# 1,3,4-Oxadiazol-2(3*H*)-one Formation from *N*-Acylaminobiurets and Related Compounds and from *S*-Benzyl 3-Acyl(thiocarbazates)

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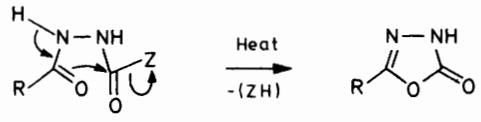
The formation of 1,3,4-oxadiazol-2(3*H*)-ones by thermal cyclisation of 1-acylsemicarbazides has been shown to occur with equal facility by use of readily available *N*-acylaminobiurets. Cyclisation by thermolysis of *S*-benzyl 3-acylcarbazates also proceeds smoothly though in lower yields.

THE thermal cyclisation of 1-acylsemicarbazides (1; $Z = NH_2$) to give 1,3,4-oxadiazol-2(3*H*)-ones(2) with elimination of ammonia is well known (Scheme 1).[1-4] For example, 1-isonicotinoylsemicarbazide (1a) provides the 5-(4-pyridyl) derivative (2a) in 87% yield.[1] We report some related processes with alternative leaving groups (Z) (see Table).




(1) (2)

SCHEME 1

Starting compounds (1) which on cyclisation eliminate a primary amine (Z = NHR, Scheme 1) can be prepared by treatment of the corresponding hydrazide with an isocyanate. For example, compound (1b),* formed at room temperature by use of phenyl iso-cyanate, cyclises thermally to the 1,2,4-oxadiazol-2(3*H*)-one (2b) in 61% yield. Analogues with Z = NHEt and NHMe ring close with equal facility. In the case of (1b), if an increased temperature is used for its preparation a co-product is obtained, *viz.* the acylaminobiuret RCO·NH·NH·CO·NPh·CO·NHPh (1c), and with an excess of PhNCO in refluxing xylene then (1c) is exclusively the product.

The ease of formation of such acylaminobiurets enabled us to ascertain whether these also could act as substrates for 1,3,4-oxadiazolone formation. The eliminated molecule ZH from (1) would then be a *sym*-diarylurea. We were encouraged in this proposal by the mass spectrum of the biuret (1c) which showed *m/e* 423 (43%) as a major fragment ion, corresponding to the oxadiazolone (2b), and a peak at *m/e* 212 (13%) corresponding to *sym*-diphenylurea.†

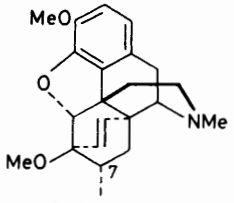
Vacuum sublimation of (1c) provided a colourless sublimate from which the oxadiazolone (2b) could be removed into chloroform, leaving the *sym*-diphenylurea as insoluble residue. Evaporation gave (2b) in 76% yield. An analogous sequence using the biuret (1d) from *p*-chlorophenyl isocyanate again gave the oxadiazolone in high yield. Application of the method to the cyclohexyl analogue (1e) provided 5-cyclohexyl-1,3,4-oxadiazol-2(3*H*)-one (2c) (50%). This was achieved not by sublimation, since the product was an oil, but by a prolonged period under reflux in xylene.

TABLE

Formation of 1,3,4-oxadiazol-2(3*H*)-ones (Scheme 1)

| Starting material | R [a] | Z | Product | Yield (%) |
|---|---|---|---|---|
| (1a) | 4-pyridyl | $NH_2$ | (2a) | 87 [1] |
| (1b) | T | NHPh | (2b) | 61 [b] |
| (1c) | T | NPh·CO·NHPh | (2b) | 76 |
| (1d) | T | (4-$ClC_6H_4$)NCO·NH(4-$ClC_6H_4$) | (2b) | 84 |
| (1e) | $[CH_2]_5CH$ | NPh·CO·NHPh | (2c) | 50 |
| (1f) | T | $SCH_2Ph$ | (2b) | 68 |
| (1g) | Ph | $SCH_2Ph$ | (2d) | 22 |

[a] T = 7α-(6,7,8,14-tetrahydro-6,14-*endo*-ethenothebainyl).

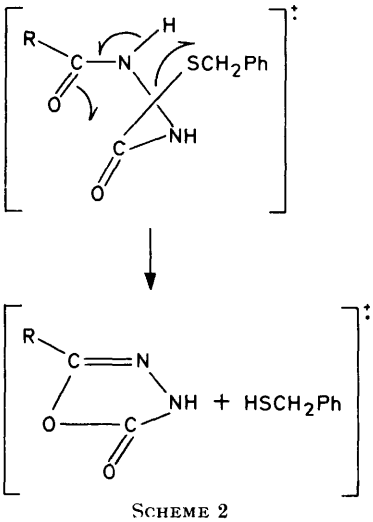



[b] Isolated as its hydrochloride salt.

A further route to 1,2,4-oxadiazol-2(3*H*)-ones, though probably less useful due to less ready availability of starting material, involves a thiol as leaving molecule (Z = $SCH_2Ph$, Scheme 1). The starting benzyl thioester was obtained by treatment of the corresponding 1,3,4-oxadiazole-2(3*H*)-thione (formed from the hydrazide and $CS_2$–pyridine) with benzyl bromide in aqueous ethanol. Vacuum sublimation of (1f) gave the oxadiazolone (2b) in 68% yield, a procedure again suggested by mass spectral fragmentation: the mass spectrum of (1f) showed an ion with *m/e* 124, equivalent to benzyl mercaptan, as base peak and a peak for the oxadiazolone (2b) at *m/e* 423 (14%) (Scheme 2). Application of the method to the benzyl thioester (1g) of 3-benzoylcarbazic acid gave crystalline 5-phenyl-1,3,4-oxadiazol-2(3*H*)-one (2d) though in lower yield.

* Examples of (1) and (2) with a bridged thebaine unit as R were chosen for their potential pharmacological interest: *cf.* K. W. Bentley and J. W. Lewis in 'Agonist and Antagonist Actions of Narcotic Analgesic Drugs,' eds. H. W. Kosterlitz, H. O. J. Collier, and J. E. Villarreal, Macmillan, London, 1972, p. 7.

† Analogies between thermal and electron-impact induced processes are not uncommon: *cf.* H. Heaney and A. P. Price, *Chem. Commun.*, 1971, 894.




SCHEME 2

## EXPERIMENTAL

1-(6,7,8,14-*Tetrahydro*-6,14-endo-*ethenothebain*-7α-*yl*)-4-*phenylsemicarbazide* (1b).—To a solution of 6,7,8,14-tetrahydro-6,14-*endo*-ethenothebaine-7α-carbohydrazide [5] (3.0 g, 7.56 mmol) in cold absolute ethanol (125 ml) was added phenyl isocyanate (0.99 g, 8.32 mmol) and the solution was shaken for 5 min and then concentrated under reduced pressure. Water was added and immediate precipitation occurred. The precipitate was taken up by the addition of hot ethanol and on cooling the *phenylsemicarbazide* (1b) crystallised out and was filtered off (2.62 g, 67%); it formed plates m.p. 152—155 °C from ethanol–water (7 : 3), $\nu_{max.}$ (Nujol), 3 280 (NH) and 1 665 $cm^{-1}$ (C=O) (Found: C, 64.9; H, 6.4; N, 10.1%. $C_{29}H_{32}N_4O_5 \cdot H_2O$ requires C, 65.15; H, 6.4; N, 10.5%).

1-(6,7,8,14-*Tetrahydro*-6,14-endo-*ethenothebain*-7α-*yl*)-4-*ethylsemicarbazide*.—By use of ethyl isocyanate in an analogous procedure but heating under reflux for 5 h the *ethylsemicarbazide* crystallised from ethanol as needles (48%), m.p. 142—144 °C (Found: C, 64.4; H, 6.85; N, 11.9%. $C_{25}H_{32}N_4O_5$ requires C, 64.1; H, 6.9; N, 12.0%).

1-(6,7,8,14-*Tetrahydro*-6,14-endo-*ethenothebain*-7α-*yl*)-4 *methylsemicarbazide*.—By use of methyl isocyanate in an analogous procedure but heating under reflux for 2.5 h the *methylsemicarbazide* crystallised from ethanol as needles (95%), m.p., 148—152 °C (Found: C, 62.0; H, 6.5; N, 12.0. $C_{24}H_{30}N_4O_5 \cdot O \cdot 5H_2O$ requires C, 62.2; H, 6.7; N, 12.1%).

7α-(2,3-*Dihydro*-2-*oxo*-1,3,4-*oxadiazol*-5-*yl*)-6,7,8,14-*tetrahydro*-6,14-endo-*ethenothebaine* (2b) *by Semicarbazide Cyclisation*.—The phenylsemicarbazide (1b) (0.1843 g), was heated under reflux in dry xylene (25 ml) for 24 h. Evaporation of the xylene *in vacuo* afforded a brown glass [$\nu_{max.}$ ($CHCl_3$), 1 775 $cm^{-1}$]. The glass was dissolved in the minimum amount of chloroform and dry ethereal HCl was added. The precipitated *hydrochloride* of the oxadiazolone (2b) was crystallised from ether–ethanol (61%), m.p. 270 °C (decomp.) (Found: C, 60.5; H, 6.0; N, 9.0%. $C_{23}H_{25}N_3O_5 \cdot HCl$ requires C, 60.1; H, 5.7; N, 9.1%).

Under the same conditions the ethyl- and methylsemicarbazides similarly produced the oxadiazolone (2b).

1-(6,7,8,14-*Tetrahydro*-6,14-endo-*ethenothebain*-7α-*ylcarbonlyamino*)-3,5-*diphenylbiuret* (1c).—The 7α-hydrazide [5] (2.0 g, 5.04 mmol) and phenyl isocyanate (4.0 g, 33.6 mmol) were heated under reflux in sodium-dried xylene (50 ml) for 24 h. The solution was evaporated to dryness and the residue dissolved in the minimum of chloroform and purified by application to an alumina column which was eluted with light petroleum–chloroform (1 : 1). The *biuret* (1c) crystallised from ethanol as needles (1.87 g, 58%), m.p. 205—208 °C (Found: C, 67.9; H, 5.9; N, 11.0%: $C_{36}H_{37}N_5O_6$ requires C, 68.0; H, 5.9; N, 11.0%), *m/e* (635, $M^{+\cdot}$ not detected), 423.1815 (43%, $C_{23}H_{25}N_3O_5$ requires 423.1794), 397.1996 (14%, $C_{22}H_{27}N_3O_4$ requires 397.2002), 212.0931 (13%, $C_{13}H_{12}N_2O$ requires 212.0949), and 119.0371 (100%, $C_7H_5NO$ requires 119.0371).

1 (6,7,8,14-*Tetrahydro*-6,14-endo-*ethenothebain*-7α-*ylcarbonylamino*-3,5-*bis*(p-*chlorophenyl*)*biuret* (1d).—Use of *p*-chlorophenyl isocyanate in a similar procedure gave the *biuret* (1d), m.p. 191—193 °C, as needles from ethanol–chloroform (Found: C, 61.1; H, 5.0: N, 9.8. $C_{36}H_{35}Cl_2N_5O_6$ requires C, 61.4; H, 5.0; N, 9.9%).

7α-(2,3-*Dihydro*-2-*oxo*-1,3,4-*oxadiazol*-5-*yl*)-6,7,8,14-*tetrahydro*-6,14-endo-*ethenothebaine* (2b) *from Biuret Cyclisation*. —(*a*) The biuret (1c) (0.1297 g) was sublimed at 250 °C/0.1 mmHg. The colourless sublimate was treated with chloroform and the insoluble *sym*-diphenylurea (0.0282 g) filtered off (identified by comparison with an authentic sample [6]). Evaporation of the filtrate gave the oxadiazolone (2b) (0.0661 g, 76%), $\nu_{max.}$ (Nujol), 1 780 $cm^{-1}$. The i.r. spectrum showed traces of *sym*-diphenylurea. The oxadiazolone (2b) gave a crystalline hydrochloride identical with the sample prepared previously.

(*b*) The biuret (1d) on sublimation similarly gave the oxadiazolone (2b) (84%). The *sym*-bis-*p*-chlorophenylurea (m.p. 306—309 °C) also isolated was identical with an authentic sample.[7]

1-*Cyclohexylcarbonylamino*-3,5-*diphenylbiuret* (1e).—Cyclohexanecarbohydrazide [8] (1.0 g, 7.03 mmol) and phenyl isocyanate (5.63 g, 47.2 mmol) were heated under reflux in dry xylene for 18 h. As the mixture cooled crystals of the *biuret* (1e) were obtained (0.77 g, 29%), m.p. 181—184 °C (Found: C, 65.9; H, 6.3; N, 14.5. $C_{21}H_{24}N_4O_3$ requires C, 66.3; H, 6.4; N, 14.7%).

5-*Cyclohexyl*-1,3,4-*oxadiazol*-2(3H)-*one* (2c).—The biuret (1e) (0.1 g) was heated under reflux in xylene for 17 h. Evaporation of the xylene and addition of chloroform to the residual oil precipitated the *sym*-diphenylurea. Evaporation of the filtrate gave 5-*cyclohexyl*-1,3,4-*oxadiazol*-2(3H)-*one* (2c) (0.0223 g, 50%) as an oil, $\nu_{max.}$ (film) 3 290 (NH) and 1 780 $cm^{-1}$ (C=O) (Found: C, 56.6; H, 7.3; N, 16.5. $C_8H_{12}N_2O_2$ requires C, 57.1; H, 7.2; N, 16.7%).

7α-(2,3-*Dihydro*-2-*thioxo*-1,3,4-*oxadiazol*-5-*yl*)-6,7,8,14-*tetrahydro*-6,14-endo-*ethenothebaine*.—Carbon disulphide (6.0 g) and the 7α-hydrazide (6.0 g) in dry pyridine (125 ml) were heated under reflux for 20 h. The solvent was removed and trituration of the residue with methanol gave the *oxadiazolethione* (6.38 g, 96%). The product crystallised as needles from ethanol, m.p. 258—260 °C (Found: C, 59.4; H, 5.8; N, 8.9, $C_{23}H_{25}N_3O_4S \cdot 1 \cdot 5H_2O$ requires C, 59.2; H, 6.05; N, 9.0%).

5-*Benzyl* 3-(6,7,8,14-*Tetrahydro*-6,14-endo-*ethenothebain*-7α-*ylcarbonyl*)*thiocarbazate* (1f).—The oxadiazolethione (3.0 g) from the previous experiment and benzyl bromide (6.0 g) were heated under reflux in aqueous ethanol (125 ml) for 3 h. The hydrobromide salt which precipitated was filtered off and added to water. The mixture was basified with ammonia, extracted with chloroform, and the extract dried

($K_2CO_3$) and evaporated to provide the *ester* (1f) which crystallised from ethanol as needles (1.16 g., 32%), m.p. 120—123 °C (Found: C, 65.1; H, 6.8; N, 6.9. $C_{30}H_{33}N_3O_5S{\cdot}C_2H_5OH$ requires, C, 64.7; H, 6.6; N, 7.1%) *m/e* (547, $M^+$, not detected), 423.1808 (14%, $C_{23}H_{25}N_3O_5$ requires 423.1794), 124 (100%).

7α-(2,3-*Dihydro*-2-*oxo* 1,3,4-*oxadiazol*-5-*yl*)-6,7,8,14-*tetrahydro*-6,14-endo-*ethenothebaine* (2b) *by Sublimation of the Ester* (1f).—The ester (1f) (0.0916 g) was sublimed at 325 °C/0.05 mmHg. The sublimate was washed off the cold finger with chloroform. Evaporation gave the oxadiazolone (2b) as a glass (0.0481 g, 68%), $\nu_{max.}$ (Nujol) 1 780 $cm^{-1}$ (C=O) the i.r. spectrum of which was identical with the product obtained previously.

S-*Benzyl* 3-*Benzoyl*(*thiocarbazate*) (1g).—5-Phenyl-1,3,4-oxadiazole-2(3*H*)-thione[9] (1.0 g) and benzyl bromide (4.93 g, 28.8 mmol) were heated under reflux in absolute ethanol for 3 h. Evaporation and chromatography of the residue on alumina gave the *ester* (1g) as pale yellow needles from aqueous ethanol (0.86 g, 54%), m.p. 125—127 °C (Found: C, 62.55; H, 4.8; N, 9.6. $C_{15}H_{14}N_2O_2S$ requires C, 62.9; H, 4.9; N, 9.8%).

5-*Phenyl*-1,3,4-*oxadiazol*-2(3H)-*one* (2d) *by Sublimation of the Ester* (1g).—The ester (1g) (0.1027 g) was sublimed at 260 °C/0.05 mmHg. Crystallisation of the sublimate from water gave the oxadiazolone (2d) as needles (0.0115 g, 22%), m.p. 138 °C (lit.,[10] m.p. 138 °C).

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