Heterocyclic Syntheses with Malonyl Chloride. Part 12.[1] Confirmatory and Revisionary Evidence for Structures of Products derived from 2-Alkyl-(or -Aryl-)thio-7-chloropyrano[3,4-*e*][1,3]oxazine-4,5-diones

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The structures previously proposed for the title compounds and various of their transformation products, have now been confirmed by ^{13}C n.m.r. spectroscopy with one exception. For the products thought to be *S*-alkyl or -aryl (6-chloro- and -benzylamino-3-alkoxycarbonyl-2-oxopyran-4-yl)thiocarbamates, *O*-alkyl or -aryl (6-chloro- and -benzylamino-3-*S*-alkoxythiocarbonyl-2-oxopyran-4-yl)carbamate structures are now proposed on the basis of the chemical shift of the carbon bearing the *S*-alkoxy-group. A possible mode of formation of the products is outlined.

ALKYL and phenyl thiocyanates react with malonyl chloride to afford the bicyclic heterocycles (1).[2] Evidence for the constitution of these products came from their composition and light absorption properties, from the analogy with products earlier obtained from nitriles [3] and isocyanates,[4] and from stepwise degradation with amines.[2] Interaction with water and with alcohols, however, gave unexpected products,[1] so that the structural evidence for the compounds (1) and their products came under close examination. In particular we have more recently used ^{13}C n.m.r. spectroscopy to provide further independent information. The results are now reported.

TABLE 1

2-Substituted-thio-pyrano[4,5-*e*][1,3]oxazines

Carbon	Compound (1a)	(1b)	(1c)
2	175.5 t (6)	177.0	176.3
4	162.9	164.7	164.3
4a	153.8	155.5	154.7
5	151.5	152.8	152.3
7	92.2 d (6.5)	93.8 d	92.6
8	111.5 d (179.4)	113.0 d (180.1)	112.4
8a	147.3 d (4.4)	149.1 d (5)	148.3
Side chain	Me 13.7 q	CH_2 36.5 t	C(1) 122.7,
	CH_2 26.6 t	C(1) 128.4, 128.9, 129.2, p 134.1	129.3, p 130.7 134.6

The proton-decoupled ^{13}C n.m.r. spectrum of compound (1a) from ethyl thiocyanate and malonyl chloride showed two lines at high field from the side chain and seven lines at lower field from the bicyclic ring system, as expected. The assignments, listed in Table 1 together with those for the analogues (1b) and (1c), were made partly from the chemical shifts and line intensities. Considerable help came from the splittings observed in 'gated-decoupled' spectra. These are high-resolution ^{13}C spectra obtained by interruption of proton irradiation: the ^{13}C resonances show the full coupling to protons and yet have substantial nuclear Overhauser enhancement (NOE). Thus the assignments of the side-chain and C(H)–8 resonances were confirmed through the large direct C–H couplings revealed. The gated spectrum of (1a) showed that the weak signal at δ 92.2 and the stronger one at δ 147.3 were weakly split as doublets, evidently by two-bond coupling to 8-H, and so were assigned to C-7 and C-8a. This ordering followed from the chemical shifts and the expectation that the C(Cl) line intensity and height would be low,[5] as a result of decreased NOE and of line broadening, respectively, caused by the chlorine quadrupole nucleus.[6] The weak signal at δ 175.7 was split as a triplet and so arose from C-2, there evidently being coupling through sulphur to the side-chain methylene protons. This assignment was at once confirmed by the strong line in the spectrum from a sample of (1a) in which C-2 had been enriched in ^{13}C by a synthesis [1] from ethyl [^{13}C]thiocyanate. Of the three remaining weak signals in the spectrum of (1a), all from quaternary carbons, the strongest at δ 153.8 was assigned to C-4a because that nucleus was most likely to be subject to NOE from 8-H. The weakest line (in height) at δ 162.9 was assigned to

[1] Part 11, J. M. A. Al-Rawi and J. A. Elvidge, *J.C.S. Perkin I*, 1976, 2462.
[2] J. M. A. Al-Rawi and J. A. Elvidge, *J.C.S. Perkin I*, 1973, 2432.
[3] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 1962, 3553.
[4] M. A. Butt, J. A. Elvidge, and A. B. Foster, *J. Chem. Soc.*, 1963, 3069.
[5] L. F. Johnson and W. C. Jankowski, 'Carbon-13 NMR Spectra', Wiley–Interscience, New York, 1972.
[6] G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists', Wiley–Interscience, New York, 1972, pp. 6—7.

C-4, adjacent to the (quadrupole) nitrogen.[6,7] Support for this last assignment came from the spectrum of the 33% [2-^{13}C] enriched compound (1a) in which the signal in question appeared twice: one third of the total C-4 signal was shifted slightly downfield (0.39 p.p.m.) by the isotopic effect of the ^{13}C label at C-2.

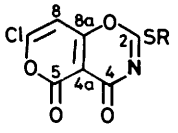
The related 2-ethoxy-compound (2), obtained [1] from (1a) through addition of ethanol to the 2,3-double bond and elimination of ethanethiol, had a mainly similar ^{13}C n.m.r. spectrum (Table 2). Again, the assignments

TABLE 2

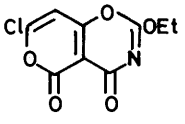
Carbon	(2)	Compound (3)	(4)
2	161.2 t	150.0 sx (4)	109.2 sp (4.8)
4	169.0	157.4	154.6 *
4a	155.8	150.4	157.8
5	153.1	154.4	155.2 *
7	91.6 d	101.1 d	91.0 d (2.9)
8	111.6 d (170.8)	107.0 d (179.4)	99.6 d (182.4)
8a	149.6 d	188.5 d	182.2 d (2)
Side chain Me	13.9 q	14.0 q	2 × Me 25.6 q
Side chain CH_2	69.1 t	25.3 t	
		MeO 53.8 q	

* or *vice versa*.
sx = sextet; sp = septet

were confirmed from the gated spectrum. In particular, the resonance at δ 161.2 was a weak triplet and so assignable to C-2.



(1) a; R = Et
b; R = CH_2Ph
c; R = Ph



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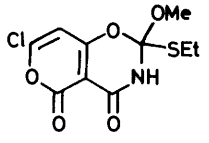

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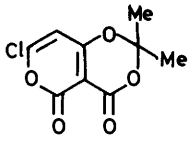
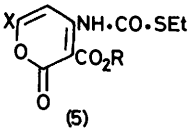


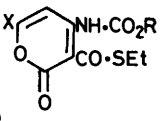
(4)

The immediate product of the action of methanol on (1a) was the addition compound (3). In agreement with that structure, the gated spectrum showed that C-2 (δ 150.0) was coupled to the protons of both the *O*-methyl and *S*-methylene groups. Of note was the low-field chemical shift of C-8a in this pyrone structure (3) which lacked aromatic-type conjugation or resonance in the second-ring. Similar features characterised the ^{13}C spectrum of the well established pyrone derivative (4), formed from malonyl chloride and acetone.[8] The only ambiguity in this last case was assignment of the very close C-4 and C-5 resonances (Table 2).

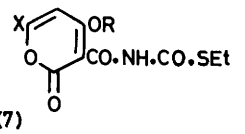
Another product from compound (1a) and methanol, accompanying the addition product (3) and isomeric with it, was a compound we had formulated as *S*-ethyl *N*-(6-chloro-3-methoxycarbonyl-2-oxopyran-4-yl)-thiocarbamate (5a).[1] We suggested [1] that ring-opening of (1a) by methanol at the 4-position gave an intermediate iminothiocarbonic ester which then rearranged to (5a). An analogous compound (5b) arose from a similar reaction of (a) with ethanol, and further analogues had been obtained from (1b) and (1c).[1] Compound (5a) had been converted into (5c) by a mild reaction



(5)

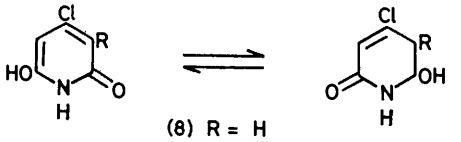


(6)



(7)

a; R = Me, X = Cl
b; R = Et, X = Cl
c; R = Me, X = NH·CH_2Ph



(8) R = H
(9) R = CO_2Et

with benzylamine. The seemingly, more straightforwardly-derived 4-alkoxypyrone constitution (7) for these products had been rejected [1] on light absorption evidence and, moreover, was disfavoured by the ^{13}C n.m.r. spectra. Thus, there was no resonance in the δ 170—190 region, which could be assigned to C-4 in (7), by analogy with C-8a in compounds (3) and (4) (Table 2), and with C-4 (δ 171.4) [9] in 4-methoxy-6-methyl-2-pyrone. There *was* a line at δ 187.5 in the ^{13}C spectrum of (5a) but this was necessarily assigned to the carbon-bearing the *S*-ethyl group because of the triplet splitting of the resonance in the gated spectrum. The chemical shift was strongly indicative of carbonyl in an *S*-alkyl thioester group.[5] This would be directly attached to the pyrone nucleus and not to nitrogen as in the thiocarbamate (5a) for which the shift in question should have been near δ 165, as in compounds (14). For the supposed compounds (5), the new constitution (6) thus emerged. This was fully consistent with all the previous findings [1] as well as with the remaining detail of the ^{13}C n.m.r. spectrum (see Table 3). The lines at δ 92.8, 115.6, and 151.5 were assigned severally to C-5, C-6, and C-4 in (6a), partly from the chemical shifts and line intensities but particularly from the splittings in the gated spectrum. A weak singlet at δ 156.9 was assignable to the 4-carbamic ester carbonyl in (6a), leaving lines at δ 154.3 and 154.4 to be assigned to C-2 and C-3 or *vice versa*. The homologous ethyl ester (6b) had a closely similar ^{13}C spectrum. That of the benzylamine substitution product (6c) was essentially analogous apart from identifiable changes in the

[7] Cf. G. C. Levy, *J.C.S. Chem. Comm.*, 1972, 47.
[8] S. J. Davis and J. A. Elvidge, *J. Chem. Soc.*, 1952, 4109.
[9] W. V. Turner and W. H. Pirkle, *J. Org. Chem.*, 1974, **39**, 1935.

chemical shifts of C-2 and C-6, and the additional resonances arising from the new side-chain. The previously proposed constitution (5) for these products [1] had therefore to be revised to (6).

Formation of the compounds (6a) and (6b) from the treatment of (1a) with methanol and ethanol was

TABLE 3

Carbon	Compound (6a)	(6b)	(6c)
2	154.3	154.3	161.9
3	154.4	154.3	155.7
4	151.5 d (3)	150.8 d (3)	152.3 d (4)
5	92.8 d (180.8)	92.8 d (184.5)	78.6 d (175)
6	115.6 d (4.4)	115.3 d (4.4)	90.9 d (4)
3-CO	187.5 t (5)	187.4 t (4.4)	190.8 t (5)
CH_2S	24.4 t	24.4 t	22.2 t
Me	14.3 q	2 × Me 14.2 q	14.2 q
CO·N	156.9	156.8	159.1
MeO	53.7 q	63.1 t	52.8 q
CH_2N			46.3 t

envisaged as first involving addition of the alcohol to the 2,3-double-bond, followed by elimination of ethanethiol. Then ring-opening by the thiol at the 4-position would give an iminocarbonic ester, rearrangement of which would yield the carbamate products (6a, b, *etc.*) (see ref. 1).

When the bicyclic compounds (1) were treated in boiling dioxan with 3 molar proportions of water, 4-chloro-6-hydroxy-2-pyridone was obtained.[1] From u.v., i.r., and ^{1}H n.m.r. observations, this compound evidently existed in a state of dynamic tautomerism, as indicated at (8). In agreement with the resulting effective molecular symmetry, C-3 and C-5 had the same ^{13}C chemical shift and the shift of C-2 was the same as that of C-6 (Table 4). The bicyclic compound (1a) with

TABLE 4

Carbon	Pyridones (8)	(9)
2	158.8	158.3
3	98.6 d (170.6)	105.4
4	145.8	143.5
5	96.8 d (170.6)	94.1 d (166.2)
6	158.8	157.7 *
3-CO		163.2
CH_2		60.2 t
Me		13.8 q

* More intense than C-2, being next to CH.

ethanol under similar conditions gave the chloro-hydroxy-pyridone carboxylic ester (9).[1] No evidence was apparent from the i.r. and ^{1}H n.m.r. spectra for intramolecular chelation between the adjacent ester carbonyl and hydroxy functions,[1] which was a marked difference from analogous pyrones [3,10] but understandable if the pyridone was undergoing rapid tautomerism, as shown at (9). Some additional support for this came from the closeness in chemical shift of the intrinsically non-equivalent C-2 and C-6.

Treatment of the bicyclic compound (1a) with 1 molar proportion of water in dioxan at 85 °C effected, as intended, less extensive degradation than had given rise to the simple 4-chloropyridone (8). However, the product unexpectedly appeared to have the 4-chloropyrone constitution (10).[1] Useful additional evidence came from the ^{13}C n.m.r. spectrum (Table 5). The

TABLE 5

Carbon	Compound (10)	(14a)	(14b)
2	153.7 d (3)	155.8 d (3)	156.2
3	97.6 d (179.4)	103.9 d (177)	107.8
4	148.4 d (4)	151.7	151.8
5	161.9	90.5 d (179)	99.9
6	158.6 *	151.7	150.3
Side chain CO	184.9 t (5)	164.3 t (5)	166.3
Side chain CH_2	23.7 t	23.4 t	24.5
Side chain Me	14.0 q	14.8 q	14.4
MeN			33.8

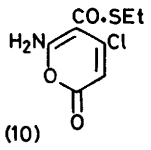
* Relatively broadened in the ^{1}H decoupled spectrum; signal intensity strengthened in the gated spectrum

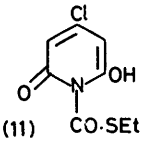
assignments, made as in previous cases, at once showed there was a single ring C(H) group and so eliminated structures such as (11) as indeed the ^{1}H n.m.r. results had done.[1] The ^{13}C n.m.r. observations also ruled out 6-chloro-pyrone structures such as (12), in that the C(Cl) chemical shift was downfield at δ 148.8 as for 4-chloro-6-methyl-2-pyrone,[9] rather than in the δ 90—115 region as for compounds (1)—(4) and (6). Neither structure (12) nor the 4-chloropyrone (13) accommodated the lowfield carbonyl resonance at δ 184.9 which, being weakly split as a triplet (in the gated spectrum), had to be assigned to a carbonyl bearing the *S*-ethyl group. Thus the ^{13}C spectrum was consistent with the structure (10) earlier proposed and excluded the isomeric pyridone structure, corresponding to the thioester analogue of (9), because the C-5 chemical shift of (10) was quite different from that of C-3 in (9).

By interacting the bicyclic compound (1a) with 2 molar proportions of water at a lower temperature (74 °C in dioxan) but in the presence of an excess of hydrogen chloride, *S*-ethyl *N*-(4-chloro-2-oxopyran-6-yl)thiocarbamate (14a) was obtained, which with diazomethane yielded the *N*-methyl derivative (14b).[1] The ^{13}C n.m.r. results (Table 5) at once confirmed the presence of two, separated, ring-CH groups in both compounds (14) and of a 4-CCl group in compound (14b). The C(Cl)-4-resonance in the spectrum of (14a) was accidentally coincident with that from C-6. In the spectrum of (14b), the lines at δ 150.3 and 156.2 were assigned to C-6 and C-2, respectively, because the former line was both the more intense and the broader of the two. The relative assignment of the C(H) lines at δ 90.5 and 103.9 in the spectrum of (14a) to C-5 and C-3 was made partly by comparison with the shifts for simple pyrones [9] and partly because the higher field resonance was relatively less intense. This slight intensity weakening could be attributed to the C(H)-5 being flanked by carbons each bearing a quadrupole nucleus.[6,7] The carbon which bore the *S*-ethyl group in compound (14a) was identified with the resonance at lowest field (δ 164.3) by the weak triplet splitting which appeared in the gated spectrum.

[10] J. A. Elvidge, *J. Chem. Soc.*, 1962, 2606.

Confirmation came from the specific signal enhancement in the spectrum of compound (14a) prepared [1] from the 33% [2-^{13}C] enriched compound (1a).


(10)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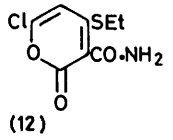
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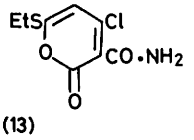
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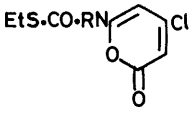
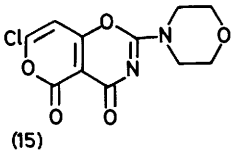

(14) a; R = H
b; R = Me


(15)

The products from the compounds (1) and primary amines had appeared to be mixtures of tautomers [2] were made from similar considerations to those employed for assigning the resonances from the parent compounds (1) (Table 1). In particular, the splitting in a gated spectrum of the 2-octylamino derivative (16d) established the assignment of C-2, C-7, C-8, and C-8a. That for C-2 was further confirmed by the signal enhancement in the spectrum of a [2-^{13}C] enriched sample prepared [2] from the enriched compound (1a). Of the remaining three low-field lines in the ^{13}C spectrum of (16d), that at δ 157.0 was assigned to the quaternary C-4a because, as for (1a), this line was more intense than the other two. These last, at δ 168.8 and 154.2, were assigned to C-4 and C-5 respectively because in the gated spectrum the former line was appreciably broadened, possibly by long-range coupling to NH. It was of interest that the imino-tautomer (17d) showed small changes in chemical shift from the amino-tautomer only for C-7, C-8, C-5, and C-2. The same was true of compounds (17b) and (17c). Tautomeric shifts for C-4 and C-4a were only observed with the 2-anilino-derivative (16e). In the case of the 2-amino-compound (16a), for which there appeared to be good i.r. evidence for tautomerism,[2] only a single set of resonance lines appeared in the ^{13}C spectrum. Evidently, tautomerism in this compound at ambient temperature was fast, averaging the ^{13}C signals.

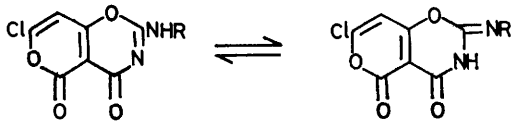
TABLE 6

Ring ^{13}C shifts and coupling data for the 2-morpholino-pyrano-oxazine (15) and the amino-imino tautomeric compounds (16) and (17)

	Carbon						
Compound	2	4	4a	5	7	8	8a
(15)	157.5	168.6	156.8	153.8	87.6	107.0 [a]	149.4
(16a)⇌(17a)	161.0	169.1	156.9	154.3	87.9	106.7	149.6
(16b)	158.6	168.6	156.7	154.0	87.9	106.7	149.5
(17b)	159.1	168.6	156.7	153.8	86.9	106.3	149.5
(16c)	157.8	168.7	156.8	154.7	87.9	106.6	149.5
(17c)	158.4	168.7	156.8	153.9	87.0	106.2	149.5
(16d)	159.0 [b]	168.8	157.0	154.2	88.1 [c]	106.8 [d]	149.7 [e]
(17d)	159.4	168.8	157.0	154.0	87.2	106.4 [f]	149.7
(16e)	157.7	168.4	156.8	154.4	87.2	108.1	149.2
(17e)	157.7	171.9	157.8	154.4	87.2	108.1	149.2

[a] d(167.6). [b] t(3.4). [c] d(6.5). [d] d(170.7). [e] d(5.5). [f] d(170.4)

(16) ⇌ (17) and this was confirmed in several cases by the ^{13}C n.m.r. spectra (Table 6). The major tautomer in each case was identified as the 2-amino-form (16)


(16) (17)

a; R = H
b; R = Et
c; R = CHMe$_2$
d; R = [CH$_2$]$_7$Me
e; R = Ph

by comparison with the data for the 2-morpholino-derivative (15). The assignments given in Table 6

EXPERIMENTAL

The ^{13}C spectra (^{1}H decoupled, and gated) were obtained at 25 °C on solutions in perdeuteriodimethyl sulphoxide with a Brüker WH90 spectrometer operating at 22.6 MHz (nominal), mostly with 10 μs pulses (*ca.* 40° flip angle) at 5 s intervals in order to maximise the intensities of carbonyl resonances. Typically, 1.2 × 10^4 transients were accummulated into 8 K channels and Fourier transformed to give a spectral display width of 365 p.p.m. Field-frequency locking was to the solvent deuteron signal. ^{13}C Chemical shifts, δ (p.p.m.) measured from tetramethylsilane, with multiplicities ($^{1,2,\text{ or }3}J_{CH}$/Hz) from gated spectra, are given in the Tables.

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