Action of 2-Phenyl-Δ^2-oxazolin-5-one on 2-Alkyl-Δ^2-Thiazolines

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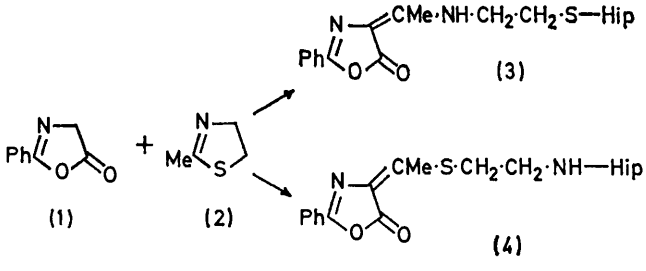
2-Alkyl-Δ^2-thiazolines react with 2-phenyl-Δ^2-oxazolin-5-one to give 4-[1-(2-hippuroylamino-alkylthio)alkylidene]-2-phenyl-Δ^2-oxazolin-5-ones and 4-[1-(2-hippuroylthio-alkylamino)alkylidene]-2-phenyl-Δ^2-oxazolin-5-ones. 3-Phenylisoxazolin-5-one and 2-methylthio-1-azacycloalkanes react analogously to give 4-alkylidene compounds.

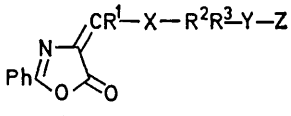
REACTION of 2-phenyl-Δ^2-oxazolin-5-one (1) with the >C=N- group of benzylideneaniline leads to α-benzamidocinnamanilide.[1] Analogous nucleophilic attack on C-2 of methyl 5,5-dimethyl-Δ^2-thiazoline-4-carboxylate takes place with 2-benzyl-Δ^2-oxazolin-5-one to give methyl penicillenate.[1] In the case of the simpler 2-alkylthiazolines a similar initial attack by the 2-aryloxazolin-5-ones takes place at C-2, but the subsequent fission of the thiazoline ring can take place at either the 1,2- or the 2,3-bond. Thus, for example, 2-methyl-Δ^2-thiazoline (2) and 2-phenyl-Δ^2-oxazolin-5-one (1) in refluxing benzene give a mixture of 4-[1-(2-hippuroylthioethylamino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (3) and 4[1-(2-hippuroylaminoethylthio)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (4). Compound (3) and its analogues are obtained exclusively in high yield when the reaction is carried out in pyridine at room temperature.



Hip = Hippuroyl

The 4-(1-thioalkylidene)oxazolones, *e.g.* (4), show two i.r. absorption peaks in the regions 1740—1760 and 1770—1780 cm^{-1}, characteristic of many 4-unsaturated oxazolones.[2] The 4-(1-aminoalkylidene)oxazolones, *e.g.* (3), give two peaks at lower wavenumber in the regions 1700 and 1620—1640 cm^{-1}, and a pair of weaker peaks at around 1580 and 1600 cm^{-1} (see Table 4). The peaks at lower wavenumber are probably an expression of the fact that the nitrogen atom is more highly conjugated with the oxazolone system [2] than the sulphur atom. This would be in keeping with the greater stability of compounds of type (3) and their lack of basic character.

TABLE 1



(EtOH)

Compounds	R^1	X	R^2	R^3	Z	Y
(4)	Me	S	CH_2	CH_2	NH	Hip
(12)	Et	S	CH_2	CH_2	NH	Hip
(13)	Me	S	CHMe	CH_2	NH	Hip
(14)	Me	S	CH_2·CH_2	CH_2	NH	Hip
(3)	Me	NH	CH_2	CH_2	S	Hip
(15)	Me	NH	CMe_2	CH_2	S	Hip
(16)	Me	NH	CH_2	CHMe	S	Hip
(17)	Et	NH	CH_2	CH_2	S	Hip
(18)	Pr^n	NH	CH_2	CH_2	S	Hip
(19)	CH_2Ph	NH	CH_2	CH_2	S	Hip
(20)	Me	NH	CH_2·CH_2	CH_2	S	Hip
(8)	Me	NH	CH_2	CH_2	S	CH_2Ph
(21)	Me	NH	CH_2	Ph		

The u.v. absorption data (Table 5) are characteristic of alkylideneoxazolones and the change of absorption in alkaline solution shows the greater reactivity of the thioalkylidene derivatives, *e.g.* (4).

The reaction most probably proceeds by way of the intermediate (5). This could rearrange in either of two ways to give a thiol (path a) or a primary amine (path b).

[1] A. B. A. Jansen and R. Robinson, *Monatsh.*, 1967, **98**, 1017.
[2] E. Baltazzi, *Quart. Rev.*, 1955, 150.

Both the amine and the thiol would then be hippuroylated by free oxazolone. In pyridine, path b, giving a base would be suppressed and thiolate formation favoured.

TABLE 2

Reactions of the oxazolone (1) with Δ^2-thiazolines in pyridine

Starting material	Product	Yield (%)	M.p. (°C)
2,4,4-Trimethylthiazoline	(15)	75	161—163 (EtOH)
2,5-Dimethylthiazoline	(16)	58	152—153 (Butan-2-one)
2-Ethylthiazoline	(17)	52	160—163 (EtOH)
2-Propylthiazoline	(18)	75	165—166 (EtOH)
2-Benzylthiazoline	(19)	82	176—177 (Cellosolve–EtOH)
5,6-Dihydro-2-methyl-4*H*-1,3-thiazine	(20)	11	197—199 (Cellosolve)

TABLE 3

Reactions of the oxazolone (1) with Δ^2-thiazolines in benzene

Starting material	Product	Yield (%)	M.p. (°C)	Product	Yield (%)
2-Ethylthiazoline	(12)	5	142—150 (Cellosolve)	(17)	33
2,5-Dimethylthiazoline	(13)	10	137—139 (Cellosolve)	(16)	25
5,6-Dihydro-2-methyl-4*H*-1,3-thiazine	(14)	32	195—198 (Cellosolve)		

TABLE 4

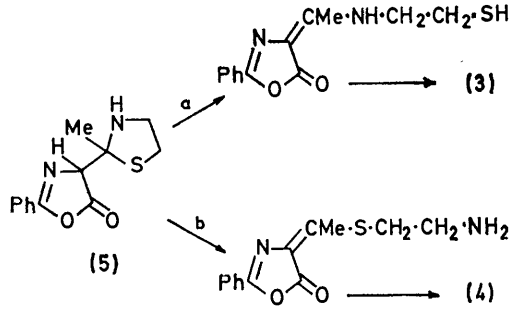
I.r. spectra

Compound	$\nu_{max.}$/cm^{-1}
(4)	1553, 1645, 1671, 1750, 1781, 3340
(12)	1553, 1645, 1658, 1760, 1776, 3300
(13)	1553, 1636, 1640, 1665, 1745, 1774, 3320
(14)	1635, 1644, 1678, 1739, 1777, 3300, 3430
4-Cyclohexylidene-2-phenyl-Δ^2-oxazolin-5-one	1659, 1748, 1772
4-(α-Ethoxyethylidene)-2-phenyl-Δ^2-oxazolin-5-one	1641, 1745, 1776
(3)	1587, 1600sh, 1632, 1658, 1688, 1707, 1750w, 3340
(15)	1580, 1593sh, 1621, 1650, 1681, 1708sh, 1719, 1750w, 3320
(16)	1585, 1601, 1634, 1641, 1689, 1712, 3290
(17)	1588, 1603, 1635, 1639, 1686, 1705, 3290
(18)	1585, 1602, 1635, 1642, 1686, 1705, 3280
(19)	1586, 1602, 1635, 1643, 1678, 1707, 3280

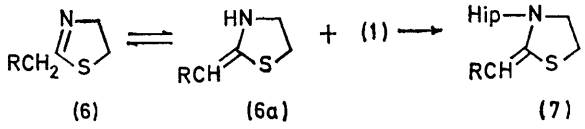
TABLE 5

Compound	Neutral $\lambda_{max.}$/nm	Neutral ε	Alkaline * $\lambda_{max.}$/nm	Alkaline * ε
(3)	349	28,000	352	29,500
(17)	347	25,500	353	26,500
(15)	348	30,000	352	30,000
(16)	350	28,000	355	26,000
(9)	343	30,000	350	31,000
(4)	349	25,000	288	14,500
(13)	356	24,000	293	18,000
(12)	353	25,500	293	18,000
(14)	358	26,000	290	18,000

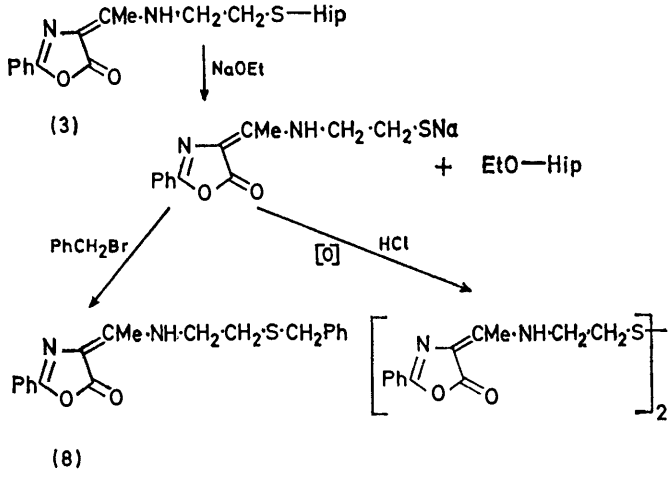
* 'Neutral' refers to the spectrum of a solution of the compound in absolute ethanol. 'Alkaline' refers to the absorption immediately after the addition of 1 drop of 10% NaOH to the cell; hippuroyl absorption at *ca.* 230 nm is omitted. Both compounds (3) and (4) were stable in refluxing ethanol.



In benzene, 2-benzyl-Δ^2-thiazoline (6; R = Ph) gives only 2-benzylidene-3-hippuroylthiazolidine (7; R = Ph); similarly a small amount of 2-ethylidene-3-hippuroylthiazolidine (7; R = Me) is formed from 2-ethyl-Δ^2-thiazoline (6; R = Me). This difference from the 2-methylthiazolines may be due to greater stability of the 2-alkylidenethiazolidine tautomer (6a; R = Me or Ph), in these cases. Neither of these two products reacts further with the oxazolone.



Chemical evidence for structure (3) was provided by cleaving the hippuroyl group with sodium alkoxide. Thus treatment with sodium ethoxide followed by neutralisation gives the corresponding thiol, isolated as its disulphide. In the presence of benzyl bromide, 4-[1-(2-benzylthioethylamino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (8) is formed by benzylation of the first-formed thiol. Compound (8) exhibits characteristic i.r. and n.m.r. absorption and, like other aminoalkylidene-oxazolones,[3] resists both ring opening and substitution by benzylamine.



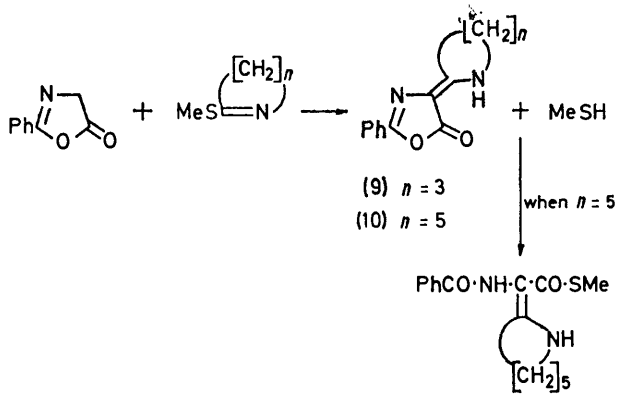
In contrast, the aminoalkylthio group of compound (4) is readily replaced by benzylamine to give 4-(1-benzyl-

[3] J. W. Cornforth in 'Heterocyclic Compounds,' vol. 5, ed. R. C. Elderfield, Wiley, New York, 1957, p. 363.

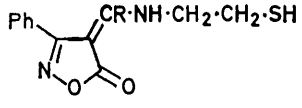
aminoethylidene)-2-phenyl-Δ^2-oxazolin-5-one (21a), which when left overnight in pyridine is converted to the more stable geometric isomer (21b), obtained directly by reaction of benzylamine with 4-(ethoxyethylidene)-2-phenyl-Δ^2-oxazolin-5-one [4] (Scheme).

These reactions are characteristic of the labile alkylthio- and alkoxy-alkylideneoxazolones, in contrast with the stability of the corresponding alkylamino-compounds, and justify the assignment of structures (3) and (4).

2-Phenyl-Δ^2-oxazolin-5-one reacts with 2-methylthio-Δ^2-pyrroline to give 2-phenyl-4-pyrrolidin-2-ylidene-Δ^2-oxazolin-5-one (9) (or its geometric isomer), which shows the expected i.r. spectrum and resists oxazolone ring-opening. 4-(Hexahydroazepin-2-ylidene)-2-phenyl-Δ^2-oxazolin-5-one (10), prepared similarly, however, is cleaved by the methanethiol produced in the reaction, to give *S*-methyl α-(hexahydroazepin-2-ylidene)thiohippurate.

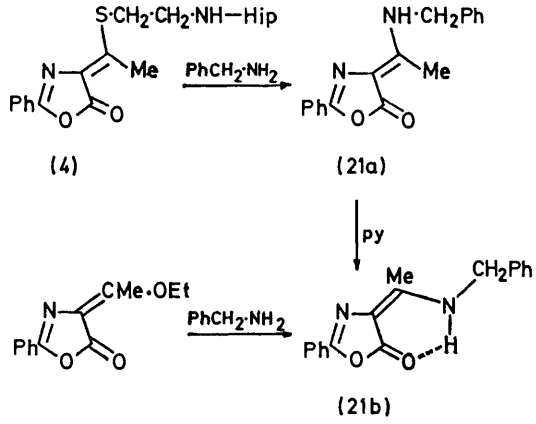


When the oxazolone system is replaced by a similar one also containing an active methylene group but having no acylating action, *viz.* 3-phenyl-Δ^2-isoxazolin-5-one, in the reaction with 2-alkylthiazolines again attack takes place at the 2-position of the thiazoline but to give only the thiols corresponding to (3), *e.g.* (11) and (22). Δ^2-Thiazoline itself gives the analogous compound (23) though no products were isolated from its reaction with 2-phenyl-Δ^2-oxazolin-5-one (1). Compound (11) is *S*-hippuroylated by (1).



Compound	R	M.p. (°C)	Yield (%)	$\nu_{max.}$/cm^{-1}
(11)	Me	135—137 (EtOH)	58	1590, 1661, 1682, 2530w
(22)	$PhCH_2$	163—166 (EtOH)	16	1602, 1677, 1688
(23)	H	180—182 (EtOH)	64	1630, 1640, 1700, 2550w

The geometrical configuration of these compounds about the alkylidene group is not known. However, it may be significant that, as already mentioned, reaction of compound (4) with benzylamine yields the less stable isomer of 4-(1-benzylaminoethylidene)-2-phenyl-Δ^2-oxazolin-5-one (21a). This suggests the sequence (Scheme) starting with compound (4) in which the large, electronegative sulphur atom and the carbonyl group are *trans* and ending in the more stable hydrogen-bonded product (21b).



SCHEME

EXPERIMENTAL

I.r. spectra were determined for potassium bromide discs; n.m.r. spectra were measured at 60 MHz; all thiazolines were prepared by the method of Wenker.[5]

4-[1-(2-Hippuroylthioethylamino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (3).—(*a*) 2-Methyl-Δ^2-thiazoline (2·0 g) and 2-phenyl-Δ^2-oxazolin-5-one [6] (6·4 g, 2 mol. equiv.) were dissolved in dry pyridine (30 ml) and left overnight. The solvent was removed and the oily residue triturated with ethanol. The crude material was collected and washed with ethanol then ether; yield 5·5 g (75%), m.p. 155—157° (from MeOH), τ [$(CD_3)_2SO$] 0·6br (1H), 1·4br (1H), 2·0—2·6 (5H, m), 5·75 (2H, d), 6·3—6·9 (4H, m), and 7·50 (3H, s) (Found: C, 62·3; H, 4·8; N, 9·7; S, 7·5. $C_{22}H_{21}N_3O_4S$ requires C, 62·4; H, 4·95; N, 9·95; S, 7·55%). More *product* was recovered from the mother liquors. Analogous compounds were prepared similarly (Table 2).

Bis-{2-[1-(5-Oxo-2-phenyl-Δ^2-oxazolin-4-ylidene)ethylamino]ethyl} Disulphide.—Compound (3) (7·2 g) was dissolved in sodium ethoxide [ethanol (40 ml) and sodium (0·46 g)]. The solution was quickly neutralised with hydrochloric acid and the solvent removed. After addition of ethanol and removal of the sodium chloride, light petroleum was added; *crystals* slowly formed, m.p. 138—139° (from ethanol), $\nu_{max.}$ 3300w, 1703, 1688, 1631, 1602, and 1585 cm^{-1}, τ [$(CD_3)_2SO$] 1·5br (1H), 2·0—2·6 (5H, m), 6·9 (2H, t), 7·5 (2H, s), and 7·6 (2H, t) (Found: C, 59·7; H, 5·2; N, 10·6; S, 12·15. $C_{26}H_{26}N_4S_2O_4$ requires C, 59·6; H, 5·3; N, 10·6; S, 12·2%), *m/e* 522 (M^+).

4-[1-(2-Benzylthioethylamino)ethylidene]-2-phenyl-Δ^2-oxazolin-5-one (8).—Compound (3) (4·0 g) was dissolved in sodium methoxide [methanol (40 ml) and sodium (0·26 g)]. Addition of benzyl bromide (1·26 ml) rapidly gave a precipitate which was washed with methanol and water; yield 2·5 g (65%), m.p. 124—125° (from ethanol), $\nu_{max.}$ 3300, 1755w, 1703, and 1633 cm^{-1}, τ ($CDCl_3$) 1·4br (1H), 2·0—2·3 (2H, m), 2·6—2·8 (8H, m), 6·29 (2H, s), 6·6 (2H, q), 7·4

[4] S. I. Lure and G. A. Ravdel, *Doklady. Akad. Nauk S.S.S.R.*, 1952, **83**, 97 (*Chem. Abs.*, 1953, **47**, 2167).

[5] H. Wenker, *J. Amer. Chem. Soc.*, 1935, **57**, 1079.

[6] R. A. F. Bullerwell and A. Lawson, *J. Chem. Soc.*, 1952, 1350.

(2H, t), and 7·7 (3H, s) (Found: C, 68·0; H, 5·8; N, 8·1; S, 9·1. $C_{20}H_{20}N_2SO_2$ requires C, 68·2; H, 5·7; N, 7·95; S, 9·1%). The *compound* was unchanged after being warmed with sodium methoxide and benzyl bromide. The filtrate from the precipitate was extracted with ether; evaporation of the extract left an oil which on hydrolysis with hydrochloric acid gave hippuric acid.

Reaction of 2-Methyl-Δ²-thiazoline with 2-Phenyl-Δ²-oxazolin-5-one in Benzene.—2-Methyl-Δ²-thiazoline (2·8 g) and 2-phenyl-Δ²-oxazolin-5-one (7·5 g) were refluxed in dry benzene for 1·5 h. The crystals, deposited during 3 days, were collected and washed with benzene and ether. The product (2 g), a mixture of compounds (4) and (3), was dissolved in hot ethanol. On cooling, 4-[1-(2-*hippuroylaminoethylthio*)*ethylidene*]-2-*phenyl*-Δ²-*oxazolin*-5-*one* (4) (0·9 g, 8·5%), m.p. 185—187° (from methanol), had crystallised after 2 h; τ [$(CD_3)_2SO$] 1·2br (1H), 4·6br (1H), 1·9—2·5 (5H, m), 6·0 (2H, d), 6·5—6·7 (4H, m), and 7·29 (3H, s) (Found: C, 62·3; H, 4·9; N, 10·0; S, 7·5. $C_{22}H_{21}N_3SO_4$ requires C, 62·4; H, 4·95; N, 9·9; S, 7·55%). The filtrate deposited crude product (3) (0·7 g, 6·5%) overnight. Compound (4) was unchanged when refluxed in ethanol for 2 h with or without the addition of a small amount of sulphuric acid or triethylamine.

4-(1-*Benzylaminoethylidene*)-2-*phenyl*-Δ²-*oxazolin*-5-*one* (21).—Compound (4) (0·5 g) was heated on a steam-bath for 5 min in ethanol (20 ml) containing benzylamine (0·2 ml). The crystalline *product* (21a) (0·1 g), obtained after 2 days, had m.p. 127—129 °C (from ethanol), $\nu_{max.}$ 1230, 1583, 1597, 1630, 1695, and 3310 cm^{-1} (Found: C, 74·0; H, 5·6; N, 9·5. $C_{18}H_{16}N_2O_2$ requires C, 74·0; H, 5·5; N, 9·6%). Leaving compound (21a) overnight in solution in pyridine, evaporating and adding ethanol gave the isomer (21b), m.p. 236—238° (from ethanol), $\nu_{max.}$ 1580, 1590sh, 1625, 1700, 1730sh, and 3330 cm^{-1} (no peak around 1230 cm^{-1}). Compounds (21a) and (21b) had many common peaks in their i.r. spectra. The latter was identical (i.r. spectrum, m.p., mixed m.p.) with the compound produced by treating 4-(1-ethoxyethylidene)-2-phenyl-Δ²-oxazolin-5-one [4] with benzylamine in refluxing ethanol.

2-*Benzylidene*-3-*hippuroylthiazolidine* (6; R = Ph).—2-Benzyl-Δ²-thiazoline (6·9 g) and 2-phenyl-Δ²-oxazolin-5-one (12·5 g) were refluxed in benzene for 1·5 h. The solvent was removed and the oil triturated with ethanol. The *solid* was collected and washed with ethanol; yield 8·4 g (63%), m.p. 142·5—144° (from ethanol), $\nu_{max.}$ 1635, 1660, and 3400 cm^{-1}, τ ($CDCl_3$) 2·0—2·8 (12H, m), 5·63 (2H, d), 6·09 (2H, t), and 7·03 (2H, t) (Found: C, 67·5; H, 5·1; N, 8·3; S, 9·6. $C_{19}H_{18}N_2O_2S$ requires C, 67·5; H, 5·3; N, 8·3; S, 9·5%). Hydrolysis of compound (6; R = Ph) with dilute hydrochloric acid yielded only hippuric acid, benzoic acid, 2-benzyl-Δ²-thiazoline, and 2-mercaptoethylamine hydrochloride.

Reaction of 2-Ethyl-Δ²-thiazoline with 2-Phenyl-Δ²-oxazolin-5-one.—2-Ethyl-Δ²-thiazoline (4·6 g) and 2-phenyl-Δ²-oxazolin-5-one (12·8 g) were refluxed in dry benzene (70 ml) for 1·5 h. The crude solid obtained on cooling was recrystallised from ethanol to give 2-*ethylidene*-3-*hippuroylthiazolidine* (4·5 g, 37·5%), m.p. 145—147° (from ethanol), $\nu_{max.}$ 1632, 1667, and 3400 cm^{-1}, τ ($CDCl_3$) 2·1—2·7 (6H, m), 4·0br (1H), 5·65 (2H, d), 6·05 (2H, t), 7·02 (2H, t), and 8·26 (3H, d) (Found: C, 60·8; H, 5·7; N, 10·5; S, 11·7. $C_{14}H_{16}SO_2$ requires C, 60·7; H, 5·8; N, 10·5; S, 11·6%). The filtrate and ethanol washings slowly deposited crude (17) (1·1 g). The benzene filtrate was evaporated and the remaining oil triturated with ethanol to give a mixture of compounds (12) and (17).

2-*Phenyl*-4-(*pyrrolidin*-2-*ylidene*)-Δ²-*oxazolin*-5-*one* (9).—2-Methylthio-Δ²-pyrroline [7] (13·8 g) and 2-phenyl-Δ²-oxazolin-5-one (19·2 g) were left overnight in solution in pyridine (100 ml); the solution was evaporated down and ethanol added to give *compound* (9) (20·6 g, 76%), m.p. 182—184° (from butan-2-one), $\nu_{max.}$ 1590, 1602, 1637, 1647, 1711, 1720, 3300, and 3380 cm^{-1}, τ ($CDCl_3$) 1·8—2·1 (3H, m), 2·3—2·6 (3H, m), 6·25 (2H, t), 6·83 (2H, t), and 7·83 (2H, quintet) (Found: C, 68·3; H, 5·2; N, 12·3. $C_{13}H_{12}N_2O_2$ requires C, 68· H, 5·25; N, 12·3%). A similar yield was obtained if the reactants were refluxed in benzene for 2 h. The analogous reaction with 2-methylthiohexahydroazepine gave 4-(*hexahydroazepin*-2-*ylidene*)-2-*phenyl*-Δ²-*oxazolin*-5-*one* (10) (4%), m.p. 132—134° (from EtOH), $\nu_{max.}$ 1580, 1598, 1625, 1631, 1690, and 3320 cm^{-1} (Found: C, 70·1; H, 6·3; N, 11·0. $C_{15}H_{16}N_2O_2$ requires C, 70·3; H, 6·25; N, 10·9%) and S-*methyl* α-(*hexahydroazepin*-2-*ylidene*)*thiohippurate* (67·0%), m.p. 200—203° (decomp.) (from ethyl acetate), $\nu_{max.}$ 1580s, 1600s, 1672, and 3340 cm^{-1} (Found: C, 63·2; H, 6·4; N, 9·3; S, 10·3. $C_{16}H_{20}N_2O_2S$ requires C, 63·2; H, 6·5; N, 9·2; S, 10·5%). Compound (9) was unaffected when refluxed for 8 h in ethanol containing benzylamine.

4-[1-(2-*Mercaptoethylamino*)*ethylidene*]-3-*phenyl*-Δ²-*isoxazolin*-5-*one* (11).—3-Phenyl-Δ²-isoxazolin-5-one (3·2 g) and 2-methyl-Δ²-thiazoline (2·0 g) were left overnight in pyridine (20 ml). The solution was evaporated and the solid recrystallised from ethanol to give *compound* (11) (3·0 g, 58%), m.p. 135—137° (from ethanol), $\nu_{max.}$ 1590, 1661w, 1682, 2530w, and 3230w cm^{-1}, τ ($CDCl_3$) −0·6br (1H), 2·6 (5H, s), 6·4 (2H, q), 7·3 (2H, q), 8·1 (3H, m), and 8·4 (1H, t) (Found: C, 59·6; H, 5·15; N, 10·75; S, 12·0. $C_{13}H_{14}N_2O_2S$ requires C, 59·5; H, 5·35; N, 10·7; S, 12·2%). When the reaction was repeated in benzene, unchanged isoxazolone was recovered. If 2-phenyl-Δ²-oxazolin-5-one (3·2 g) was used in addition to the foregoing reactants, 4-[1-(2-*hippuroylthioethylamino*)*ethylidene*]-3-*phenyl*-Δ²-*isoxazolin*-5-*one* (1·0 g, 12%), m.p. 155—157 ° (from ethanol) was obtained, $\nu_{max.}$ 1605, 1642, 1680, 1691, and 3330 cm^{-1} (Found: C, 62·4; H, 5·0; N, 9·8; S, 7·6. $C_{22}H_{21}N_3SO_4$ requires C, 62·5; H, 5·0; N, 9·95; S, 7·6%).

[2/2155 *Received*, 15*th September*, 1972]

[7] J. Tafel and P. Lawaczeck, *Ber.*, 1907, **40**, 2842.