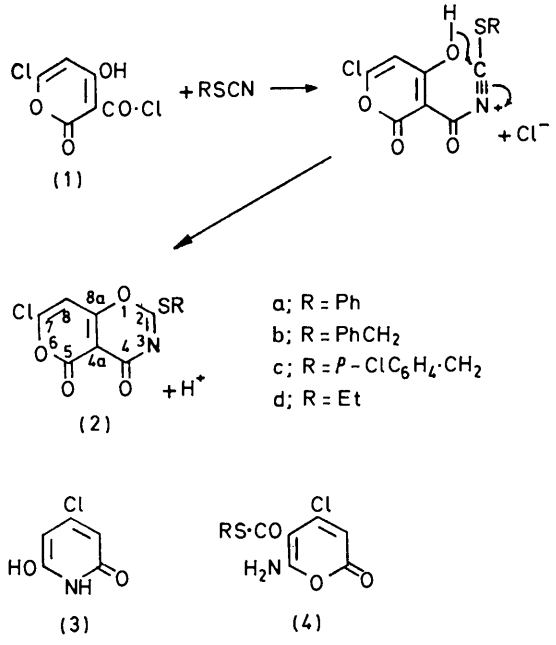
Heterocyclic Syntheses with Malonyl Chloride. Part X.[1] 2-Aryl- and -Alkyl-thio-7-chloropyrano[3,4-*e*][1,3]oxazine-4,5-diones from Thiocyanates, and their Behaviour with Amines

By **Jasim M. A. Al-Rawi** and **John A. Elvidge,*** Joseph Kenyon Laboratory, University of Surrey, Guildford GU2 5XH

Malonyl chloride reacts with alkyl and aryl thiocyanates yielding 2-alkyl- (or aryl-)thio-7-chloropyrano[3,4-*e*][1,3]-oxazine-4,5-diones (2). These react stepwise with amines, undergoing replacement of the thio-group and then of the chloro-substituent. Next, the pyrone ring is opened and finally the oxazine ring, to yield *N*-substituted β-aminoglutaconamides having an α-allophanoyl side chain. The intermediate *N*-substituted 2,7-diaminopyrano-oxazinediones (some of which are tautomeric) suffer oxazine ring scission with amine hydrochloride and yield substituted 3-allophanoyl-4,6-diaminopyran-2-ones. The parent heterocycles (2), when treated with amine hydrochloride, retain the sulphur group and yield *S*-alkyl *N*-(diamino-oxopyran-3-carbonyl)thiocarbamates.

DEPENDING on the substituents and conditions, nitriles react with malonyl chloride to yield pyrano-oxazines,[2] pyridines,[3] or pyrimidines.[1] We now find that simple thiocyanates react in the first way to give 2-(substituted thio)pyrano-oxazines (2). Because these compounds reacted with water to afford 4-chloro-6-hydroxy-2-pyridone (3) and the equally unexpected pyrone thioesters (4), amongst other products, the structure (2) came under close scrutiny. The unexpected results will be discussed in a later paper. Here, we are concerned to establish the bicyclic structure (2) for the malonyl chloride–thiocyanate products through evidence from their more straightforward behaviour with amines.

Bicyclic Products (2).—Treatment of phenyl thiocyanate with malonyl chloride afforded hydrogen chloride and a crystalline product, $C_{13}H_6ClNO_4S$. This showed carbonyl i.r. absorption at 1775—1750 cm^{-1}, and was also formed from the pyrone acid chloride (1) and phenyl thiocyanate. These close analogies with previous findings concerning nitriles,[2] isocyanates,[4] and ketones [5,6] indicated that the product was 7-chloro-2-(phenylthio)-pyrano[3,4-*e*][1,3]oxazine-4,5-dione (2a), derived through self-condensation of malonyl chloride to give the pyrone acid chloride (1) and then reaction with the thiocyanate, as indicated. Benzyl, *p*-chlorobenzyl, and ethyl thiocyanate, similarly afforded the bicyclic products (2b—d).



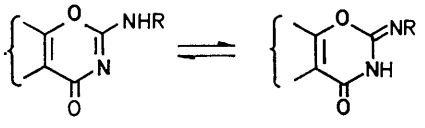
(1) (2) (3) (4)

[1] Part IX, J. A. Elvidge and N. A. Zaidi, *J. Chem. Soc.* (*C*), 1968, 2188.
[2] S. J. Davis and J. A Elvidge, *J. Chem. Soc.*, 1962, 3553.
[3] S. J. Davis, J. A. Elvidge, and A. B. Foster, *J. Chem. Soc.*, 1962, 3638.
[4] M. A. Butt, J. A. Elvidge, and A. B. Foster, *J. Chem. Soc.*, 1963, 3069.
[5] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 1952, 4109.
[6] J. A. Elvidge, *J. Chem. Soc.*, 1962, 2606.

These all showed u.v. absorption maxima near 345 and 280 nm (Table).

Mono- and Di-amino-substituted Products [(5) *and* (6)]. The new bicyclic compounds (2) differed from the pyrano-dioxins obtained from malonyl chloride and ketones,[5] and from the pyrano-oxazines from nitriles,[2] in that the most reactive site towards amines was not the 7-chloro-substituent. The sulphur substituent reacted preferentially. Thus the 2-benzylthio-compound (2b) with pyrrolidine and with aniline gave the 7-chloro-2-pyrrolidino- and -2-anilino-products (5a and b), with displacement of toluenethiol. Analogous products (5) were obtained from the 2-ethylthio-compound (2d) with benzylamine, butylamine and other alkylamines, and ammonia. The same 7-chloro-2-morpholino-compound (5g) was obtained from each of the thio-compounds (2a—d) with morpholine. Hence the primary mode of reaction was seen to be independent of the amine or the nature of the 2-thio-group.

These amino-chloro-compounds (5) showed characteristic u.v. absorption near 340 and 295 nm and the expected i.r. carbonyl absorption in the 1770—1750 cm^{-1} region (Table). In the NH stretching region, most of the products (5) derived from primary amines showed two sets of bands (Table), indicating tautomerism as illustrated. This was confirmed for solutions in deuteriochloroform by the ^1H n.m.r. spectra which showed two singlets (total intensity one proton) from the lone ring H-8, and two broadened lines (again totalling one proton) attributable to NH in each tautomer. In other solvents there was little indication of tautomerism. For the 2-butyl- and -octyl-amino-compounds (5d and e) (in $CDCl_3$) over the range −60 to +60°, the lines in each



pair of signals moved towards one another and changed in relative intensity as the rate of establishment of the equilibrium and the position of equilibrium changed. From extrapolation of the line shifts, the coalescence temperature appeared in each case to be *ca.* 240°.

However, attempts to find a solvent more suitable for a detailed study of the equilibrium failed.

U.v. and i.r. absorptions

	$\lambda_{max.}$/nm ($\varepsilon \times 10^{-3}$) in $CHCl_3$		$\nu_{max.}$ (Nujol) in cm^{-1} NH	CH	CO		
Compounds (2)							
a	347	(14·8)		3080w	1755sh	1590s	
	279·5	(10·7)			1750s	1510br	
b	346	(13·9)		3070w	1780sh	1590s	1538s
	280	(9·8)			1755s	1555	
c	341·5	(17·0)		3080w	1785s	1555	
	278·5	(15·0)			1750s	1515s	
d	344	(15·9)			1775	1590s	1515s
	280	(14·8)			1745s	1540w	
Compounds (5)	in MeCN						
a	341	(12·5)		3090w	1785	1637s	1555s
	298·5	(7·6)			1740s	1583	1522s
b	347	(12·7)	3260w	3100w	1760	1655s	1590
	296	(7·8)	3220w		1730s	1610w	1536
c	338	(18·6)	3250	3090w	1775s	1630	1580s
	293	(15·4)	3150w		1715s	1615	1550w
d	336·5	(16·9)	3245	3080w	1770sh	1626s	1530
	294	(13·8)	3150		1735s	1580	
h			3250	3090	1762sh	1635s	1535s
					1735s	1580	
i			3245	3080w	1743s	1640s	1517
						1580	
e	338	(16·8)	3330		1766	1652s	1507w
	294·5	(13·0)	3270w		1716s	1680s	
f	333·5	(16·8)	3360		1750	1654s	1550s
	291	(11·6)	3330w		1710s	1578	1500
			3230w				
			3170w				
g	340	(20·3)		3090w	1785s	1620s	1574s
	297·5	(12·5)			1740s	1584s	1535s
							1520s
Compounds (6)	in $CHCl_3$						
a	323	(7·9)	3180	3060w	1767s	1636s	1545
	287	(20·9)			1690s	1576	1510s
b	325	(7·7)		3060w	1764	1621	1514
	289·5	(15·5)			1714s	1580	
Compound (13)	in EtOH						
	222	(11·6)	3350	3070sh	1708s	1630w	1595s
			3270sh		1672s	1601br	1505w
					1652s		
Compounds (14)	in MeCN						
a	311·5	(14·7)	3250	3090w	1710	1610	1535
	249	(10·7)			1660s	1575s	
b	311	(17·0)	3400	3080sh	1690sh	1618w	1555br
	247·5	(12·2)	3230		1660s	1590w	1540sh
					1646h		
c	312	(16·4)	3250		1690	1620s	1580
	252	(12·9)			1675s	1600	1550
Compounds (15)	in MeCN						
a	327·5	(25·4)	3230w		1705	1618s	1550
	251	(22·5)			1690s	1598s	
b	327	(24·5)	3150br		1705	1633sh	1598
	251·5	(21·2)			1680s	1614s	1550br

The substituted 2-amino-7-chloro-compounds (5) could be recrystallised from ethanol and appeared not to react with water. Amines, however, displaced the 7-chloro-substituent. Thus the 2-butylamino-7-chloro-compound (5d), with two molecular proportions of morpholine in boiling chloroform gave morpholine hydrochloride and the 2-butylamino-7-morpholino-product (6a), which separated out. Similarly, the chloro-morpholino-compound (5g) gave the 2,7-dimorpholino-derivative (6b), which was also prepared directly from the 2-benzylthio-compound (2b) with 3 molecular proportions of morpholine in chloroform. Analogously, the 2,7-bisbenzylamino-derivative (6c) was obtained from the 2-ethylthio-compound and benzylamine, but in low yield, this product being more soluble. Diamino-pyrano-oxazine remaining in solution evidently underwent further change.

The diamino-pyrano-oxazines (6) were distinguishable from the bicyclic precursors (5) and (2) by their u.v. absorption near 324 and 288 nm (Table). The ^1H n.m.r. spectrum of the 2,7-bisbenzylamino-derivative (6c) (in $CDCl_3$) showed there were two tautomers present, with the diamino-form predominating. There was a one-proton triplet signal from the 7-N*H*R group (coupled to the adjacent methylene), and at lower field there were two fractional signals, a broadened one from the 2-N*H*R group together with a singlet from the ring NH of the tautomer, their relative intensities being 0·72 : 0·28. The 2-butylamino-7-morpholino-compound (6a) was likewise a tautomeric mixture in chloroform.

Degradation to Glutaconamides.—On attempting to recrystallise the 2-butylamino-7-morpholino-derivative (6a) from ethanol, both of the rings reacted with the solvent and the glutaconic ester amide (7) was obtained. The nature of the substituents on the bicyclic system thus profoundly affect its reactivity, the amino-chloro-compounds (5) being unchanged in ethanol.

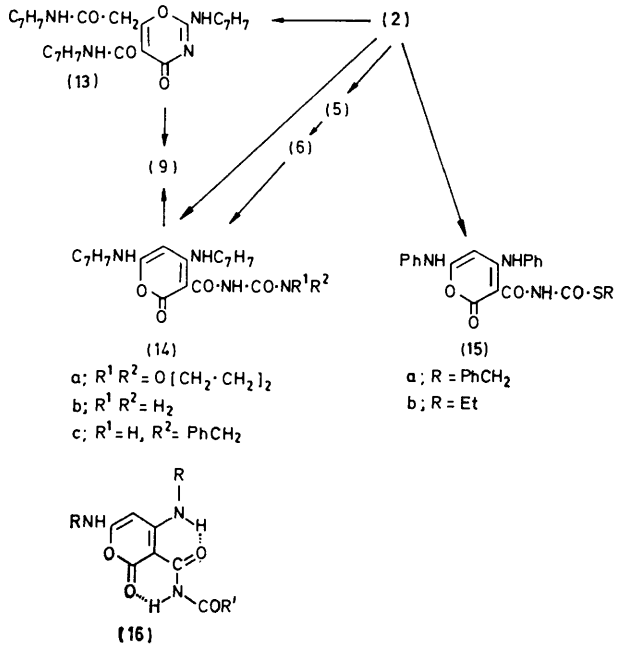
When the dimorpholino-derivative (6b) was treated with an excess of morpholine in boiling chloroform, β-morpholino-*NN'*-glutaconoyldimorpholine (8) was produced. Its structure was indicated by its composition, mass spectrum, and ^1H n.m.r. characteristics. Thus the pyrone ring had been opened, as expected, but an acyl-ureido chain, which should have been produced from opening of the oxazine ring, had been lost. This was attributed to traces of water in the morpholine opening the oxazine ring by attack at the 8a-position [2] in (6), followed by hydrolysis of the side chain and decarboxylation. Normal condensation of the *NN'*-acetone-1,3-dicarbonyldimorpholine product with morpholine then provided the end product (8). In previous reactions involving acetonecarboxamides,[2,7] conditions had not been so vigorous as to cause the replacement of the enolic hydroxy-group by amine. This suggested route to compound (8) was preferred to the alternative involving attack by morpholine at the 8a-position in compound (6) and then hydrolysis of the ureido side-chain because this side chain in the compounds (9a and b) resisted water in boiling ethanol.

When the 2-butylamino-7-morpholino-compound (6a) was treated with 2 molecular proportions of *dry* morpholine in boiling chloroform, the expected disubstituted

[7] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 1953, 2251.

glutaconamide (9a) was produced, this structure being supported by the ^1H n.m.r. spectrum (the coupling between the NH and adjacent CH_2 protons of the butylamine residue facilitated a complete assignment). Analogously, the ethylthio-compound (2d) with 5 molecular proportions of dry benzylamine in boiling chloroform yielded the disubstituted *NN'*-glutaconoylbisbenzylamine (9b). Cleavage of this product by heating with benzylamine in dioxan afforded *NN'*-dibenzylmalonamide (10) and the acylureide (11). The latter was degraded further in boiling benzylamine to *NN'*-dibenzylurea (12) and the diamide (10). The essential arrangement of the skeletal structure in the bicyclic compounds (2) was thus confirmed. To provide additional structural evidence, the conversion of compounds (2) into simple substituted pyrones and into 1,3-oxazines was also investigated.

1,3-*Oxazine Product* (13).—The foregoing results, and previous experience,[2,7] suggested that by heating the 2-benzylthio-compound (2b) in chloroform with 4 molecular proportions of dry benzylamine [1 more than required to yield the 2,7-bisbenzylaminopyrano-oxazine (6c)] cleavage of the pyrone ring would, additionally, be effected. This occurred and the 2-benzylamino-1,3-oxazine-dicarboxamide derivative (13) was obtained, but in poor yield. The major product was the disubstituted *NN'*-glutaconoylbisbenzylamine (9b) already encountered, which was also formed (in high yield) by heating the oxazine (13) with 1 molecular proportion of benzylamine in dioxan.



Aminopyrone Products (14) *and* (15).—It was then realised that if a 7-chloro-pyrano-oxazine [(2) or (5)] was heated with 3 or 2 molecular proportions of amine, respectively, under conditions such that the diamino product (6) and the amine hydrochloride by-product *both* remained in solution in the reaction medium, then the oxazine ring was cleaved preferentially so that the product was a pyrone. In this way, the 7-chloro-2-morpholino-pyrano-oxazine (5g) was converted by benzylamine in boiling chloroform into the 4,6-bisbenzylaminopyrone derivative (14a), which absorbed strongly in the u.v. near 311 nm. Possibly, hydrogen chloride addition or proton-assisted amine addition to the 4a,8a-double bond initiated the specific ring opening. In dimethyl sulphoxide, the 2-amino-7-chloro-compound (5f) with benzylamine gave the 3-allophanoyl-4,6-bisbenzylaminopyrone (14b). Furthermore, the 2-benzylamino-7-chloro-compound (5c) in dioxan with benzylamine provided the benzylallophanoyl homologue (14c). This last product was also obtained direct from the 7-chloro-2-ethylthio-compound (2d) with 3 molecular proportions of benzylamine in dioxan, a marked but now understandable contrast to the same reaction in chloroform which had yielded the 2,7-bisbenzylamino-pyrano-oxazine (6c). Degradation of the pyrone (14c) with benzylamine yielded the glutaconoylbisbenzylamine derivative (9b).

Yet other examples of the selectivity which could now be exercised were provided by the interactions of the 2-benzyl- and -ethyl-thio-7-chloro-compounds (2b and d) with aniline hydrochloride in dioxan solution. There was attack at the 8a-position with opening of the oxazine ring as well as displacement of the chloro-substituent by aniline, to yield the *S*-alkyl *N*-(4,6-dianilino-2-oxopyran-3-carbonyl)thiocarbamates (15a and b). The alkylthio-groups remained unaffected, in strong contrast to their preferential displacement by free aniline. The pyrone structure of these products (15) was confirmed by the u.v. absorptions (Table).

For both sets of pyrones (14) and (15), the i.r. spectra indicated that the 2-pyrone carbonyl group was hydrogen-bonded, as expected from the properties of analogous derivatives.[2] Indeed, double hydrogen-bonding, as in structure (16), was strongly indicated by the ^1H n.m.r. spectra, which each showed two signals from NH protons at rather low field.

Simple pyran-2-ones with monosubstituted amino-groups attached directly to the ring, such as compounds (14) and (15), are novel. Only a few with fully-substituted amino-groups have been described before.[2,7,8]

EXPERIMENTAL

U.v. and i.r. (Nujol) spectra were measured with Unicam SP 800B and SP 200 spectrophotometers, respectively. ^1H N.m.r. spectra ($CDCl_3$ unless specified) were recorded with a Perkin-Elmer R10 60 MHz spectrometer. Molecular ions were observed with an A.E.I. MS 12 instrument.

Procedure A.—Malonyl chloride [9] (14·1 g, 0·1 mol) and the thiocyanate (0·05 mol) were heated together (evolution of HCl) on a steam-bath with exclusion of moisture until

[8] G. Opitz and F. Zimmermann, *Chem. Ber.*, 1964, **97**, 1266.
[9] C. Raha, *Org. Synth.*, 1963, Coll. Vol. IV, p. 263.

solidification was complete. The product was crystallised from carbon tetrachloride (charcoal).

Procedure B.—To the 2-alkylthio-7-chloro-compound (2) (0·01 mol) in dry chloroform (35 ml; freshly shaken with P_2O_5 and decanted), the amine (0·01 mol) in dry chloroform (10 ml) was added dropwise, with stirring. The solution was heated under reflux for 1 h, then evaporated under reduced pressure, and the residue was washed with water to remove amine hydrochloride.

Procedure C.—The 2-amino-7-chloro-compound (5) (0·01 mol) was treated as in B with amine (0·02 mol); refluxing was performed for 1·5 h, and, after work-up, the residue was triturated with methanol.

2-Aryl- (and -Alkyl-)thio-7-chloropyrano[3,4-e][1,3]*oxazine-4,5-diones* (2).—By procedure A, phenyl thiocyanate [10] (6·7 g) gave the *2-phenylthio-compound* (9·2 g, 60%) as pale yellow needles, m.p. 191° (decomp.) (Found: C, 50·7; H, 2·3; Cl, 11·4; N, 4·7; S, 10·4. $C_{13}H_6ClNO_4S$ requires C, 50·7; H, 2·0; Cl, 11·5; N, 4·6; S, 10·4%), *m/e* 307 and 309, τ 3·65 (s, 8-H) and 2·42 (m, Ph). The same compound (60%; from CCl_4), m.p. and mixed m.p. 191° (decomp.), was obtained by converting 6-chloro-4-hydroxy-2-oxopyran-3-carboxylic acid (0·25 g) with thionyl chloride into the acid chloride,[6] and heating on a steam-bath with phenyl thiocyanate (0·22 g) until solidification was complete.

By procedure A, benzyl thiocyanate [11] (7·5 g) gave the pale yellow *2-benzylthio-compound* (10·4 g, 64%), m.p. 138—140° (Found: C, 52·2; H, 2·6; Cl, 10·95; N, 4·3; S, 9·4. $C_{14}H_8ClNO_4S$ requires C, 52·3; H, 2·5; Cl, 11·05; N, 4·35; S, 9·95%), *m/e* 321 and 323, τ 5·58 (s, CH_2), 3·65 (s, 8-H), and 2·64 (s, Ph). Similarly *p*-chlorobenzyl thiocyanate [12] (9·2 g) gave the pale yellow 2-p-*chlorobenzyl compound* (11 g, 62%), m.p. 163° (decomp.) (Found: C, 47·2; H, 2·0; N, 4·0. $C_{14}H_7Cl_2NO_4S$ requires C, 47·2; H, 2·0; N, 3·9%), *m/e* 355, 357, and 359, τ 5·64 (s, CH_2), 3·68 (s, 8-H), and 2·70 (s, C_6H_4).

Ethyl thiocyanate [13] (4·4 g) was mixed at 0° with malonyl chloride (14·1 g). The reaction was completed as in procedure A to afford the pale yellow *2-ethylthio-compound* (9·2 g, 72%), m.p. 116° (Found: C, 41·6; H, 2·3; N, 5·4. $C_9H_6ClNO_4S$ requires C, 41·6; H, 2·3; N, 5·4%), *m/e* 259 and 261, τ 8·56 (t, Me), 6·80 (q, CH_2, *J* 7 Hz), and 3·70 (s, 8-H).

2-Amino-7-chloropyrano[3,4-e][1,3]*oxazine-4,5-diones* (5).—By procedure B, the 2-benzylthio-compound (2b) (3·21 g) and pyrrolidine (0·92 ml) afforded the *2-pyrrolidino-compound* (2·38 g, 84%) as yellow plates (from dichloromethane), m.p. 267° (decomp.) (Found: C, 49·0; H, 3·4; N, 10·45. $C_{11}H_9ClN_2O_4$ requires C, 49·2; H, 3·35; N, 10·45%), *m/e* 268 and 270, τ 7·90 (m, 2 × β-CH_2 of pyrrolidine), 6·40 (m, 2 × α-CH_2 of pyrrolidine), and 3·87 (s, 8-H); aniline (0·83 g) gave the *2-anilino-compound* (2·7 g, 95%), m.p. 184° (decomp.) (from acetic acid) (Found: C, 53·6; H, 2·5; N, 9·5. $C_{13}H_7ClN_2O_4$ requires C, 53·7; H, 2·4; N, 9·6%), *m/e* 290 and 292, τ (Me_2SO) 3·73 (s, 8-H), 2·9—2·2 (Ph), and −1·55br (NH); morpholine (0·87 g) gave the *2-morpholino-compound* (2·3 g, 80%), m.p. 249° (decomp.) (from acetic acid) (Found: C, 46·3; H, 3·3; N, 9·8. $C_{11}H_9ClN_2O_5$ requires C, 46·4; H, 3·2; N, 9·8%), *m/e* 284 and 286, τ *ca.* 6·20 (complex, 4 × CH_2) and 3·95 (s, 8-H). The same compound (m.p. and mixed m.p. 249°) was similarly formed from the 2-*p*-chlorobenzyl-, 2-phenyl-, and 2-ethyl-thio-compounds (2) in 85, 85, and 80% yields, respectively.

Also by procedure B, the 2-ethylthio-compound (2d) (2·6 g) and benzylamine (1·07 g) yielded the *2-benzylamino-compound* (2·73 g, 90%) as pale yellow needles, m.p. 186° (decomp.) (from acetic acid) (Found: C, 54·8; H, 3·0; N, 9·3. $C_{14}H_9ClN_2O_4$ requires C, 55·2; H, 2·95; N, 9·2%), *m/e* 304 and 306, τ (Me_2CO) 5·35 (d, CH_2·N, *J* 6 Hz), 3·95 (s, 8-H), 2·63br (NH), and 2·63 (Ph); butylamine (0·74 g) gave the *2-butylamino-compound* (2·2 g, 81%), m.p. 142° (from carbon tetrachloride) (Found: C, 48·7; H, 4·0; N, 10·4. $C_{11}H_{11}ClN_2O_4$ requires C, 48·9; H, 4·1; N, 10·4%), *m/e* 270 and 272, τ 9·04 (*ca.* t, Me, *J* 6 Hz), 8·8—8·1 ($[CH_2]_2$), 6·48 (q, CH_2·N, *J* 6·3 Hz), 3·93 and 3·91 (0·4H, s, and 0·6H, s, 8-H), and 3·34br and 1·98br (0·6H and 0·4H, NH in the two tautomers) (when the solution was shaken with D_2O the last pair of signals vanished and the quartet at τ 6·48 collapsed to a triplet); ethylamine (0·45 g) gave the *2-ethylamino-compound* (20 g, 85%), m.p. 180° (decomp.) (from ethanol) (Found: C, 44·7; H, 2·8; N, 11·6. $C_9H_7ClN_2O_4$ requires C, 44·5; H, 2·9; N, 11·5%), *m/e* 242 and 244, τ [$(CD_3)_2SO$] 8·84 (t, Me, *J* 7 Hz), 6·70 (q, CH_2·N), 3·88 and 3·83 (s and s, 8-H), and 0·4br (NH); isopropylamine (0·59 g) gave the *2-isopropylamino-compound* (1·9 g, 74%), m.p. 200° (decomp.) (from ethanol) (Found: C, 46·75; H, 3·55; N, 11·0. $C_{10}H_9ClN_2O_4$ requires C, 46·8; H, 3·5; N, 10·9%), *m/e* 256 and 258, τ (dioxan) 8·78 (d, 2 × Me, *J* 7 Hz), 3·88 and 3·85 (s, s, 8-H), and 2·35br (NH); n-octylamine (1·29 g) gave the *2-octylamino-compound* (2·2 g, 80%), m.p. 199° (decomp.) (from carbon tetrachloride) (Found: C, 55·3; H, 5·7; N, 8·4. $C_{15}H_{19}ClN_2O_4$ requires C, 55·1; H, 5·8; N, 8·6%), τ 9·13 (*ca.* t, Me, *J* 5·1 Hz), 9·0—8·1 (complex, 6 × CH_2), 6·53 (q, CH_2·N), 3·94 and 3·90 (0·37H, s, and 0·63H, s, 8-H), and 3·35br and 2·12br (NH in the two tautomers).

Liquid ammonia (0·4 ml) was added to a stirred solution of the 2-ethylthio-compound (2d) (2·6 g) in chloroform (50 ml; previously treated with P_2O_5) at −80°. After the solution had reached ambient temperature, it was heated under reflux for 30 min, then evaporated, and the residue was washed with acetone to afford the pale yellow *2-amino-compound* (1·4 g, 65%), m.p. >300° (decomp.) (from acetic acid–dimethyl sulphoxide) (Found: C, 39·0; H, 1·45; N, 12·9. $C_7H_3ClN_2O_4$ requires C, 39·2; H, 1·4; N, 13·0%), *m/e* 214 and 216, τ (Me_2SO) 3·84 (s, 8-H), and 1·0br and 0·85br (NH_2).

2,7-Diaminopyrano[3,4-e][1,3]*oxazine-4,5-diones* (6).—By procedure C, the 2-butylamino-compound (5d) (2·7 g) and morpholine (1·8 g) afforded the *2-butylamino-7-morpholino-compound* (1·7 g, 50%), m.p. 182° (decomp.) (from ethyl acetate) (Found: C, 56·1; H, 5·9; N, 13·1. $C_{15}H_{19}N_3O_5$ requires C, 56·05; H, 6·0; N, 13·45%), *m/e* 321, τ 9·05 (t, Me, *J* 6·8 Hz), 8·8—8·1 (2 × CH_2 of Bu), 6·53 (q, CH_2·N of Bu, *J* 6 Hz), 6·85 (*ca.* t, CH_2·N·CH_2 of morpholine), 6·15 (*ca.* t, CH_2·O·CH_2), 4·85 and 4·78 (s and s, 8-H), and 3·8br and 1·9br (NH from each tautomer). Similarly the 2-morpholino-compound (5g) (2·9 g) and morpholine (1·8 g) gave the *2,7-dimorpholino-compound* (1 g, 30%) as needles, m.p. 215° (decomp.) (from ethyl acetate) (Found: C, 53·7; H, 5·0; N, 12·6. $C_{15}H_{17}N_3O_6$ requires C, 53·7; H, 5·1; N, 12·5%), *m/e* 335, τ 6·82 (*ca.* t, CH_2·N·CH_2 of 7-substituent), 6·15 (complex, 6 × CH_2), and 4·82 (s, 8-H).

[10] L. Gatterman and W. Haussknecht, *Ber.*, 1890, **23**, 738.
[11] L. Henry, *Ber.*, 1869, **2**, 636.
[12] C. L. Jackson and A. W. Field, *Amer. Chem. J.*, 1880–1881 **2**, 85.
[13] P. Walden, *Ber.*, 1907, **40**, 3214.

The same compound [m.p. and mixed m.p. 215° (decomp.)] (1 g, 30%) was obtained from the 7-chloro-2-ethylthio-compound (2d) (2·6 g, 0·01 mol) by procedure B and using morpholine (2·7 g, 0·03 mol). Similarly, using benzylamine (3·2 g, 0·03 mol), the 2,7-*bisbenzylamino-compound* was obtained (0·5 g, 13·5%), m.p. 212° (decomp.) (from acetonitrile) (Found: N, 11·4. $C_{21}H_{17}N_3O_4$ requires N, 11·2%), *m/e* 375, $\nu_{max.}$ 3190br (NH), 1712s and 1664s (CO, bonded), 1600s, 1570w, 1542, and 1500w cm^{-1}, τ [$(CD_3)_2SO$] 5·57br (2 × CH_2), 4·85 (s, 8-H), 2·70 (2 × Ph), 1·21br (t, 7-NH, *J* 6 Hz), −0·85br (2-NH), and −1·19 (s, ring NH of tautomer).

Glutaconamides and Simpler Products.—On recrystallising the 2-butylamino-7-morpholino-compound (6a) (1·7 g) from ethanol, only part was recovered (1·4 g). Evaporation of the filtrate afforded *ethyl* 2-(4-*butylallophanoyl*)-3-*ethoxy*-5-*morpholino*-5-*oxopent*-2-*enoate* (7) (0·2 g), m.p. 112° [(from light petroleum (b.p. 80—100°)] (Found: C, 55·4; H, 7·7; N, 10·0. $C_{19}H_{31}N_3O_7$ requires C, 55·5; H, 7·3; N, 10·2%), $\nu_{max.}$ 3320s (NH), 1740s (ester CO), 1698s [2-CO and C(5)O], 1670 (urea CO), 1630s (NH def.), and 1540br cm^{-1}, τ 9·09 (*ca.* t, Me of Bu), 8·75 (t, Me of 3-EtO, *J* 6·8 Hz), 8·69 (t, Me of EtO·CO, *J* 6·8 Hz), 8·9—8·3 (2 × CH_2 of Bu), 6·77 (*ca.* t, CH_2·N·CH_2), 6·3 (s, 4-H_2), 6·15 (complex, CH_2·N of BuN and CH_2·O·CH_2), 5·83 and 5·78 (q and q, 2 × CH_2·O of Et), 1·35br (t, NH of NHBu, *J* 5·6 Hz), and −0·35br (s, CO·NH·CO).

The 2,7-dimorpholino-compound (6b) (0·35 g) in dry chloroform (35 ml) was heated under reflux with an excess of morpholine (5 ml; not rigorously dried) for 1 h. The excess of amine was washed out with water, the chloroform solution was dried (Na_2SO_4) and evaporated, and the residue was triturated with ethanol to afford β-*morpholino*-*NN'*-*glutaconoyldimorpholine* (8) (0·2 g, 55%), m.p. 207° (decomp.) (from ethanol) (Found: C, 57·4; H, 7·7; N, 11·85. $C_{17}H_{27}N_3O_5$ requires C, 57·7; H, 7·6; N, 11·9%), *m/e* 353, $\nu_{max.}$ 1658s (CO), 1620s, and 1570s cm^{-1}, τ 6·87 (complex, CH_2·N·CH_2 at β), 6·37 (complex, 10 × CH_2), 5·88 (s, α-CH_2), and 4·88 (s, γ-CH).

The 2-butylamino-7-morpholino-compound (6a) (0·32 g) in dry chloroform (5 ml) was heated under reflux with dry morpholine (0·19 ml, 0·002 mol) for 1·5 h. Evaporation, and crystallisation of the residue from acetonitrile yielded 2-(4-*butylallophanoyl*)-3-*morpholino*-*NN'*-*glutaconoyldimorpholine* (9a) (0·4 g, 96%), m.p. 160° (decomp.) (Found: C, 55·4; H, 7·6. $C_{23}H_{37}N_5O_7$ requires C, 55·8; H, 7·5%), *m/e* 495, $\nu_{max.}$ 3310 and 3130 (NH), 1700s and 1640 (CO), 1595, and 1530br cm^{-1}, τ 9·08 (*ca.* t, Me), 8·9—8·2 (CH_2·CH_2 of Bu), 6·7 (complex, CH_2·N·CH_2 at position 3), 6·35 (*ca.* s, 12 × CH_2), 1·63br (*ca.* t, NH of NHBu), and 0·77br (CO·NH·CO).

To the 7-chloro-2-ethylthio-compound (2d) (2·6 g, 0·01 mol) in dry chloroform (40 ml), dry benzylamine (5·5 g, 0·05 mol) in chloroform (10 ml) was added slowly with stirring. The solution was heated under reflux for 2·5 h and evaporated, and the residue was washed with water, yielding 3-*benzylamino*-2-(4-*butylallophanoyl*)-*NN'*-*glutaconoyldibenzylamine* (9b) (3 g, 52%), m.p. 165° (from ethanol) (Found: 71·4; H, 6·1; N, 12·0. $C_{35}H_{35}N_5O_4$ requires C, 71·3; H, 5·9; N, 11·9%), $\nu_{max.}$ 3250 (NH), 3080w, 1674s and 1650s (CO), 1634s, 1597s, and 1550s cm^{-1}, τ 6·57 (s, 4-H_2), *ca.* 5·73 (4 × CH_2 of benzyl), 2·82 (4 × Ph), 2·33br, 1·67br, and 1·23br (3 × NH), −0·22br (s, CO·NH·CO), and −0·70br (NH bonded). This product (1 g) in dry dioxan (15 ml) was heated under reflux with benzylamine (1·5 ml) for 1·5 h; the solution was evaporated, and the residue washed with ethanol. Evaporation of the washings afforded *NN'*-dibenzylmalonamide (10) (0·2 g, 40%), m.p. and mixed m.p. 140° (lit.,[14] 142°), $\nu_{max.}$ 3300s (NH), 3080w, and 1640s (CO), τ 6·83 (s, CO·CH_2·CO), 5·65 (d, 2 × CH_2, *J* 5·5 Hz), 2·77 (s, 2 × Ph), and 2·50br (2 × NH). Crystallisation of the foregoing residue from ethanol afforded needles of N-*benzyl*-N'-(N-*benzylmalonamoyl*)*urea* (11) (0·52 g, 80%), m.p. 182° (decomp.) (Found: C, 66·8; H, 5·8; N, 12·9. $C_{18}H_{19}N_3O_3$ requires C, 66·5; H, 5·8; N, 12·9%), *m/e* 325, $\nu_{max.}$ 3300s (NH), 1680s, and 1640s (CO) cm^{-1}, τ [$(CD_3)_2SO$] 6·69 (s, CO·CH_2·CO), 5·72 and 5·62 (d and d, 2 × CH_2), 2·70 (s, 2 × Ph), 1·45br and 1·36br (t and t, 2 × NH of NHC_7H_7), and 0·41br (s, CO·NH·CO), τ (CF_3·CO_2H) 6·16 (s, CO·CH_2·CO), 5·41 (d, 2 × CH_2, *J* 5·1 Hz), 2·66 (s, 2 × Ph), and 1·76br and 1·02br (2 × NH of NHC_7H_7). This urea derivative (11) (0·4 g) was boiled in benzylamine (10 ml) for 1·5 h; the excess of amine was removed under reduced pressure, and the residue was washed with ethanol (20 ml). Evaporation of the washings gave *NN'*-dibenzylmalonamide (10) (0·19 g, 70%), m.p. and mixed m.p. 140° (from ethanol). Crystallisation of the foregoing residue from ethanol afforded *NN'*-dibenzylurea (12) (0·09 g), m.p. 169° (lit.,[15] 169°), *m/e* 240, $\nu_{max.}$ 3350s (NH), and 1625s and 1590 (CO, NH def.) cm^{-1} (*cf.* ref. 16), τ 5·75 (d, 2 × CH_2, *J* 6 Hz), 5·0br (2 × NH), and 2·78 (s, 2 × Ph).

Oxazine Derivative (13).—To the 7-chloro-2-ethylthio-compound (2d) (2·6 g) in dry dioxan (35 ml), dry benzylamine (4·5 g, 0·04 mol) in dioxan (10 ml) was added slowly, with stirring. After being heated under reflux for 2 h, the solution was evaporated to dryness under reduced pressure, and the residue washed with water and then extracted with boiling ethanol. Cooling of the extract afforded the glutaconoylbisbenzylamine (9b) (1·5 g), m.p. 165°. Repeated crystallisation of the remaining residue from acetonitrile gave needles of 2-*benzylamino*-5-*benzylcarbamoyl*-4-*oxo*-1,3-*oxazin*-6-*yl*-(N-*benzylacetamide*) (13) (0·3 g), m.p. 199° (decomp.) (Found: C, 69·9; H, 5·5; N, 11·5. $C_{28}H_{26}N_4O_4$ requires C, 69·7; H, 5·4; N, 11·6%), τ [$(CD_3)_2SO$] 6·06 (s, 6-CH_2), 5·85—5·47 (3 × CH_2), 2·7 (3 × Ph), 1·45br (2-NH), 0·83br (NH of acetamide), and 0·26 (NH of 5-substituent).

The oxazine (0·2 g) in dry dioxan (10 ml) was heated under reflux with benzylamine (0·4 g) for 1·5 h. Evaporation gave the glutaconoylbisbenzylamine (9b) (0·14 g, 60%), m.p. and mixed m.p. 165°.

4,6-*Diaminopyrones* (14) *and* (15).—By procedure C, the 7-chloro-2-morpholino-compound (5g) (2·9 g) and benzylamine (2·2 g) gave 4,6-*bisbenzylamino*-3-(*morpholinocarbonylcarbamoyl*)*pyran*-2-*one* (14a) (1·8 g, 40%), m.p. 216° (decomp.) (from ethanol) (Found: C, 64·7; H, 5·6; N, 12·1. $C_{25}H_{26}N_4O_5$ requires C, 64·9; H, 5·6; N, 12·1%), *m/e* 376 (M^+ − 86), τ 6·47br (4 × CH_2 of morpholine), 5·75 (d, 2 × CH_2, *J* 6 Hz), 5·21 (s, 5-H), 2·76 (c, 2 × Ph), 3·8br (6-NH), −1·05br (4-NH, bonded), and −1·50br (3-CO·NH, bonded). Similarly, but using dimethyl sulphoxide (40 ml), the 2-amino-7-chloro-compound (5f) (2·1 g) with benzylamine (2·2 g) gave 3-*allophanoyl*-4,6-*bisbenzylaminopyran*-2-*one* (14b) (1 g, 30%), m.p. 244° (decomp.) (from ethanol) (Found: C, 64·5; H, 5·1; N, 14·5. $C_{21}H_{20}N_4O_4$ requires

[14] J. V. Backes, R. W. West, and M. A. Whiteley, *J. Chem. Soc.*, 1921, **119**, 359.

[15] W. Jones, *Amer. Chem. J.*, 1912, **48**, 1.

[16] Sadtler Standard Spectra, Nos. 3903, 11740.

C, 64·3; H, 5·1; N, 14·3%), *m/e* 392, τ [$(CD_3)_2SO$] 5·61 (complex, 2 × CH_2 overlapped), 4·9 (s, 5-H), 2·73 (s, 2 × Ph), 2·50br (NH_2), 1·30br (6-NH), −0·4br (4-NH, bonded), and −0·88 (s, CO·NH·CO, bonded). Again by procedure C but using dry dioxan as solvent, the 2-benzylamino-7-chloro-compound (5c) (1·5 g) with benzylamine (1·1 g) afforded 3-(4-*benzylallophanoyl*)-4,6-*bisbenzylaminopyran*-2-*one* (14c) (0·5 g, 20%), m.p. 200° (decomp.) (from ethanol) (Found: C, 69·6; H, 5·45; N, 11·6. $C_{28}H_{26}N_4O_4$ requires C, 69·7; H, 5·4; N, 11·6%), *m/e* 482, τ 5·75, 5·72, and 5·52 (3 × d, 3 × CH_2, *J* 6 Hz), 5·28 (s, 5-H), 3·0—2·53 (3 × Ph), 3·24br (t, 6-NH), 1·15br (t, NH remote at position 3), −0·58br (t, 4-NH, bonded), and −1·15br (s, CO·NH·CO, bonded). The same compound (1 g), m.p. and mixed m.p. 200° (decomp.), was obtained similarly from the 7-chloro-2-ethylthio-compound (2d) (2·6 g) and benzylamine (3·1 g, 0·03 mol). The bisbenzylaminopyrone product (14c) (0·5 g) in dry dioxan (10 ml) was heated under reflux with benzylamine (0·1 g) for 1·5 h. The solution was evaporated and the residue crystallised from ethanol to yield the glutaconamide derivative (9b) (0·4 g, 70%), m.p. and mixed m.p. 165°.

The 2-benzylthio-7-chloro-compound (2b) (1·5 g) was dissolved in dry dioxan (30 ml) and aniline hydrochloride (3 g) was added. The solution was heated under reflux for 2·5 h and then evaporated to dryness. After being washed with water, the residue was crystallised from acetic acid (charcoal) to yield plates, m.p. 213° (decomp.), of S-*benzyl* N-(4,6-*dianilino*-2-*oxopyran*-3-*carbonyl*)*thiocarbamate* (15a) (1·3 g, 50%) (Found: C, 66·1; H, 4·65; N, 8·8. $C_{26}H_{21}N_3O_4S$ requires C, 66·1; H, 4·65; N, 8·9%), *m/e* 471, τ 5·85 (s, CH_2), 4·09 (s, 5-H), 3·0—2·3 (3 × Ph), −0·57br (6-NH), −1·30br (4-NH, bonded), and −2·11 (carbamate NH, bonded). Similarly, the 7-chloro-2-ethylthio-compound (2d) (1·3 g) and aniline hydrochloride (3 g) afforded S-*ethyl* N-(4,6-*dianilino*-2-*oxopyran*-3-*carbonyl*)*thiocarbamate* (15b) (1·0 g, 50%), m.p. 203° (decomp.) [from acetic acid (charcoal)] (Found: C, 61·5; H, 4·5; N, 10·35. $C_{21}H_{19}N_3O_4S$ requires C, 61·6; H, 4·6; N, 10·3%), *m/e* 409, τ 8·68 (t, Me, *J* 7·1 Hz), 7·05 (q, CH_2), 4·04 (s, 5-H), 2·75 (complex, 2 × Ph), −0·62br (6-NH), −1·35br (4-NH, bonded), and −2·17br (carbamate NH, bonded).

We gratefully acknowledge the award by Basrah University, Iraq, of a Calouste Gulbenkian Foundation Scholarship to J. M. A. Al-Rawi.

[3/772 *Received*, 11*th April*, 1973]