Potential Centrally-acting Drugs: the Structure of an 8,14-But-1-eno-codeinone

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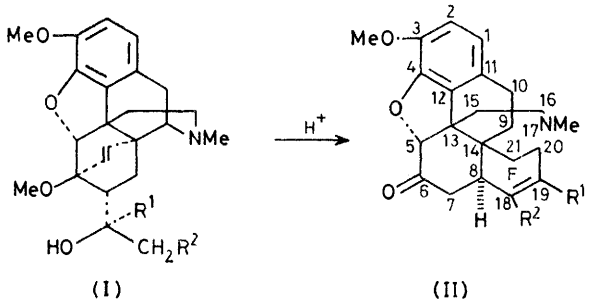
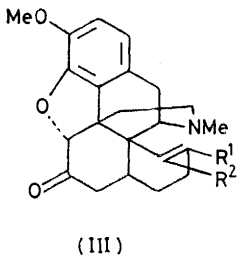
The structure of 8,14-but-1-eno-18-ethyl-7,8-dihydro-19-methylcodeinone is confirmed by mass spectrometry and *X*-ray crystallography. The chemical reactivity of the extra ring is examined.

THE potent analgesics (I) were shown by Bentley *et al.*[1] to produce butenocodeinones (II) on acid-catalysed rearrangement; this results in loss of analgesic properties but retention of other central effects.[2] The structures of the compounds (II) were established as far as was possible by mechanistic arguments and by chemical and analytical methods, but there remained a doubt about the nature of ring F and its orientation with respect to the dihydrocodeinone nucleus. An alternative structure, for example, might have been (III); which could arise by migration of the side chain from C(14) to C(8) before cyclisation of the new ring (see ref. 3).


(I) (II)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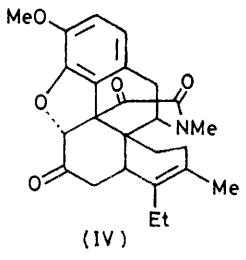
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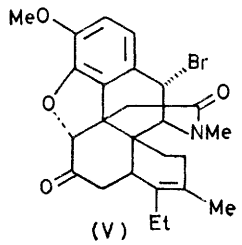
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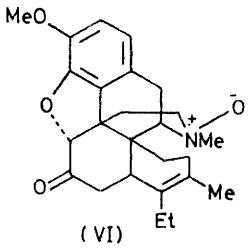
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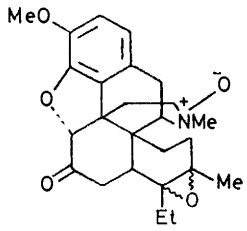
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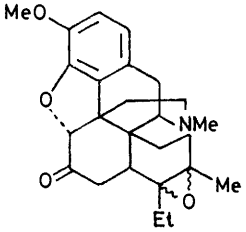

(VIII)

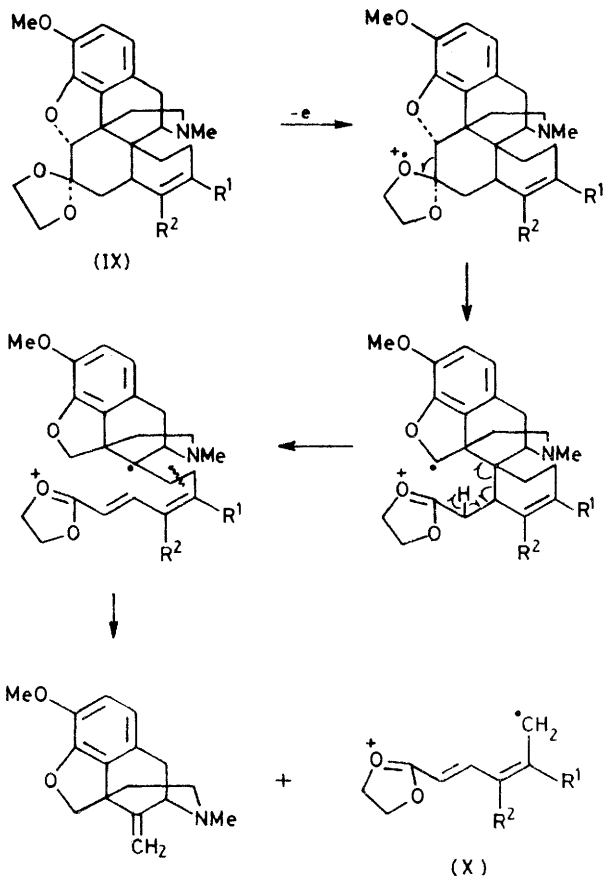
In preliminary experiments to distinguish between structures (II), (III), and possible variants we sought to effect reactions at the double bond in ring F using compound (II; R^1 = Me, R^2 = Et) † as the substrate. It became clear, however, that the double bond in ring F is relatively inert, presumably because of steric hindrance, so that reactions first occurred at other sites. For example, reaction of compound (II; R^1 = Me, R^2 = Et) with a catalytic amount of OsO_4 in the presence of $KClO_3$ in aqueous dioxan at 85° for 4 h gave a single product identified as compound (IV) by spectroscopic techniques.[3] Secondly an attempt to add hypobromous acid across the double bond of compound (II; R^1 = Me, R^2 = Et), with perchloric acid and 1.5 mol. equiv. of *N*-bromosuccinimide in dioxan at room temperature for 35 min gave a mixture. Two components were identified spectroscopically as the 10α-bromo-lactam (V) (major product) and the 1,10α-dibromo analogue (minor product). Thirdly, treatment of compound (II; R^1 = Me, R^2 = Et) with approximately one mol. equiv. of *m*-chloroperbenzoic acid (see Experimental section) gave the *N*-oxide (VI) as the only product. Although the nitrogen atom of compound (VI) is asymmetric, we are unable to say whether the product is a single diastereoisomer; the existence of isomeric *N*-oxides of morphine, codeine, and thebaine has been demonstrated.[4] The *N*-oxide (VI) forms a stable hydrochloride salt.

On treatment of the compound (II; R^1 = Me, R^2 = Et) with approximately two mol. equiv. of *m*-chloroperbenzoic acid the *N*-oxide epoxide (VII) was formed, of undetermined stereochemistry. The *N*-oxide epoxide (VII) could be reduced with SO_2 to the epoxide (VIII) but attempts to open the epoxide ring of this compound led to complex mixtures.

Having failed to establish structural details of ring F by these chemical reactions, we made use of mass spectrometry. The ketone (II; R^1 = Me, R^2 = Et) readily formed a 6-acetal (IX; R^1 = Me, R^2 = Et) which fragmented to a distinctive ion at *m/e* 180, shown by accurate mass measurement to correspond to $C_{11}H_{16}O_2$. Taking the structure (II) as written, and having in mind

† Code no. RX 389M.

the known fragmentation pattern of acetals,[5] we were able to rationalise formation of the ion as shown in the scheme; this was supported by four other examples (see Table 1) in which R^1 and R^2 were varied.



SCHEME

The corresponding acetal derived from structure (III) does not offer similar prospects of generating the ion (X), the mass of which is dependent on R^1 and R^2. On this basis structure (II) is preferred for the ketones. Conclusive proof for this assignment rests, however, on the *X*-ray crystallographic study of the ketone (II; R^1 = Me, R^2 = Et).

TABLE 1

Mass spectra of compound (IX)

Compound (IX)		Expected *m/e* for	Observed
R^1	R^2	fragment (X)	*m/e*
Me	Et	180.1150	180.1139
Pr^n	Et	208	208
Me	n-C_6H_{11}	236.1776	236.1766
Me	Ph	228	228
Me	$PhCH_2CH_2$	256	256

The crystal structure was elucidated by direct phasing procedures and least-squares adjustment of the atomic parameters converged to $R = 0.048$ over 1 796 independent reflections measured with Mo-K_α radiation on a four-circle diffractometer. The derived molecular structure is shown in the Figure and structure (XI). Atomic co-ordinates are listed in Table 2, bond lengths and valency angles are in Tables 3 and 4. The torsion angles for rings A—E are compared with results for other morphinelike alkaloids [6-11] in Table 5; the remaining torsion angles are listed in Table 6.

An important aspect in which 8,14-(1-ethyl-2-methylbut-1-eno)codeinone, naloxone, and 6-deoxy-6-azidodihydroisomorphine differ from morphine and codeine is that the latter alkaloids have a double bond at C(7)–C(8) in the six-membered ring D. The torsion

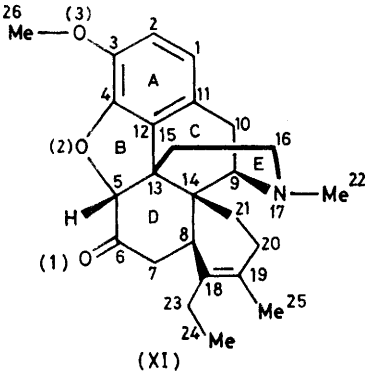
TABLE 2

Fractional atomic co-ordinates

	x	*y*	*z*
N	0.037 8(3)	−0.383 5(*)	0.715 3(3)
C(1)	0.289 5(4)	−0.013 2(5)	0.650 0(4)
C(2)	0.380 8(4)	−0.046 2(6)	0.612 0(4)
C(3)	0.437 2(3)	−0.201 3(5)	0.639 8(4)
C(4)	0.394 0(3)	−0.318 2(5)	0.703 9(4)
C(5)	0.388 6(3)	−0.520 4(5)	0.847 1(4)
C(6)	0.460 4(3)	−0.442 7(5)	0.979 7(4)
C(7)	0.404 0(3)	−0.412 4(6)	1.078 2(4)
C(8)	0.296 8(3)	−0.306 9(5)	1.020 2(3)
C(9)	0.116 4(3)	−0.279 1(5)	0.818 8(3)
C(10)	0.153 1(3)	−0.112 4(5)	0.767 7(4)
C(11)	0.247 4(3)	−0.133 5(5)	0.714 6(4)
C(12)	0.301 8(3)	−0.286 8(5)	0.736 6(3)
C(13)	0.270 7(3)	−0.442 8(5)	0.796 5(4)
C(14)	0.214 9(3)	−0.396 0(5)	0.898 3(4)
C(15)	0.190 0(4)	−0.547 2(6)	0.681 5(5)
C(16)	0.082 7(4)	−0.448 5(7)	0.617 0(5)
C(18)	0.248 9(3)	−0.270 7(6)	1.128 7(4)
C(19)	0.165 4(3)	−0.359 3(6)	1.141 6(4)
C(20)	0.111 9(4)	−0.501 5(6)	1.047 8(5)
C(21)	0.168 6(3)	−0.550 5(5)	0.950 0(4)
C(22)	−0.069 1(3)	−0.305 5(7)	0.652 0(4)
C(23)	0.301 0(3)	−0.120 2(7)	1.216 8(4)
C(24)	0.249 3(5)	+0.046 6(7)	1.157 3(6)
C(25)	0.116 5(4)	−0.326 1(7)	1.249 8(5)
C(26)	0.581 4(5)	−0.112 0(8)	0.561 5(7)
O(1)	0.555 2(2)	−0.405 8(5)	0.998 6(3)
O(2)	0.436 8(2)	−0.479 0(4)	0.746 6(3)
O(3)	0.529 1(3)	−0.242 3(4)	0.610 6(3)
H(1)	0.249(4)	+0.092(8)	0.623(5)
H(2)	0.403(4)	+0.024(8)	0.559(5)
H(5)	0.383(4)	−0.643(8)	0.857(5)
H(7a)	0.389(4)	−0.498(8)	1.110(5)
H(7b)	0.460(3)	−0.372(6)	1.160(4)
H(8)	0.321(3)	−0.204(6)	0.992(4)
H(9)	0.073(3)	−0.251(5)	0.880(4)
H(10a)	0.086(3)	−0.070(6)	0.698(4)
H(10b)	0.175(4)	−0.043(8)	0.846(5)
H(15a)	0.173(4)	−0.649(8)	0.714(5)
H(15b)	0.221(3)	−0.564(6)	0.603(4)
H(16a)	0.034(4)	−0.492(8)	0.559(5)
H(16b)	0.096(4)	−0.367(8)	0.552(5)
H(20a)	0.026(4)	−0.482(7)	0.997(5)
H(20b)	0.103(4)	−0.604(8)	1.098(5)
H(21a)	0.116(3)	−0.601(6)	0.877(4)
H(21b)	0.226(3)	−0.593(5)	0.992(3)
H(22a)	−0.096(3)	−0.286(6)	0.719(5)
H(22b)	−0.127(6)	−0.364(10)	0.599(7)
H(22c)	−0.069(5)	−0.277(9)	0.580(6)
H(23a)	0.381(3)	−0.108(6)	1.226(4)
H(23b)	0.291(3)	−0.113(6)	1.308(4)
H(24a)	0.279(6)	+0.126(12)	1.229(8)
H(24b)	0.250(4)	+0.061(7)	1.068(5)
H(24c)	0.161(4)	+0.049(8)	1.140(5)
H(25a)	0.088(3)	−0.229(6)	1.237(4)
H(25b)	0.038(5)	−0.336(9)	1.207(6)
H(25c)	0.157(5)	−0.334(8)	1.334(6)
H(26a)	0.650(4)	−0.146(7)	0.549(5)
H(26b)	0.535(4)	−0.099(7)	0.473(5)
H(26c)	0.609(5)	−0.051(10)	0.633(7)

* The *y* co-ordinate of N was fixed to define the origin.

angles in Table 5 show that the unsaturated ring D in morphine hydrochloride,[6] morphine,[7] and codeine hydrobromide [8] adopts a distorted boat conformation, whereas



(XI)

the saturated ring D in 8,14-(1-ethyl-2-methylbut-1-eno)-codeinone, naloxone hydrochloride,[9] and 6-deoxy-6-azidodihydroisomorphine [10] has a distorted chair con-

TABLE 3

Bond lengths (Å)

C(1)–C(2)	1.392(6)	C(13)–C(15)	1.551(6)
C(1)–C(11)	1.393(6)	C(14)–C(21)	1.547(5)
C(2)–C(3)	1.409(6)	C(15)–C(16)	1.530(7)
C(3)–C(4)	1.379(6)	C(18)–C(19)	1.329(6)
C(4)–C(12)	1.368(5)	C(18)–C(23)	1.528(7)
C(5)–C(6)	1.534(6)	C(19)–C(20)	1.511(6)
C(5)–C(13)	1.551(5)	C(19)–C(25)	1.518(6)
C(6)–C(7)	1.490(6)	C(20)–C(21)	1.517(6)
C(7)–C(8)	1.549(5)	C(23)–C(24)	1.520(8)
C(8)–C(14)	1.540(5)	N–C(9)	1.474(4)
C(8)–C(18)	1.517(5)	N–C(16)	1.457(6)
C(9)–C(10)	1.565(5)	N–C(22)	1.447(5)
C(9)–C(14)	1.565(5)	O(1)–C(6)	1.201(5)
C(10)–C(11)	1.513(5)	O(2)–C(4)	1.403(5)
C(11)–C(12)	1.383(5)	O(2)–C(5)	1.452(5)
C(12)–C(13)	1.510(5)	O(3)–C(3)	1.360(5)
C(13)–C(14)	1.541(5)	O(3)–C(26)	1.427(7)

TABLE 4

Valency angles (°)

C(2)–C(1)–C(11)	121.7(4)	C(5)–C(13)–C(12)	96.1(3)
C(1)–C(2)–C(3)	121.8(4)	C(5)–C(13)–C(14)	118.9(3)
C(2)–C(3)–C(4)	115.4(4)	C(5)–C(13)–C(15)	111.9(3)
C(2)–C(3)–O(3)	125.8(4)	C(12)–C(13)–C(14)	110.9(3)
C(4)–C(3)–O(3)	118.9(4)	C(12)–C(13)–C(15)	107.6(3)
C(3)–C(4)–C(12)	122.4(4)	C(14)–C(13)–C(15)	110.1(3)
C(3)–C(4)–O(2)	126 5(4)	C(8)–C(14)–C(9)	112.3(3)
C(12)–C(4)–O(2)	111.1(3)	C(8)–C(14)–C(13)	111.2(3)
O(2)–C(5)–C(6)	108.7(3)	C(8)–C(14)–C(21)	107.2(3)
O(2)–C(5)–C(13)	105.3(3)	C(9)–C(14)–C(13)	104.1(3)
C(6)–C(5)–C(13)	111.7(3)	C(9)–C(14)–C(21)	109.1(3)
C(5)–C(6)–C(7)	115 9(3)	C(13)–C(14)–C(21)	112.9(3)
C(5)–C(6)–O(1)	120.6(4)	C(13)–C(15)–C(16)	109.8(4)
C(7)–C(6)–O(1)	123.5(4)	C(15)–C(16)–N	112.0(4)
C(6)–C(7)–C(8)	112.6(3)	C(14)–C(17)–C(20)	112.2(3)
C(7)–C(8)–C(14)	110.4(3)	C(8)–C(18)–C(19)	122.2(4)
C(7)–C(8)–C(18)	109.4(3)	C(8)–C(18)–C(23)	114.5(3)
C(14)–C(8)–C(18)	113.5(3)	C(19)–C(18)–C(23)	123.3(4)
N–C(9)–C(10)	115.1(3)	C(20)–C(19)–C(18)	121.8(4)
N–C(9)–C(14)	107.1(3)	C(20)–C(19)–C(25)	115.1(4)
C(10)–C(9)–C(14)	114.1(3)	C(18)–C(19)–C(25)	123.2(4)
C(9)–C(10)–C(11)	114.4(3)	C(21)–C(20)–C(19)	115.7(4)
C(10)–C(11)–C(12)	117.1(3)	C(18)–C(23)–C(24)	112.8(4)
C(10)–C(11)–C(1)	127.4(4)	C(9)–N–C(16)	113.8(3)
C(1)–C(11)–C(12)	115.4(4)	C(9)–N–C(22)	114.1(3)
C(4)–C(12)–C(11)	123.2(3)	C(16)–N–C(22)	111.1(3)
C(4)–C(12)–C(13)	109.7(3)	C(4)–O(2)–C(5)	103.2(3)
C(11)–C(12)–C(13)	127.1(3)	C(3)–O(3)–C(26)	117.8(4)

TABLE 5

Torsion angles (°) in rings A–E of morphine-like alkaloids

	Alkaloid						
	(XI)	(XII)	(XIII)	(XIV)	(XV)	(XVI)	(XVII)
Ring A							
1–2	−2	−1	−1	*	−2	−3	−7
2–3	2	−1	2	*	3	4	5
3–4	1	4	0	*	1	1	5
4–12	−3	−7	−3	*	−5	−6	−14
11–12	3	5	4	5	6	7	12
11–1	−1	−1	−2	−1	−2	−2	−2
Ring B							
4–12	−5	−4	−5	−2	−2	−3	−3
4–0	−19	−18	−17	−13	−13	−11	−19
0–5	36	31	31	21	21	20	35
5–13	−37	−31	−33	−22	−21	−21	−33
12–13	25	21	23	15	14	15	21
Ring C							
9–10	41	33	36	26	31	29	40
10–11	−10	−4	−5	3	0	0	−11
11–12	6	4	3	3	2	4	9
12–13	−31	−33	−29	−36	−33	−34	−34
13–14	55	56	54	58	61	58	57
9–14	−62	−60	−61	−58	−63	−60	−65
Ring D							
5–6	41	31	44	−29	−29	−30	†
6–7	−54	−48	−61	41	42	41	†
7–8	59	61	54	−4	−5	−3	†
8–14	−52	−59	−42	−41	−39	−40	†
14–13	44	44	38	50	47	48	†
13–5	−37	−29	−34	−16	−13	−13	†
Ring E							
N–9	−64	−63	−63	−65	−64	−64	−60
9–14	66	65	67	66	65	65	60
14–13	−64	−65	−66	−64	−61	−62	−61
13–15	57	58	57	58	54	55	59
15–16	−49	−52	−51	−53	−52	−52	−52
16–N	55	57	56	58	57	57	55

(XI), 8,14-(1-Ethyl-2-methylbut-1-eno)codeinone; (XII), naloxone hydrochloride dihydrate;[9] (XIII), 6-deoxy-6-azidodihydroisomorphine;[10] (XIV), morphine hydrochloride trihydrate;[6] (XV), morphine hydrate;[7] (XVI), codeine hydrobromide dihydrate;[8] (XVII), phototheba inehydroquinone hydrobomide.[11]

* The co-ordinates published for C(3) in compound (XIV) are in error and torsion angles involving this atom are consequently not available. † Ring D in (XVII) is not six-membered.

formation in which torsion angles range from *ca.* 30—60°, with the smallest angle associated with C(5)–C(13). The five-membered ring B adopts a C(5)-envelope conformation in all the alkaloids and the torsion angles indicate that the ring is flatter in the alkaloids that have a ring D boat conformation. The torsion angles of the aromatic ring A differ by a few degrees from the ideal value of 0° appropriate to planar geometry. Since there is a common pattern to the signs of the ring A torsion angles of the various alkaloids in Table 5, the small departures from planarity must be regarded as firmly established molecular features. Ring E in these alkaloids is consistently a slightly distorted chair with minimum torsion angle (mean 52°) about C(15)–C(16) and maximum torsion angle (mean 65°) about C(9)–C(14); protonation of the nitrogen atom has no significant effect on the torsion angles in this ring. Ring C is closer to a C(14)-envelope (C_s) form than a half-chair (C_2) form in all these alkaloids. The cyclohexene ring F in 8,14-(1-ethyl-2-methylbut-1-eno)codeinone also departs ap-

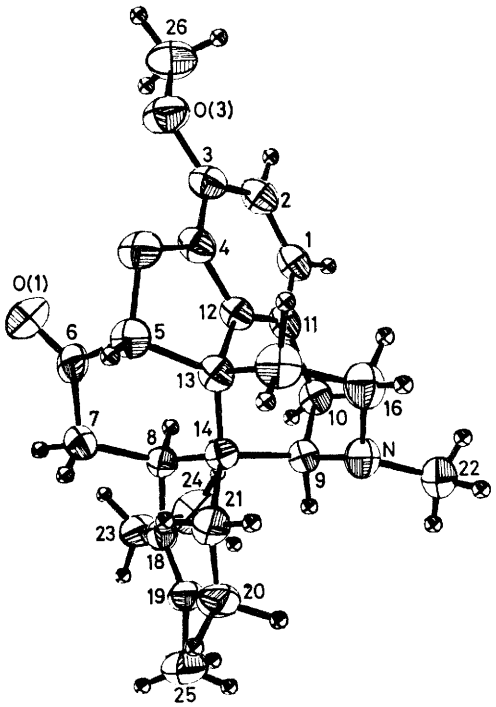
TABLE 6

Torsion angles (°) *

C(2)–C(1)–C(11)–C(10)	177	N–C(9)–C(14)–C(21)	−55
C(1)–C(2)–C(3)–O(3)	−178	C(10)–C(9)–N–C(16)	64
C(2)–C(3)–O(3)–C(26)	8	C(10)–C(9)–N–C(22)	−65
C(4)–C(3)–O(3)–C(26)	−171	C(14)–C(9)–N–C(22)	167
C(2)–C(3)–C(4)–O(2)	−178	C(9)–C(10)–C(11)–C(1)	173
O(3)–C(3)–C(4)–O(2)	2	C(1)–C(11)–C(12)–C(13)	−176
O(3)–C(3)–C(4)–C(12)	180	C(10)–C(11)–C(12)–C(4)	−174
C(3)–C(4)–O(2)–C(5)	159	C(4)–C(12)–C(13)–C(14)	149
C(3)–C(4)–C(12)–C(13)	176	C(4)–C(12)–C(13)–C(15)	−90
O(2)–C(4)–C(12)–C(11)	175	C(11)–C(12)–C(13)–C(5)	−155
O(2)–C(5)–C(6)–O(1)	−21	C(11)–C(12)–C(13)–C(15)	89
O(2)–C(5)–C(6)–C(7)	157	C(5)–C(13)–C(14)–C(9)	165
C(13)–C(5)–C(6)–O(1)	−137	C(5)–C(13)–C(14)–C(21)	−77
O(2)–C(5)–C(13)–C(14)	−154	C(12)–C(13)–C(14)–C(8)	−66
O(2)–C(5)–C(13)–C(15)	75	C(12)–C(13)–C(14)–C(21)	173
C(6)–C(5)–C(13)–C(12)	81	C(15)–C(13)–C(14)–C(8)	175
C(6)–C(5)–C(13)–C(15)	−167	C(15)–C(13)–C(14)–C(21)	54
C(6)–C(5)–O(2)–C(4)	−84	C(5)–C(13)–C(15)–C(16)	−169
O(1)–C(6)–C(7)–C(8)	124	C(12)–C(13)–C(15)–C(16)	−64
C(6)–C(7)–C(8)–C(18)	−176	C(8)–C(14)–C(21)–C(20)	58
C(7)–C(8)–C(14)–C(9)	−168	C(9)–C(14)–C(21)–C(20)	−64
C(7)–C(8)–C(14)–C(21)	72	C(13)–C(14)–C(21)–C(20)	−179
C(18)–C(8)–C(14)–C(9)	69	C(15)–C(16)–N–C(22)	−174
C(18)–C(8)–C(14)–C(13)	−175	C(8)–C(18)–C(23)–C(24)	84
C(18)–C(8)–C(14)–C(21)	−51	C(19)–C(18)–C(23)–C(24)	−93
C(7)–C(8)–C(18)–C(19)	−100	C(20)–C(19)–C(18)–C(8)	−1
C(7)–C(8)–C(18)–C(23)	83	C(20)–C(19)–C(18)–C(23)	177
C(14)–C(8)–C(18)–C(19)	24	C(25)–C(19)–C(18)–C(8)	180
C(14)–C(8)–C(18)–C(23)	−153	C(25)–C(19)–C(18)–C(23)	−3
N–C(9)–C(10)–C(11)	−84	C(21)–C(20)–C(19)–C(25)	−173
C(10)–C(9)–C(14)–C(8)	58	C(21)–C(20)–C(19)–C(18)	7
C(10)–C(9)–C(14)–C(21)	177	C(14)–C(21)–C(20)–C(19)	−37
N–C(9)–C(14)–C(8)	−173		

* The sign of the torsion angle is positive if a clockwise rotation is required of atom (1) to eclipse atom (4) whilst looking along the (2)–(3) bond. Mean standard deviation of torsion angles is 0.6°.

preciably from a half-chair form and approximates to an envelope form in which C(14) constitutes the out-of-plane atom.



Molecular structure of (II; R^1 = Me, R^2 = Et)

EXPERIMENTAL

Crystal Data.—8,14-(1-Ethyl-2-methylbut-1-ene)codeinone, $C_{25}H_{31}NO_3$, M = 393.5. Monoclinic, a = 12.847(1), b = 7.942(1), c = 10.708(1) Å, β = 109.99(6)°, U = 1 026.7 Å^3, D_m = 1.31, Z = 2, D_c = 1.30 g cm^{-3}, $F(000)$ = 424. Space group $P2_1(C2)$. Mo-K_α radiation, λ = 0.710 69 Å; μ(Mo-K_α) = 0.89 cm^{-1}.

Crystallographic Measurements.—Final values of the cell dimensions were determined by least-square analysis of angular settings, measured on a Hilger and Watts computer-controlled diffractometer. Intensities were measured by the θ–ω step-scan procedure and 1 796 independent reflections having $I > 3\sigma(I)$ were obtained.

Structure Analysis.—The crystal structure was elucidated by direct phasing procedures from the '*X*-Ray '72' suite of programs. Σ_2 Relationships were generated for 292 reflections with $|E| \geqslant 1.30$. The initial set of phases comprised three to define the origin, one to define the enantiomorph, and two to which values of $\pm\pi/4$, $\pm 3\pi/4$ were given. This procedure yielded 16 sets of phases, characterised by R_K 0.16—0.31, and an E map calculated for the phases with the lowest value of R_K yielded positions for all the carbon, nitrogen, and oxygen atoms. After four cycles of least-squares adjustment of these atoms (R 0.11), a difference electron-density distribution disclosed the hydrogen atom positions and subsequent least-squares refinement, with anisotropic thermal parameters for the carbon, nitrogen, and oxygen atoms, and isotropic thermal parameters for the hydrogen atoms, converged to R 0.048. The weighting scheme adopted in the closing stages of the calculations was $w^{1/2} = A/|F_o|$, with A 16.0.

Observed and calculated structure amplitudes, thermal parameters of the atoms, and the initial set of phases are included in Supplementary Publication No. SUP 22412 (16 pp.).*

M.p.s are uncorrected. N.m.r. spectra were determined on a Varian Associates T60 spectrometer with tetramethylsilane as internal standard. For solvent mixtures, percentages are quoted on a v/v basis. *m*-Chloroperbenzoic acid was a commercial grade (80—84% peroxyacid).

8,14-(1-Ethyl-2-methylbut-1-eno)codeinone N-Oxide (VI) *and Hydrochloride.*—To a solution of 8,14-(1-ethyl-2-methylbut-1-eno)codeinone [3] (3.0 g) in dry chloroform (250 ml) at 0 °C was added *m*-chloroperbenzoic acid (1.8 g) during 0.5 h. After a further 2 h the solution was washed with 10% sodium sulphite solution, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was chromatographed on grade III neutral alumina (100 g). Elution with 25% benzene in chloroform gave the *codeinone N-oxide* (VI) (2.82 g) as a solid. Recrystallisation from aqueous ethanol gave a sample (2.10 g, 60%), m.p. 162—163°, $\nu_{max.}$($CHBr_3$) 3 300 (H_2O), 1 725, and 950 cm^{-1}, δ($CDCl_3$) 0.85 (3 H, t, J 7 Hz, Me). 1.64 (3 H, s, Me), 3.34 (3 H, s, NMe), 3.93 (3 H, s, OMe), 4.65 (1 H, s, 5-H), and 6.74 (2 H, s, ArH) (Found: C, 67.9; H, 7.6; N, 3.4. $C_{25}H_{31}NO_4,2H_2O$ requires C, 67.4; H, 7.9; N, 3.1%).

The *hydrochloride salt* formed crystals from aqueous ethanol, m.p. >220° (decomp.), $\nu_{max.}$($CHBr_3$) 2 500 and 1 725 cm^{-1}, δ[$CDCl_3$–$(CD_3)_2SO$] 0.80 (3 H, t, J 7 Hz, Me), 1.60 (3 H, s, Me), 3.17 (3 H, s, NMe), 3.81 (3 H, s, OMe), 4.87 (1 H, s, 5-H), and 6.80 (2 H, s, ArH) (Found: C, 67.1;

* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1978, Index issue.

H, 7.15; Cl, 7.75; N, 3.0. $C_{25}H_{31}NO_4$,HCl requires C, 67.3; H, 7.2; Cl, 7.95; N, 3.1%).

8,14-(1,2-*Epoxy*-1-*ethyl*-2-*methylbutano*)*codeinone* (VIII).—(a) N-*Oxide epoxide* (VII). An ice-cooled solution of *m*-chloroperbenzoic acid (7.54 g) in dichloromethane (250 ml) was added to a similarly cooled solution of 8,14-(1-ethyl-2-methylbut-1-eno)codeinone (5 g) in dichloromethane (50 ml). After four days at room temperature the solvent was removed *in vacuo* and the residue chromatographed on alumina (200 g) with 33% chloroform in benzene. Crystallisation of the appropriate fraction from ethyl acetate gave the *N*-oxide epoxide (VII) (0.57 g, 10.5%), m.p. 177—178°, δ($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, Me), 1.40 (3 H, s, Me), 3.40 (3 H, s, NMe), 3.93 (3 H, s, OMe), 4.60 (1 H, s, 5-H), and 6.77 (2 H, ABq, *J* 8.5 Hz, ArH), *m/e* 425 (M^+) and 409 (100%). A further crop of similar amount and quality was obtained by concentration of the crystallisation liquors.

(b) *Epoxide* (VIII). A solution of 8,14-(1-ethyl-2-methylbut-1-eno)codeinone (10 g) and *m*-chloroperbenzoic acid (15.1 g) in dichloromethane (600 ml) was kept at room temperature for three days; SO_2 was then bubbled through the solution for 2 h. The resulting solution was washed with aqueous sodium hydrogencarbonate and water, dried, and evaporated *in vacuo*. Crystallisation of the residue from methanol gave the crude product (3.6 g, 34.6%), a portion of which was chromatographed on grade III alumina with toluene and further crystallised from methanol to provide the *epoxide* (VIII), m.p. 214—220°, δ($CDCl_3$) 0.9 (3 H, t, *J* 7 Hz, Me), 1.35 (3 H, s, Me), 2.33 (3 H, s, NMe), 3.90 (3 H, s, OMe), 4.50 (1 H, s, 5-H), and 6.72 (2 H, ABq, *J* 8.5 Hz, ArH) (Found: C, 73.1; H, 7.7; N, 3.5. $C_{25}H_{31}NO_4$ requires C, 73.3; H, 7.6; N, 3.4%).

TABLE 7

Comparison of chemical shifts for compound (II; R^1 = Me, R^2 = Et) and derivatives (solvent $CDCl_3$)

	Chemical shift δ			
Proton(s)	(II)	(VI)	(VII)	(VIII)
5-H	4.53	4.65	4.60	4.50
NMe	2.35	3.34	3.40	2.33
19-Me	1.63	1.64	1.40	1.35

6,6-*Ethylenedioxy*-8,14-(1-*ethyl*-2-*methylbut*-1-*eno*)*codeine* (IX; R^1 = Me, R^2 = Et).—8,14-(1-Ethyl-2-methylbut-1-eno)codeinone (250 mg) was heated under reflux in benzene (5 ml) with toluene-*p*-sulphonic acid (25 mg) and ethylene glycol (0.5 ml) for 24 h. The water formed during the reaction was removed by means of a Dean and Stark trap. The benzene solution was washed with saturated sodium hydrogencarbonate solution, dried (Na_2SO_4), and the solvent removed *in vacuo* to give a gum. The gum was fractionated by preparative t.l.c. on alumina with chloroform; 'crystallisation' of the appropriate fraction from ethanol gave an amorphous solid, the *acetal* (IX; R^1 = Me, R^2 = Et) (50 mg, 18%), m.p. 153—157°, δ($CDCl_3$) 0.86 (3 H, t, *J* 7 Hz, Me), 1.60 (3 H, s, Me), 2.33 (3 H, s, NMe), 3.87 (3 H, s, OMe), 3.97 (4 H, m, OCH_2CH_2O), 4.47 (1 H, s, 5-H), and 6.70 (2 H, ABq, *J* 8 Hz, ArH) (Found: C, 74.0; H, 8.25; N, 3.5. $C_{27}H_{35}NO_4$ requires C, 74.1; H, 8.1; N, 3.2%).

The other acetals of Table 1 were prepared similarly from the corresponding ketones.[1]

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