

Heterocyclic Studies. Part XXXV.¹ Cleavage of Fervenulin and 3-Methylfervenulin by Nucleophiles

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Treatment of fervenulin {6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione} and 3-methylfervenulin with primary amines gave 6-(3-alkyl-1-methylureido)-5-methylcarbamoyltriazines by attack at position 7 and cleavage of the 6,7-bond. Reactions with hydrazine and 1,1-dimethylhydrazine similarly gave triazin-6-ylsemicarbazides. Fervenulin and methylhydrazine gave 5,6-diamino-1,3-dimethyluracil and an unknown compound by cleavage of the triazine ring. The 6-(1-methyl-3-alkylureido)-5-methylcarbamoyltriazines were converted by cold nitrous acid into open-chain compounds. ¹H N.m.r., mass, and u.v. spectra are tabulated and discussed.

FERVENULIN {6,8-dimethylpyrimido[5,4-*e*]-*as*-triazine-5,7(6*H*,8*H*)-dione} is a crystalline antibiotic first isolated from cultures of *Streptomyces fervens*² and unwittingly synthesised by Pfeleiderer and Schundehütte³ before its structure was appreciated. This paper describes the

reactions of fervenulin (2; R¹ = H) and its 3-methyl derivative (2; R¹ = Me) with some nucleophiles, as an extension of our work on the cleavage of fused pyrimidine derivatives.⁴⁻⁸

¹ Part XXXIV, J. Clark and I. W. Southon, preceding paper.

² T. E. Elbe, E. C. Olson, C. M. Lange, and J. W. Shell, 'Antibiotics Annual,' 1959—1961, Antibiotics Inc., New York, 1960, p. 227.

³ W. Pfeleiderer and K. H. Schundehütte, *Annalen*, 1958, **615**, 42.

⁴ J. Clark, G. Neath, and C. Smith, *J. Chem. Soc. (C)*, 1969, 1297.

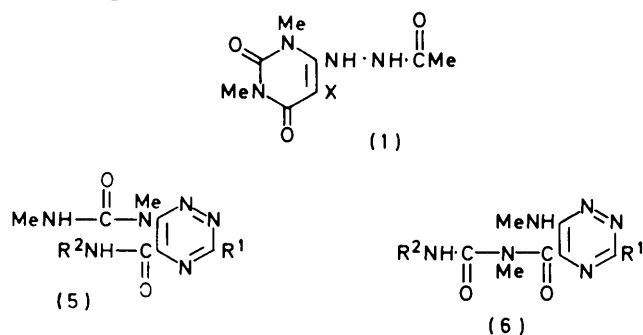
⁵ J. Clark and G. Neath, *J. Chem. Soc. (C)*, 1966, 1112.

⁶ J. Clark and G. Neath, *J. Chem. Soc. (C)*, 1968, 919; J. Clark and C. Smith, *ibid.*, 1969, 2777.

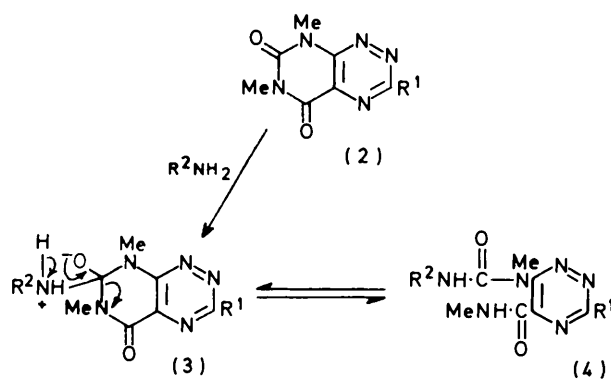
⁷ J. Clark and C. Smith, *J. Chem. Soc. (C)*, 1971, 1948.

⁸ J. Clark and M. S. Morton, *J.C.S. Perkin I*, 1974, 1812.

Fervenulin was prepared by the published method³ but we were unable to prepare its 3-methyl derivative by the method described in the same paper. We believe that the synthesis failed at the stage where 6-(2-acetylhydrazino)-1,3-dimethyl-5-nitrosouracil (1; X = NO) was to be reduced to the amine (1; X = NH₂) by hydrogen over Raney nickel. In our hands ammonia was always produced, probably by hydrogenolysis of the hydrazino-group (*cf.* ref. 9). Reduction of the nitroso-compound (1; X = NO) with sodium dithionite avoided the trouble and 3-methylfervenulin was obtained on cyclisation and oxidation of the resulting amine (1; X = NH₂).



Treatment of fervenulin and its 3-methyl derivative with primary amines yielded crystalline products of ring cleavage (Table 1) which were assigned *N*-triazin-6-ylurea structures (4; R¹ = H or Me, R² = Me, Et, CHMe₂, [CH₂]₃CH₃, or CH₂Ph) in preference to the likely alternatives (5) and (6). The isomers (4) and (6) could be formed by attack at the 7-position followed by cleavage of the 6,7- or 7,8-bond, respectively; isomer (5) could be formed by attack at the 5-position and cleavage of the 5,6-bond.

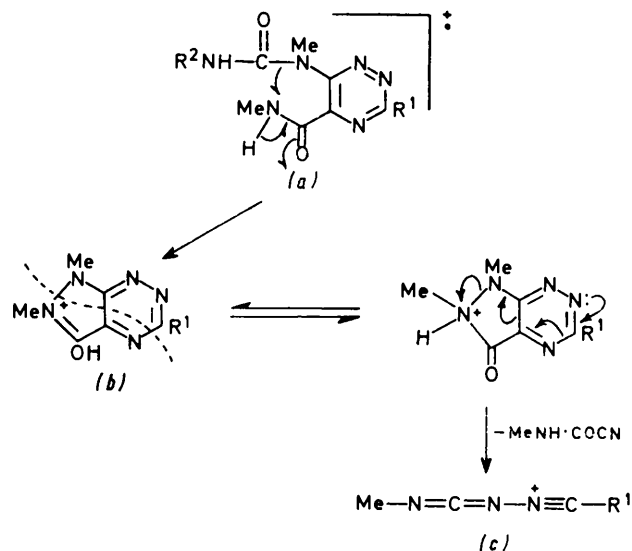


SCHEME 1

The methylamino-structure (6) was eliminated by u.v. spectroscopy (Table 2); the compounds formed showed no absorption at wavelengths greater than 276 nm. The spectra of compounds (6) would have been similar to those of 6-amino-5-carbamoyl-*as*-triazine (7; R = H),¹⁰ its dimethyl derivative (7; R = Me) (see

later), and the closely related pyrazine derivatives (8; Y = X = R = H)¹¹ and (8; X = R = H, Y = Cl),¹² which have long wavelength absorptions in the 350–380 nm region (Table 2). Acylation of the amino-group of these compounds causes marked hypsochromic shifts so that acylamino-derivatives, *e.g.* (8; X = H, R = CHO, Y = Cl)¹² and (8; Y = X = H, R = CHO)¹³ absorb at much shorter wavelengths, as do the compounds under investigation.

The mass spectra of the compounds were very simple and strongly supported the proposed structures (4). Molecular ions were absent but all the compounds (4; R¹ = H) from fervenulin gave a dominant fragment ion of *m/e* 166 (base peak) and all those (4; R¹ = Me) from 3-methylfervenulin gave a corresponding ion of *m/e* 180 (base peak). There was usually no ion of any significance at a higher *m/e* value but at high source pressures very small (*M* + 1)⁺ peaks (relative abundance <0.2%) appeared. The ions of *m/e* 166 (*b*; R¹ = H) were shown by accurate mass measurement to have the composition C₆H₈N₅O and those of *m/e* 180 (*b*; R¹ = Me) C₇H₁₀N₅O, and were therefore formed by loss of R²NHCO from the



SCHEME 2

molecular ions. A peak at *m/e* 82 (C₃H₄N₃) and an associated metastable peak (*m*^{*} 40.5) showed that ion (*b*; R¹ = H) lost MeNHCOCN to yield ion (*c*; R¹ = H) (Scheme 2). Ions of *m/e* 180 from the methyl derivatives decomposed in a similar fashion to give ions of *m/e* 96 (*c*; R¹ = Me).

¹H N.m.r. spectra (Table 3) confirmed that the triazine ring was intact and were consistent with the proposed structures (4), but did not help materially in ruling out the alternative structures (5).

As a whole the foregoing evidence made it virtually certain that the products were the triazin-6-ylureas (4), formed by nucleophilic attack at position 7 of the

⁹ C. Ainsworth, *J. Amer. Chem. Soc.*, 1954, **76**, 5774.

¹⁰ C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, 1969, **34**, 2102.

¹¹ D. D. Perrin, *J. Chem. Soc.*, 1962, 645.

¹² A. Albert and J. Clark, *J. Chem. Soc.*, 1964, 1666.

¹³ A. Albert and H. Yamamoto, *J. Chem. Soc. (C)*, 1968, 2289.

pyrimidotriazines (2) (Scheme 1). This is in accord with the fact that alkaline ring cleavages of closely related pyrimido[4,5-*c*]-*as*-triazines (10) yield compounds such as the methylamide (11), which must result from attack at the corresponding position of the pyrimidine ring.¹⁴ Furthermore the reported cases of nucleophilic attack on 1,3-dimethyl-lumazines (9) occur at position 2, which again corresponds to position 7 of our compounds.^{7,15}

The pyrimidotriazines (2; R¹ = H or Me) were both cleaved by hydrazine even at 20° to give similar triazine derivatives whose molecular formulae suggested that they were analogues (4; R² = NH₂) of the cleavage products already discussed. Fervenulin also reacted with 1,1-dimethylhydrazine, at 100°, to give a triazine, but the 3-methyl compound (2; R = Me) was unaffected by treatment with dimethylhydrazine at 100° for 4 days. Neither pyrimidotriazine reacted with hydroxylamine or methoxyamine at 100°.

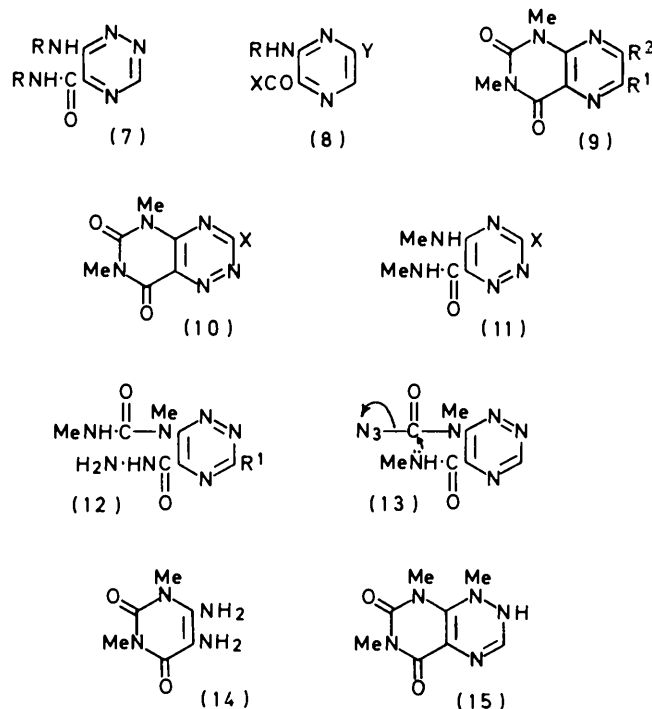
The structure of the product from fervenulin and 1,1-dimethylhydrazine (4; R¹ = H, R² = NMe₂) was clearly analogous to those of products of ring-opening by amines. The mass spectrum, with major peaks at *m/e* 166 and 82 linked by a metastable peak (*m** 40.5) was characteristic, and the ¹H n.m.r. spectrum (Table 3) showed signals for the two methyl groups and the triazine proton of the original molecule at very similar chemical shifts to those of the previous triazinylureas (4; R¹ = H, R² = alkyl).

The product of cleavage by hydrazine hydrate also proved to be a semicarbazide of type (4; R¹ = H, R² = NH₂) rather than the other possible isomer (12; R¹ = H). It reacted with nitrous acid in dilute acetic acid to regenerate fervenulin, presumably *via* the azide (13), and with nitrous acid in hydrochloric acid to give the methylamide (7; R = Me). Fervenulin could have been formed from either isomer [(4; R¹ = H, R² = NH₂) or (12; R¹ = H)] but the methylamide could only have come from the former. The possibility that it was formed from the isomer (12; R¹ = H) by cyclisation to fervenulin and then ring-cleavage of the latter was eliminated when fervenulin was shown to be stable to nitrous acid.

The structure of the methylamide (7; R = Me) was firmly established by its u.v. spectrum (Table 2) and by its mass spectrum, which showed losses of 28 (N₂) and 27 (HCN) mass units, characteristic of the 1,2,4-triazine ring,¹⁶ and a peak at *m/e* 82 (MeN=C=N-N⁺≡CH), expected by analogy with the other compounds discussed.

The mass spectrum of the semicarbazide (4; R¹ = H, R² = NH₂) differed from those of all the other cleavage products (4; R¹ = H) in showing a dominant peak at *m/e* 167 (C₅H₇N₆O) instead of 166. The loss of MeNHCO

from the molecular ion (*d*) is explained by formation of a very stable ion (*e*) (Scheme 3) which could only be



SCHEME 3

produced from a compound bearing the NH·NH₂ group. In agreement, the product (4; R¹ = Me, R² = NH₂)

broke down in similar fashion to give a dominant peak at *m/e* 181.

Although the mass spectrum could equally well be explained by loss of MeNHCO from the molecular ion of the isomer (12; R¹ = H), and hydrazine does sometimes give cleavages inconsistent with those from other reagents,⁴ the other evidence shows conclusively that hydrazine attacks at position 7, like other reagents.

Treatment of fervenulin with methylhydrazine gave unexpected results. In benzene solution 5,6-diamino-1,3-dimethyluracil (14) was obtained by an apparent preferential cleavage of the pyrazine ring. In ethanolic solution a product, C₈H₁₁N₅O₂, of uncertain structure [but probably (15) or an isomer with an intact pyrimidine ring] was formed. 3-Methylfervenulin was unchanged by similar treatment with methylhydrazine except for formation of a water soluble π -complex, which reverted to 3-methylfervenulin on acidification.

¹⁴ W. A. Paudler and R. E. Herbener, *J. Heterocyclic Chem.*, 1967, **4**, 224; T. Sasaki, K. Minamoto, M. Nishikawa, and T. Shima, *Tetrahedron*, 1969, **25**, 1021; W. Paudler and T. K. Chen, *J. Heterocyclic Chem.*, 1971, **8**, 317.

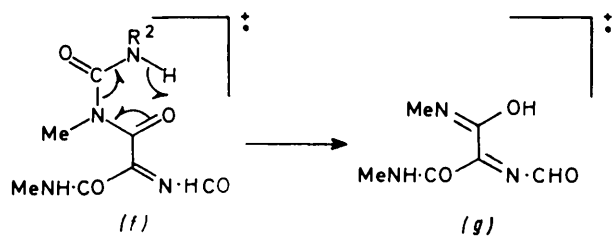
¹⁴ L. Heinisch, *J. prakt. Chem.*, 1969, **311**, 438; *Chem. Ber.*, 1967, **100**, 893; L. Heinisch, W. Ozegowski, and M. Mühlstädt, *ibid.*, 1964, **97**, 5.

¹⁵ A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 1956, 2066; G. P. G. Dick, H. C. S. Wood, and W. R. Logan, *ibid.*, p. 2131; E. C. Taylor, H. M. Loux, E. A. Falco, and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1965, **77**, 2243; E. C. Taylor, C. K. Cain, and H. M. Loux, *ibid.*, 1954, **76**, 1874.

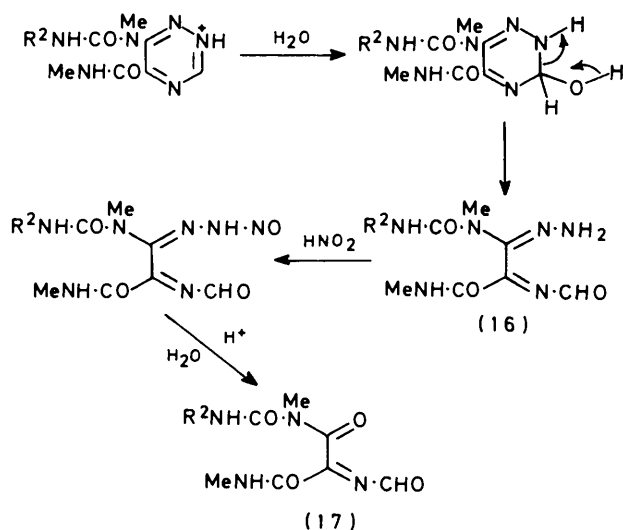
Further work is necessary to elucidate the apparent preferential triazine ring cleavage reactions, but it seems unlikely that methylhydrazine alone specifically attacks the triazine ring so a sequence of cleavages and re-cyclisations involving both rings may be involved.

Certain *as*-triazine ring cleavage reactions are known¹⁷ and indeed the triazinylureas (4; R¹ = H) proved to be amenable to ring-opening. They were stable to boiling hydrazine hydrate, sodium carbonate, and ethanolic hydrogen chloride, but were degraded by cold nitrous acid with loss of two nitrogen atoms and gain of two oxygen atoms to give open-chain compounds which were assigned structures (17). Under similar conditions the 3-methyltriazinylureas (4; R = Me) only gave nitrate salts of the unchanged ureas. This suggests that ring-cleavage involves attack at the 3-position at some stage and is inhibited by the 3-methyl group.

Assignment of structures (17) was based mainly on results of microanalysis, accurate mass measurements, and ¹H n.m.r. spectra (Table 3). There was no strong absorption at wavelengths above 225 nm in the u.v.,



SCHEME 4



SCHEME 5

and i.r. spectra contained several peaks in the carbonyl (1630—1790 cm⁻¹) and the ν_{NH} (ca. 3300 cm⁻¹) regions. ¹H n.m.r. spectra showed one low-field proton (τ ca. 1.8), two *N*-methyl groups, two exchangeable protons, and signals appropriate for RNHCO. Mass spectra showed a loss of RNCO in each case, which was readily explained by a McLafferty rearrangement (f) → (g) (Scheme 4) and subsequent losses of H₂O (D₂O if the NH groups were

first converted to ND) and HCN from ion (g). Alternatively (g) lost CHO. These losses, which were postulated on the basis of metastable peaks and mass measurements, can be accounted for by a series of rearrangements and cleavages.

The function of nitrous acid in the triazine ring-cleavages (Scheme 5) may be to prevent recyclisation and assist hydrolysis of an intermediate (16) by nitrosation. This would explain why the system is stable to hydrochloric acid but cleaved by nitrous acid.

EXPERIMENTAL

U.v. spectra were measured on a Unicam SP 800 spectrometer.

Mass Spectra.—These were measured on A.E.I. MS12 and MS902S spectrometers with source temperature ca. 220°, ionising voltage 70 eV, and resolving power ca. 1000 (low resolution spectra) or 10,000 (accurate mass measurements). Samples were introduced on direct insertion probes. (a) Triazine derivatives (relative abundance ≥5%; *m/e* ≥40): (4; R¹ = H, R² = Bu) *m/e* 167 (9%), 166 (100), 83 (7), and 82 (14); (4; R¹ = Me, R² = Bu) *m/e* 181 (10), 180 (100), 96 (9), and 42 (8); (4; R¹ = H, R² = NMe₂) *m/e* 167 (10), 166 (100), 83 (8), 82 (13), 67 (5), 60 (6), 59 (6), and 42 (8); (4; R¹ = H, R² = NH₂) *m/e* 168 (9), 167 (100), 166 (5), 82 (6), 70 (9), 58 (7), 57 (5), and 42 (5); (4; R¹ = Me, R² = NH₂) *m/e* 182 (9), 181 (100), 180 (8), 168 (8), 167 (14), 166 (5), 84 (6), 82 (6), 67 (8), 57 (12), 43 (6), 42 (27), and 41 (9); (7; R = Me) (≥10%) *m/e* 167 (45), 139 (10), 112 (18), 111 (18), 82 (100), 81 (11), 58 (10), 55 (23), 54 (12), and 41 (11). (b) Ketones (≥10%): (17; R² = Et) *m/e* 171 (54%), 153 (36), 144 (16), 143 (29), 142 (100), 128 (10), 126 (16), 69 (16), 58 (36), 57 (72), 56 (22), 44 (16), 42 (22), and 41 (10); (17; R² = Me) *m/e* 171 (36), 170 (14), 153 (15), 143 (16), 142 (100), 126 (10), 83 (13), 69 (14), 58 (36), 57 (90), 56 (16), 55 (18), 43 (17), 42 (24), and 41 (21).

3,5,7-Trimethylpyrimido[5,4-*e*]-as-triazine-5,7(6H,8H)-dione.—6-(2-Acetylhydrazino)-1,3-dimethyl-5-nitrosouracil³ (3.8 g) was dissolved in formamide (23 ml) and formic acid (15 ml) at 100° and reduced by the addition of small portions of sodium dithionite until the colour changed to olive green. The solution was boiled for 30 min, cooled, and poured into water (80 ml). The product was extracted with chloroform and the extract was dried (MgSO₄) and evaporated to dryness by a stream of dry air. The resulting oil was chromatographed on a silica column (ethyl acetate as eluant) to yield the pyrimidotriazine (1.5 g), m.p. 124° (lit.,³ 127°).

3-Alkyl-1-methyl-1-(5-methylcarbamoyl-1,2,4-triazin-6-yl)-ureas.—5,7-Dimethylpyrimido[5,4-*e*]-as-triazine-5,7-(6H,8H)-dione (fervenulin) (0.25 g) or its 3-methyl derivative (0.25 g), ethanol (10 ml), and the appropriate amine (1 ml) were heated under reflux for 24 h (48 h for benzylamine). Methylamine and ethylamine were in the form of 33% aqueous solutions of which 1 ml was used initially and a second portion (1 ml) was added after several hours under reflux. The mixture was evaporated to dryness under reduced pressure and the triazin-6-ylurea crystallised from a suitable solvent (Table 1).

4-Methyl-4-(5-methylcarbamoyl-1,2,4-triazin-6-yl)semi-carbazide (4; R¹ = H; R² = NH₂).—(a) Fervenulin (0.5 g),

¹⁷ J. P. Horwitz in 'Heterocyclic Compounds,' ed. R. C. Elderfield, Wiley, New York and London, 1961, vol. 7, p. 729; J. Klosa, *Arch. Pharm.*, 1955, **228**, 465.

TABLE 1
 3-Alkyl-1-methyl-1-(5-methylcarbamoyl-1,2,4-triazin-6-yl)ureas

Compound (4)	Yield (%)	M.p. (°C)	Cryst. solvent *	Formula	Found (%)			Required (%)		
					C	H	N	C	H	N
R ¹ = H, R ² = Me	97	250—251	E	C ₈ H ₁₂ N ₆ O ₂	42.6	5.5	37.9	42.9	5.4	37.5
R ¹ = H, R ² = Et	95	213—215	Bu ⁿ OH	C ₉ H ₁₄ N ₆ O ₂	45.5	5.8		45.4	5.9	
R ¹ = H, R ² = Pr ⁱ	89	213—215	EA	C ₁₀ H ₁₆ N ₆ O ₂	48.2	6.2		47.6	6.4	
R ¹ = H, R ² = Bu ⁿ	93	183—185	E	C ₁₁ H ₁₈ N ₆ O ₂	49.8	6.6	32.2	49.6	6.8	31.6
R ¹ = H, R ² = PhCH ₂	90	238—239	E	C ₁₄ H ₁₈ N ₆ O ₂	55.6	5.4	28.4	56.0	5.4	28.0
R ¹ = R ² = Me	98	239—241	H ₂ O	C ₈ H ₁₄ N ₆ O ₂ ·H ₂ O	42.3	6.2	33.3	42.2	6.3	32.8
R ¹ = Me, R ² = Et	95	216—217	EA-E-LP	C ₁₀ H ₁₆ N ₆ O ₂	47.7	5.9	33.7	47.6	6.4	33.3
R ¹ = Me, R ² = Pr ⁱ	50	152—154	H ₂ O	C ₁₁ H ₁₈ N ₆ O ₂ ·H ₂ O	46.1	7.0	29.4	46.5	7.1	29.6
R ¹ = Me, R ² = Bu ⁿ	42	166—168	EA-LP	C ₁₂ H ₂₀ N ₆ O ₂	51.6	6.9	30.1	51.4	7.2	30.0
R ¹ = Me, R ² = PhCH ₂	71	110	EA-B	C ₁₅ H ₁₈ N ₆ O ₂	57.3	5.7		57.3	5.8	

* EA = Ethyl acetate; E = ethanol; LP = light petroleum (b.p. 80—100°); B = benzene.

ethanol (10 ml), and 99% hydrazine hydrate (2.5 ml) were stirred at 20° for 48 h. The semicarbazide (0.37 g), m.p. 213—215°, was filtered off and crystallised from water (Found: C, 37.1; H, 4.6; N, 43.4. C₇H₁₁N₇O₂ requires C, 37.3; H, 4.9; N, 43.5%).

 TABLE 2
 U.v. data (H₂O)

Compound	λ _{max} /nm	log ε _{max}
(2; R ¹ = H)	342, 275, 238	3.61, 3.22, 4.23
(2; R ¹ = Me)	349, 275, 238	3.66, 3.22, 4.32
(4; R ¹ = H, R ² = Et)	276, < 225	3.31
(4; R ¹ = Me, R ² = Et)	272, < 225	3.35
(7; R = Me)	375, 428	3.49, 4.09
(7; R = H)	358, 239	3.59, 4.06
(8; R = X = Y = H) ¹¹	371, 263	3.83, 3.85
(8; R = CHO, X = Y = H) ¹³	325, 310, 266, 235	3.61, 3.75, 3.99, 3.84
(8; R = Y = H, X = NH·NH ₂) ³	352, 248	3.82, 4.06
(8; R = X = H, Y = Cl) ¹²	388, 270, 217 inf	3.80, 3.96, 3.83
(8; R = CHO, X = H, Y = Cl) ¹²	316, 272, 245	3.73, 3.89, 4.00

(b) Fervenuin (0.2 g) and 99% hydrazine hydrate (1 ml) were stirred at 20° for 45 min; the hydrazide (0.025 g), m.p. 213—215°, was filtered off and shown to be identical with the previous specimen.

The semicarbazide (0.05 g) was suspended in cold water and added dropwise to an ice-cold saturated solution of sodium nitrite in 2*N*-acetic acid. The yellow solution was immediately extracted with chloroform (3 × 20 ml) and the extract dried (MgSO₄) and evaporated to dryness, under reduced pressure, to yield fervenuin (0.01 g) [from benzene-light petroleum (b.p. 80—100°)], identical with an authentic specimen.

6-Methylamino-5-methylcarbamoyl-1,2,4-triazine.— The foregoing semicarbazide (0.1 g) was dissolved in 4*N*-hydrochloric acid (5 ml) and cooled in ice. An excess (starch-iodide paper) of similarly cooled aqueous sodium nitrite was added and the mixture was kept on ice for 10 min and then stirred at room temperature for 0.5 h. The mixture was made strongly alkaline with 2*N*-sodium hydroxide and extracted with chloroform (3 × 10 ml). The extract was

 TABLE 3
¹H N.m.r. data ^a

Compound	Solvent	τ Values (J in Hz)			
		R ¹	R ²	MeNHCO ^b	R ² NHCON.Me ^b CHO
(4; R ¹ = H, R ² = Me)	CD ₃ OD	2.35 (1H, s)	7.27 (3H, s)	7.08	6.93
(4; R ¹ = H, R ² = Et)	CD ₃ OD	2.33 (1H, s)	8.90 (3H, t, J 7.5), 6.80 (2H, q, J 7.5)	7.07	6.93
(4; R ¹ = H, R ² = Pr ⁱ)	C ₅ D ₅ N	2.33 (1H, s)	8.88 (3H, d, J 7), 8.83 (3H, d, J 7), 5.70 (1H, sept, J 7)	6.87	6.77
(4; R ¹ = H, R ² = Bu ⁿ)	CD ₃ OD	2.30 (1H, s)	8.33—9.28 (7H, m), 6.77 (2H, q, J 7.5)	7.07	6.92
(4; R ¹ = H, R ² = CH ₂ Ph)	(CD ₃) ₂ SO	2.35 (1H, s)	5.73 (2H, d, J 4), 2.58 (5H, m), 1.45br (1H) ^c	7.22	7.07
(4; R ¹ = R ² = Me)	CD ₃ OD	7.82 (3H, s)	7.26 (3H, s)	7.10	6.95
(4; R ¹ = Me, R ² = Et)	CD ₃ OD	7.80 (3H, s)	8.88 (3H, t, J 7.5), 6.72 (2H, q, J 7.5)	7.05	6.92
(4; R ¹ = Me, R ² = Pr ⁱ)	(CD ₃) ₂ SO	7.95 (3H, s)	8.99 (3H, d, J 7), 8.83 (3H, d, J 7), 6.16 (1H, m)	7.23	7.10
(4; R ¹ = Me, R ² = Bu ⁿ)	CD ₃ OD	7.80 (3H, s)	8.33—9.32 (7H, m), 6.76 (2H, q, J 7.5)	7.06	6.93
(4; R ¹ = Me, R ² = CH ₂ Ph)	CDCl ₃	7.88 (3H, s)	5.58 (2H, d, J 6), 2.63 (5H, s), 1.41br (1H) ^c	7.08	6.96
(4; R ¹ = H, R ² = NH ₂)	(CD ₃) ₂ SO	2.62 (1H, s)	4.35br, 2.40br, 1.60br ^c	7.42	6.93
(4; R ¹ = Me, R ² = NH ₂)	(CD ₃) ₂ SO	8.17 (1H, s)	4.65br, 1.90br, 1.42br ^c	7.50	6.97
(4; R ¹ = H, R ² = NMe ₂)	(CD ₃) ₂ SO	2.45 (1H, s)	7.57 (6H, s), 1.20br, 0.78br ^c	7.18	7.08 ^d
(17; R ² = Me)	(CD ₃) ₂ SO		7.36 (3H, d, J 5), 1.50br, 0.98br ^c	7.38	7.10
(17; R ² = Et)	(CD ₃) ₂ SO		8.98 (3H, t, J 7.5), 6.77 (2H, m), 1.41br, 1.0br ^c	7.38	7.10
(17; R ² = Pr ⁱ)	(CD ₃) ₂ CO— (CD ₃) ₂ SO		8.88 (6H, m), 5.97 (1H, m), 1.16 br ^c	7.32	7.05
(17; R ² = Bu ⁿ)	CDCl ₃		8.33—9.13 (7H, m), 6.48—6.73 (2H, m), 2.30br, 3.11br ^c	7.17	6.90
(17; R ² = PhCH ₂)	CDCl ₃		5.50 (2H, d, J 6), 2.55 (5H, s), 2.55, 2.30br ^c	7.25	6.98

^a Measured on a Varian A60A spectrometer at normal probe temperature using tetramethylsilane as internal standard. ^b Singlet (3H) assignments of methyls may be reversed. ^c Removed on deuteration. ^d Signals due to residual ethanol (see Experimental section) omitted. ^e Becomes triplet on deuteration.

dried (MgSO_4) and evaporated to yield the yellow *methylamide* (0.02 g), m.p. 132–134° [from light petroleum (b.p. 80–100°)] (Found: C, 42.6; H, 5.4; N, 42.1. $\text{C}_6\text{H}_9\text{N}_5\text{O}$ requires C, 43.1; H, 5.4; N, 41.9%).

4-*Methyl-4-(3-methyl-5-methylcarbamoyl-1,2,4-triazin-6-yl)semicarbazide* (4; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{NH}_2$).—3-Methylfervenulin (0.5 g), ethanol (50 ml), and 99% hydrazine hydrate (2.5 ml) were stirred at 20° for 48 h. The *semicarbazide* (0.18 g) was filtered off and crystallised from aqueous ethanol; m.p. 207° (Found: C, 40.0; H, 5.4; N, 40.8. $\text{C}_8\text{H}_{13}\text{N}_7\text{O}_2$ requires C, 40.15; H, 5.5; N, 41.0%).

1,1,4-*Trimethyl-4-(5-methylcarbamoyl-1,2,4-triazin-6-yl)semicarbazide* (4; $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{NMe}_2$).—(a) Fervenulin (0.5 g), 1,1-dimethylhydrazine (2.5 ml), and ethanol (10 ml) were heated on a boiling water-bath for 36 h and the solution was then evaporated to dryness under reduced pressure. Chloroform-soluble material was extracted and the white

under reflux for 2 h. 5,6-Diamino-1,3-dimethyluracil (0.08 g), m.p. 207–209° (from ethanol-ethyl acetate) [lit.¹⁸ 209° (decomp.)], was filtered from the cooled solution and was identical with an authentic specimen.

(b) Fervenulin (0.2 g) and methylhydrazine (1 ml) were stirred at 20° for 2 h and the mixture was evaporated to dryness. The residue crystallised from water as pale yellow granules, m.p. 234–235° (Found: C, 45.2; H, 5.2; N, 33.4. Calc. for $\text{C}_8\text{H}_{11}\text{N}_5\text{O}_2$: C, 45.9; H, 5.3; N, 33.5%).

(c) Fervenulin (0.5 g), ethanol (35 ml), and methylhydrazine (2.5 ml) were stirred at 20° for 48 h. The mixture was evaporated to dryness and the residue was crystallised from water to give a product (0.2 g), m.p. 234–235°, identical with that described in (b).

Treatment of Triazinylureas with Nitrous Acid.—The appropriate triazinylurea (4) (0.1 g) was dissolved in 4*N*-hydrochloric acid (5 ml) and cooled to 0°. Similarly cooled

TABLE 4
Ureidopropane derivatives (17)

	Yield (%)	M.p. (°C)	Cryst. solvent	Formula	Found (%)			Required (%)		
					C	H	N	C	H	N
R = Me	22	266–268	EtOH	$\text{C}_9\text{H}_{12}\text{N}_4\text{O}_4$	42.2	5.3	24.6	42.1	5.3	24.6
R = Et	60	228–230	EtOH	$\text{C}_9\text{H}_{14}\text{N}_4\text{O}_4$	44.9	5.8	23.0	44.6	5.8	23.1
R = Pr ¹	56	242–244	EtOH	$\text{C}_{10}\text{H}_{16}\text{N}_4\text{O}_4$	46.7	6.1	21.5	46.9	6.3	21.9
R = Bu ⁿ	40	171–173	PhH	$\text{C}_{11}\text{H}_{18}\text{N}_4\text{O}_4$	48.4	6.4	20.5	48.9	6.7	20.7
R = CH_2Ph	65	194–196	PhH	$\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_4$	54.8	5.2	18.4	55.3	5.3	18.4

TABLE 5
3-Alkyl-1-methyl-1-(3-methyl-5-methylcarbamoyl-1,2,4-triazin-6-yl)urea nitrates

Compound	Yield (%)	M.p. (°C) (decomp.)	Formula	Found (%)			Required (%)		
				C	H	N	C	H	N
(4; $\text{R}^1 = \text{R}^2 = \text{Me}$), HNO_3	40	161–162	$\text{C}_9\text{H}_{14}\text{N}_6\text{O}_2, \text{HNO}_3$	36.3	5.1	32.2	35.9	5.0	32.5
(4; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Et}$), HNO_3	40	158–160	$\text{C}_{10}\text{H}_{16}\text{N}_6\text{O}_2, \text{HNO}_3$	37.5	5.3	30.2	38.1	5.4	31.1
(4; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Pr}^1$), HNO_3	57	148	$\text{C}_{11}\text{H}_{18}\text{N}_6\text{O}_2, \text{HNO}_3$	39.8	5.8	29.8	40.1	5.8	29.8
(4; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Bu}^n$), HNO_3	60	146	$\text{C}_{12}\text{H}_{20}\text{N}_6\text{O}_2, \text{HNO}_3$	42.2	6.1	28.3	42.0	6.2	28.6
(4; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{PhCH}_2$), HNO_3	32	154–155	$\text{C}_{15}\text{H}_{18}\text{N}_6\text{O}_2, \text{HNO}_3$	47.8	4.8	25.3	47.7	5.1	26.0

residue crystallised from ethanol-ethyl acetate to yield the *semicarbazide* (0.2 g), m.p. 200–202° (Found: C, 43.1; H, 6.3; N, 35.8. $\text{C}_9\text{H}_{15}\text{N}_7\text{O}_2, 0.5\text{C}_2\text{H}_5\text{OH}$ requires C, 43.5; H, 6.6; N, 35.4%).

(b) Fervenulin (0.5 g) and 1,1-dimethylhydrazine (2.5 ml) were heated under reflux for 4 h before more dimethylhydrazine (2.5 ml) was added, and then for a further 20 h. The *semicarbazide* (0.3 g), m.p. 201° (from propan-2-ol), was filtered from the cooled solution and shown to be identical with the previous sample except that elemental analysis and ¹H n.m.r. spectroscopy showed the presence of a little propan-2-ol in the crystals (Found: C, 43.7; H, 6.3; N, 35.8. $\text{C}_9\text{H}_{15}\text{N}_7\text{O}_2, 0.33\text{C}_3\text{H}_8\text{O}$ requires C, 43.9; H, 6.5; N, 35.9%).

Reactions with Methylhydrazine.—(a) Fervenulin (0.2 g), benzene (15 ml), and methylhydrazine (1 ml) were heated

saturated aqueous sodium nitrite was added in excess and the mixture was stirred at 20° for 15–30 min. In the case of each 3-unsubstituted triazine (4; R = H) the solution was extracted several times with chloroform and the extract was dried (MgSO_4) and evaporated to dryness. The product was crystallised from an appropriate solvent (Table 4). For 3-methyltriazines (4; R = Me) the aqueous reaction mixture was evaporated to dryness and extracted with boiling acetone. The *nitrate salt* was crystallised from ethanol-ethyl acetate-light petroleum (b.p. 80–100°) (Table 5). Similar salts were obtained by allowing solutions of the 3-methyltriazinylureas, in dilute nitric acid, to evaporate.

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¹⁸ F. F. Blicke and H. C. Godt, *J. Amer. Chem. Soc.*, 1954, **76**, 2798.