept at 25° (40 min), then diluted with benzene (20 ml). The red, precipitated salts were collected, dissolved in water (5 ml), and layered over with ethyl acetate (10 ml). Titration of the aqueous phase with 1N hydrochloric acid till disappearance of the red coloration followed by concentration of the ethyl acetate extract provided the dinitroimidazole (55 mg), m.p. 123–126° identical (mixed m.p., i.r. spectrum) with the preparation above.

1-Methyl-4-N-methylamino-5-N-methylaminocarbonylimidazole (XII) (Caffeidin)

The following preparation is based on a method of Biltz and Rakett.[16]

A solution of caffeine (10 g) in 2N sodium hydroxide (30 ml) was heated under reflux (2 hr), cooled in ice, and acidified by dropwise addition of 15N nitric acid (7 ml). The caffeidin nitrate (3·5 g), m.p. 212° (lit.[16] 215°), which crystallized was collected and dissolved in 30% potassium carbonate solution (10 ml); the oil which then separated was extracted into chloroform (3 × 20 ml) and the extracts concentrated. Crystallization (diethyl ether) afforded caffeidin (1·6 g), m.p. 83–85° (lit.[16] 93°) (Found: C, 49·7; H, 7·2; N, 33·4. Calc. for $C_7H_{12}N_4O_2$: C, 50·0; H, 7·2; N, 33·3%).

The *acetyl* derivative from benzene had m.p. 143–145° (Found: C, 51·6; H, 6·6; N, 26·8. $C_9H_{14}N_4O_2$ requires C, 51·4; H, 6·7; N, 26·7%).

4-(N-Formyl-N-methyl)amino-1-methyl-5-N-methylaminocarbonylimidazole (XIII)

Caffeidin (9 g), cooled in ice, was dissolved in acetic formic anhydride (50 ml) and then set aside at 25° (12 hr). Concentration of the solution followed by trituration with light petroleum and crystallization of the solid formed (benzene) gave the *formyl* derivative (8 g), m.p. 141–143° (Found: C, 49·2; H, 6·1; N, 28·4. $C_8H_{12}N_4O_2$ requires C, 49·0; H, 6·2; N, 28·6%).

4-(N-Formyl-N-methyl)amino-1-methyl-5-(N-methyl-N-nitroso)aminocarbonylimidazole (XIV)

A vigorously stirred solution of the above formyl compound (10 g), in glacial acetic acid (50 ml) and acetic anhydride (250 ml), was cooled in ice and treated with sodium nitrite (75 g) portionwise over 6 hr. A temperature of 0–5° was maintained. Stirring and cooling was then

continued for a further 6 hr during which the inorganic salts accumulated as a thick suspension. The reaction products were poured onto excess ice, extracted with chloroform till the yellow colour was removed from the aqueous phase, and the extracts concentrated in four separate portions. Crystallization of the oil formed (benzene) afforded the yellow *nitrosoamide* (6·5 g), m.p. 113–114° (Found: C, 42·9; H, 5·0; N, 30·8. $C_8H_{11}N_5O_3$ requires C, 42·7; H, 4·9; N, 31·1%).

*4-(*N*-Formyl-*N*-methyl)amino-5-methoxycarbonyl-1-methylimidazole (XV)*

A solution of the above nitrosoamide (3 g) in benzene (50 ml) was heated under reflux for 16 hr. Evaporation of the solvent and crystallization of the residue (ethanol, 5 ml) yielded the *ester* (1·3 g), m.p. 109° (Found: C, 48·8; H, 5·7; N, 21·2. $C_8H_{11}N_3O_3$ requires C, 48·7; H, 5·6; N, 21·3%).

*5-Methoxycarbonyl-1-methyl-4-*N*-methylaminoimidazole (XVI)*

4-(*N*-Formyl-*N*-methyl)amino-1-methyl-5-methoxycarbonylimidazole (1·5 g) was dissolved in 1M methanolic hydrogen chloride (20 ml) and set aside at 25°. After 2 hr the *amine hydrochloride* (1 g), m.p. 205°, had crystallized (Found: C, 41·3; H, 5·6; N, 20·5. $C_7H_{11}N_3O_2$,HCl requires C, 40·9; H, 5·9; N, 20·4%).

Neutralization of an aqueous solution (10 ml) of the hydrochloride (0·8 g) followed by extraction into chloroform, concentration, and crystallization of the solid residue (light petroleum) provided the *amine* (0·5 g), m.p. 100–102° (Found: C, 49·9; H, 6·6; N, 24·9. $C_7H_{11}N_3O_2$ requires C, 49·7; H, 6·6; N, 24·8%).

*5-Methoxycarbonyl-1-methyl-4-(*N*-methyl-*N*-methylaminocarbonyl)aminoimidazole (XVII)*

5-Methoxycarbonyl-1-methyl-4-*N*-methylaminoimidazole (6 g), in benzene (35 ml), was treated with methyl isocyanate (4·3 g) and kept at 27° (2 days). The solution was then refluxed for 2 hr, cooled, and on concentration the *urea* (6·8 g), m.p. 156–157°, crystallized (Found: C, 47·9; H, 6·4; N, 25·1. $C_9H_{14}N_4O_3$ requires C, 47·8; H, 6·2; N, 24·8%).

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