bonds are equivalent. Table 6 lists pertinent torsion angles for the three molecules. The cyclobutyl ring in (II) is planar. The six-membered rings (including substituents) are essentially planar (to within 0·25 Å) and parallel to one another. There is an approximate (non-crystallographic) center of symmetry at the middle of the cyclobutyl ring. In (III) the four-membered ring is twisted and the six-membered rings also show significant deviation from planarity. The cis–syn dimers are not as stable as the trans–anti dimers and evidence has been found for monomerization of these dimers under prolonged exposure to X-rays during data collection (Karle, 1976). Some deterioration of (III) was noted during data collection; however, no evidence of a coexisting monomer was found. The crystal of (I) used in this study was a very weak scatterer and refinement of the resultant data set gave fairly high e.s.d.'s (on the order of 0·02 Å for bonds and 1·3° for angles). However, the X-ray results do indicate that the molecule is under considerable strain. The double bond formed by the loss of HF across the C(6')–C(5') bond is delocalized over the C(6)–C(5')–C(6')–N(1') system. The strain on the four-membered ring is clearly evidenced by the long C(5)–C(6) bond [1·60 Å as opposed to 1·54 and 1·52 Å in (II) and (III)], the small internal angles at C(5) and C(6) [84·3 and 85·4° compared to 89·6 and 89·1° for (II) and 89·0 and 87·8° for (III)] and the large external angles at the non-fluorinated corners. The N(1)–C(6)–C(5') angle is 121·4°, C(6)–C(5')–C(4') is 141·9° and C(5)–C(6')–N(1') is 137·7°; values for these angles in (II) are 116·5, 113·3 and 117·0°, for equivalent angles in (III) the values are 114·8, 120·6 and 113·8°. All N atoms are methylated, precluding the formation of hydrogen bonds. In molecule (I), however, there are some short intermolecular C···O approaches [C(6')···O(2') at 2·99 Å, C(6')···O(2) at 3·12 Å, C(2')···O(2') at 3·14 Å and C(1)···O(4) at 3·13 Å]. In (II) and (III) the closest intermolecular approaches are van der Waals separations.

Table 6. Selected torsion angles (°)

	Molecule (I)	Molecule (II)	Molecule (III)
N(1)–C(2)–N(3)–C(4)	0·5	−7·5	−2·9
C(2)–N(3)–C(4)–C(5)	−6·5	20·1	12·5
N(3)–C(4)–C(5)–C(6)	2·4	−13·1	−23·6
C(4)–C(5)–C(6)–N(1)	6·6	−4·2	24·3
C(5)–C(6)–N(1)–C(2)	−14·1	18·1	−15·4
C(6)–N(1)–C(2)–N(3)	11·0	−13·3	4·8
N(1')–C(2')–N(3')–C(4')	−6·2	7·8	6·4
C(2')–N(3')–C(4')–C(5')	4·9	−18·7	−8·4
N(3')–C(4')–C(5')–C(6')	0·4	12·7	−7·8
C(4')–C(5')–C(6')–N(1')	−3·6	2·0	25·2
C(5')–C(6')–N(1')–C(2')	2·3	−14·1	−29·1
C(6')–N(1')–C(2')–N(3')	2·0	10·2	13·5
C(5)–C(6')–C(5')–C(6)	5·8	−1·2	
C(6')–C(5')–C(6)–C(5)	−5·8	1·2	
C(5')–C(6)–C(5)–C(6')	4·8	−1·1	
C(6)–C(5)–C(6')–C(5')	−5·3	1·2	
C(5)–C(5')–C(6')–C(6)			17·2
C(5')–C(6')–C(6)–C(5)			−17·8
C(6')–C(6)–C(5)–C(5')			17·0
C(6)–C(5)–C(5')–C(6')			−18·0
C(4)–C(5)–C(6')–N(1')	−53·4	121·7	
C(4')–C(5')–C(6)–N(1)	57·4	−119·4	
C(4)–C(5)–C(5')–C(4')			−23·6
N(1)–C(6)–C(6')–N(1)			−25·0
Avg. s.d.	1·6	0·5	0·5

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6,7-Dimethoxy-3-(5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-g]isoquinolin-5-yl)-1(3H)-isobenzofuranone [(−)-α-Narcotine], C22H23NO7, a Structural Analogue of GABA

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Abstract. $M_r = 413·43$, orthorhombic, $P2_12_12_1$, $a = 15·295$ (9), $b = 32·593$ (20), $c = 7·945$ (5) Å, $V = 3960·7$ Å^3, $Z = 8$, D_m(flotation) = 1·38, $D_x = 1·386$ g cm^{-3}, Cu $K\alpha$ radiation, $\lambda = 1·5418$ Å, $\mu = 9·99$ cm^{-1}, $F(000) = 1744$, $T = 298$ K, $R = 0·078$ for 4166 reflections. Each of the two molecules in the

asymmetric unit consists of two planar moieties inclined at a dihedral angle of approximately 50°. The tetrahydropyridine rings are approximately in the sofa conformation. The bond joining the two moieties is axial with respect to the tetrahydropyridine ring. The N—methyl bond is equatorial.

Introduction. Narcotine is a naturally occurring phthalide isoquinoline alkaloid closely related to bicuculline, a selective antagonist of γ-aminobutyric acid (GABA) which is an inhibitory neurotransmitter in the central nervous system. The crystal structure of bicuculline has previously been determined (Gorinsky & Moss, 1973).

Experimental. Material supplied by Dr C. Gorinsky. Crystal $\sim 0.4 \times 0.2 \times 0.2$ mm. Hilger & Watts Y290 four-circle automatic diffractometer, Cu $K\alpha$ radiation. $\omega/2\theta$ scan technique, scan speed $0.01°$ s^{-1}. 2 standard reflections, variation $< \sim 8\%$. Of 4166 independent reflections measured in the range $0 < \theta < 70°$, 3887 had nett intensities greater than $3.0\sigma(I)$, where $\sigma(I)$ is the standard deviation from counting statistics, and were regarded as observed. No absorption correction. Unit-cell parameters refined by least-squares techniques using the 2θ angles measured on the diffractometer from 22 reflections. Positions of the non-hydrogen atoms determined by direct methods (*MULTAN*, Main, Woolfson, Lessinger, Germain & Declercq, 1974) and refined by full-matrix least-squares techniques using a modified version of the program originally written by Cruickshank & Smith (1964). In the first stage of the *MULTAN* program known as *NORMAL* the E values were calculated using a Debye curve. In this technique, instead of assuming random atomic positions as would be done for a Wilson curve, certain rigid groups of atoms are assumed to be present. Two rigid groups were assumed, a 10-atom fragment and a 14-atom fragment. The reflections chosen to fix the origin and enantiomorph were 1,29,0 (90°), 0,25,2 (90°) and 11,9,3 (45°). A difference Fourier synthesis phased on the structural parameters obtained from least-squares refinement revealed 40 of the 46 H atoms and they were in accordance with calculated positions (C—H = 1.0 Å). At this stage it was noticed that the assigned values of x, y, z gave the opposite hand to the already known absolute configuration (Battersby & Spencer, 1965) and so the signs of all the x coordinates were reversed to ensure conformity with their findings. Final refinement carried out by varying an overall scale factor, atomic coordinates and anisotropic thermal parameters for the non-hydrogen atoms; positional parameters of H atoms were fixed at calculated positions and they were assigned isotropic temperature factors of 0.01 Å^2. Final mean $\Delta/\sigma = 0.866$ for positional parameters and 0.886 for thermal parameters. $\sum w(|F_o| - |F_c|)^2$ minimized, where the weight applied to each observation was $w = [1 - \exp(-20\sin^2\theta/\lambda^2)]/(20 + |F_o| + 0.01|F_o|^2)$. $\Delta\rho_{max} \sim |0.4|$ e Å^{-3}. Final conventional $R = 0.078$ ($R_w = 0.111$). No correction for secondary extinction. Atomic scattering factors from *International Tables for X-ray Crystallography* (1968).

Table 1. *Fractional coordinates and equivalent isotropic thermal parameters*

$$U_{eq} = \tfrac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i\cdot\mathbf{a}_j.$$

	x	y	z	$U_{eq}(\text{Å}^2)$
Molecule (1)				
C(1)	0.8251 (3)	0.8380 (1)	0.5535 (6)	0.031
C(1A)	0.7309 (3)	0.8309 (1)	0.5035 (6)	0.030
N(2)	0.8701 (3)	0.8714 (1)	0.4622 (6)	0.050
C(3)	0.8264 (4)	0.8856 (2)	0.3099 (7)	0.048
C(4)	0.7314 (4)	0.8973 (2)	0.3495 (7)	0.045
C(4A)	0.6837 (3)	0.8611 (1)	0.4150 (6)	0.033
C(5)	0.5953 (4)	0.8556 (1)	0.3823 (8)	0.044
C(5A)	0.5568 (3)	0.8206 (2)	0.4368 (8)	0.045
O(6)	0.4708 (3)	0.8095 (2)	0.4201 (8)	0.066
C(7)	0.4653 (4)	0.7690 (2)	0.4775 (11)	0.064
O(8)	0.5464 (3)	0.7578 (1)	0.5595 (7)	0.062
C(8A)	0.6020 (3)	0.7898 (1)	0.5214 (6)	0.037
C(9)	0.6905 (3)	0.7940 (1)	0.5529 (6)	0.033
O(9A)	0.7405 (3)	0.7666 (10)	0.6403 (6)	0.052
C(10)	0.9619 (4)	0.8611 (2)	0.4220 (10)	0.064
C(11)	0.7192 (5)	0.7256 (2)	0.6351 (9)	0.060
C(1')	0.8276 (3)	0.8465 (1)	0.7433 (6)	0.032
C(1'A)	0.7863 (3)	0.8852 (1)	0.8045 (5)	0.027
O(2')	0.9179 (2)	0.8501 (1)	0.7987 (5)	0.039
C(3')	0.9332 (3)	0.8868 (2)	0.8749 (7)	0.039
C(3'A)	0.8500 (2)	0.9099 (1)	0.8811 (6)	0.032
O(3'B)	1.0038 (2)	0.8955 (1)	0.9274 (7)	0.064
C(4')	0.8313 (3)	0.9473 (1)	0.9500 (6)	0.036
O(4'A)	0.8935 (2)	0.9693 (1)	1.0350 (5)	0.045
C(5')	0.7444 (3)	0.9611 (1)	0.9463 (6)	0.036
O(5'A)	0.7285 (2)	0.9979 (1)	1.0198 (6)	0.049
C(6')	0.6803 (3)	0.9361 (1)	0.8711 (6)	0.038
C(7')	0.7002 (3)	0.8981 (1)	0.8014 (6)	0.035
C(8')	0.9233 (4)	1.0048 (2)	0.9526 (11)	0.071
C(9')	0.6436 (4)	1.0139 (2)	0.9971 (8)	0.050
Molecule (2)				
C(1)	0.3606 (3)	0.8475 (1)	0.8433 (6)	0.036
C(1A)	0.2848 (3)	0.8175 (1)	0.8317 (6)	0.032
N(2)	0.3473 (3)	0.8867 (1)	0.7536 (5)	0.048
C(3)	0.2770 (4)	0.8858 (2)	0.6275 (9)	0.061
C(4)	0.1915 (3)	0.8723 (2)	0.7077 (8)	0.049
C(4A)	0.2022 (3)	0.8300 (1)	0.7794 (6)	0.031
C(5)	0.1304 (3)	0.8038 (1)	0.7941 (7)	0.041
C(5A)	0.1454 (3)	0.7655 (1)	0.8570 (6)	0.038
O(6)	0.0845 (2)	0.7346 (1)	0.8790 (6)	0.051
C(7)	0.1307 (4)	0.7038 (2)	0.9734 (8)	0.056
O(8)	0.2217 (2)	0.7115 (1)	0.9497 (6)	0.050
C(8A)	0.2276 (3)	0.7515 (1)	0.9008 (6)	0.041
C(9)	0.2985 (3)	0.7771 (1)	0.8884 (7)	0.039
O(9A)	0.3827 (2)	0.7670 (1)	0.9247 (7)	0.061
C(10)	0.4290 (4)	0.9029 (2)	0.6761 (9)	0.069
C(11)	0.4085 (4)	0.7273 (2)	0.9278 (16)	0.085
C(1')	0.3761 (3)	0.8564 (1)	1.0315 (6)	0.035
C(1'A)	0.3083 (3)	0.8833 (1)	1.1146 (5)	0.031
O(2')	0.4566 (2)	0.8795 (1)	1.0505 (5)	0.036
C(3')	0.4417 (3)	0.9163 (1)	1.1220 (7)	0.038
C(3'A)	0.3486 (3)	0.9192 (1)	1.1657 (6)	0.032
O(3'B)	0.5008 (2)	0.9401 (1)	1.1422 (6)	0.054
C(4')	0.3053 (3)	0.9507 (1)	1.2429 (7)	0.044
O(4'A)	0.3512 (4)	0.9831 (2)	1.2988 (12)	0.117
C(5')	0.2125 (3)	0.9461 (1)	1.2633 (7)	0.044
O(5'A)	0.1700 (3)	0.9776 (2)	1.3363 (9)	0.078
C(6')	0.1743 (3)	0.9102 (2)	1.2129 (7)	0.044
C(7')	0.2203 (3)	0.8778 (2)	1.1407 (7)	0.043
C(8')	0.3283 (6)	1.0187 (3)	1.3401 (21)	0.118
C(9')	0.0789 (5)	0.9753 (3)	1.3621 (16)	0.097

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

|	Molecule (1)	Molecule (2)		Molecule (1)	Molecule (2)		Molecule (1)	Molecule (2)
C(1)–N(2)	1·479 (6)	1·477 (6)	C(7)–O(8)	1·447 (8)	1·426 (7)	C(3'A)–C(1'A)	1·405 (4)	1·383 (5)
C(1)–C(1A)	1·512 (5)	1·520 (6)	O(8)–C(8A)	1·379 (6)	1·361 (5)	C(1'A)–C(1')	1·493 (6)	1·510 (6)
N(2)–C(10)	1·478 (6)	1·489 (6)	C(8A)–C(9)	1·383 (6)	1·375 (6)	C(3'A)–C(4')	1·367 (6)	1·368 (6)
N(2)–C(3)	1·457 (7)	1·471 (8)	C(9)–C(1A)	1·410 (6)	1·403 (4)	C(4')–C(5')	1·403 (7)	1·436 (7)
C(3)–C(4)	1·535 (8)	1·519 (8)	C(9)–O(9A)	1·365 (6)	1·361 (6)	C(4')–O(4'A)	1·369 (5)	1·342 (6)
C(4)–C(4A)	1·480 (7)	1·500 (6)	O(9A)–C(11)	1·376 (6)	1·353 (6)	O(4'A)–C(8')	1·408 (7)	1·256 (9)
C(4A)–C(1A)	1·408 (6)	1·392 (6)	C(1)–C(1')	1·534 (7)	1·532 (5)	C(5')–C(6')	1·407 (6)	1·370 (7)
C(4A)–C(5)	1·389 (7)	1·396 (6)	C(1')–O(2')	1·455 (5)	1·450 (5)	C(5')–O(5'A)	1·356 (6)	1·347 (7)
C(5)–C(5A)	1·354 (6)	1·364 (7)	O(2')–C(3')	1·362 (5)	1·347 (5)	O(5'A)–C(9')	1·411 (7)	1·410 (8)
C(5A)–C(8A)	1·392 (7)	1·382 (5)	C(3')–O(3'B)	1·191 (6)	1·205 (5)	C(6')–C(7')	1·390 (6)	1·390 (7)
C(5A)–O(6)	1·371 (6)	1·384 (6)	C(3')–C(3'A)	1·480 (6)	1·470 (6)	C(7')–C(1'A)	1·386 (4)	1·374 (6)
O(6)–C(7)	1·398 (9)	1·438 (7)						
N(2)–C(1)–C(1A)	115·4 (4)	115·0 (4)	C(7)–O(8)–C(8A)	103·9 (4)	105·7 (4)	C(1'A)–C(3'A)–C(4')	123·1 (2)	123·5 (4)
N(2)–C(1)–C(1')	109·8 (4)	108·9 (3)	C(8A)–C(9)–C(1A)	117·5 (4)	118·4 (4)	C(3'A)–C(4')–O(4'A)	121·3 (4)	119·0 (5)
C(1A)–C(1)–C(1')	108·1 (4)	107·5 (3)	C(8A)–C(9)–O(9A)	125·2 (4)	125·6 (4)	C(3'A)–C(4')–C(5')	118·4 (4)	116·8 (4)
C(1)–N(2)–C(10)	112·4 (5)	113·0 (3)	C(1A)–C(9)–O(9A)	117·0 (4)	116·0 (4)	C(5')–C(4')–O(4'A)	120·0 (4)	124·2 (5)
C(3)–N(2)–C(10)	109·2 (5)	109·7 (4)	C(9)–O(9A)–C(11)	119·2 (4)	120·9 (4)	C(4')–O(4'A)–C(8')	115·3 (4)	131·8 (7)
C(3)–N(2)–C(1)	115·3 (4)	114·4 (4)	C(9)–C(1A)–C(1)	118·4 (4)	118·1 (3)	C(4')–C(5')–O(5'A)	116·5 (4)	116·5 (4)
N(2)–C(3)–C(4)	110·1 (4)	110·5 (5)	C(9)–C(1A)–C(4A)	120·8 (4)	120·3 (3)	C(4')–C(5')–C(6')	118·9 (4)	118·6 (4)
C(3)–C(4)–C(4A)	109·9 (4)	109·3 (4)	C(1)–C(1A)–C(4A)	120·8 (4)	121·5 (4)	C(6')–C(5')–O(5'A)	124·7 (4)	124·9 (5)
C(4)–C(4A)–C(5)	121·1 (4)	120·5 (4)	C(1)–C(1')–O(2')	109·7 (4)	109·3 (3)	C(5')–O(5'A)–C(9')	115·9 (4)	119·8 (6)
C(4)–C(4A)–C(1A)	118·7 (4)	118·9 (4)	C(1)–C(1')–C(1'A)	117·4 (4)	115·4 (3)	C(5')–C(6')–C(7')	122·2 (4)	123·6 (4)
C(1A)–C(4A)–C(5)	120·1 (4)	120·6 (4)	C(1'A)–C(1')–O(2')	103·6 (3)	103·7 (3)	C(6')–C(7')–C(1'A)	118·2 (4)	117·4 (4)
C(4A)–C(5)–C(5A)	118·2 (4)	117·2 (4)	C(1')–O(2')–C(3')	111·7 (3)	111·3 (3)	C(7')–C(1'A)–C(3'A)	119·7 (2)	120·1 (4)
C(5)–C(5A)–C(8A)	123·0 (5)	123·6 (4)	O(2')–C(3')–O(3'B)	121·6 (4)	120·3 (4)	C(7')–C(1'A)–C(1')	130·9 (2)	131·6 (4)
C(5)–C(5A)–O(6)	127·6 (5)	126·9 (4)	O(2')–C(3')–C(3'A)	108·5 (3)	108·6 (3)	C(3'A)–C(1'A)–C(1')	109·4 (2)	108·3 (3)
C(8A)–C(5A)–O(6)	109·4 (5)	109·5 (4)	C(3'A)–C(3')–O(3'B)	129·9 (4)	131·1 (4)	O(8)–C(8A)–C(9)	129·6 (5)	131·0 (4)
C(5A)–O(6)–C(7)	106·0 (5)	104·1 (4)	C(3')–C(3'A)–C(1'A)	106·4 (2)	108·0 (4)	O(8)–C(8A)–C(5A)	110·1 (4)	109·2 (4)
O(6)–C(7)–O(8)	109·4 (4)	106·8 (4)	C(3')–C(3'A)–C(4')	130·5 (2)	128·5 (4)	O(9)–C(8A)–C(5A)	120·3 (4)	119·8 (4)
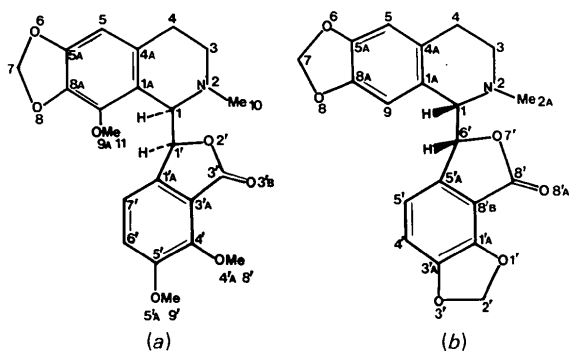
Fig. 1. Structural formulae and atom-numbering schemes for (*a*) narcotine and (*b*) bicuculline.

Discussion. The final atomic parameters are given in Table 1.*

GABA is an inhibitory neurotransmitter in the mammalian central nervous system and bicuculline is a selective antagonist of GABA. Narcotine has a very similar molecular structure to bicuculline but has the opposite absolute configuration at C(1) and C(1') and has no antagonist action on GABA. Accurate determination of the molecular conformations of GABA analogues might assist in a better understanding of the biological action of GABA and since the narcotine crystal structure was already known to contain two independent molecules per unit cell (Steward, Player &

Warner, 1973), its crystal structure determination would be doubly productive.

The bond lengths and bond angles in narcotine show no special features. They are shown together with their e.s.d.'s in Table 2. Fig. 1 shows the structural formulae of narcotine and bicuculline together with the relevant atom numbering.

It is of interest to compare the conformation of narcotine with that of bicuculline. Both molecules consist of two approximately coplanar sets of atoms with planes joined by the C(1)–C(1') (narcotine) and C(1)–C(6') (bicuculline) bonds. These planes may be defined thus:

Plane *A*: 1-1*A*-9-8*A*-8-7-6-5*A*-5-4*A*-4
Plane *B*: 1'-1'*A*-7'-6'-5'-4'-3'-3'*A*-3'*B*-2'-4'*A*-5'*A*
    (narcotine)
    1'-1'*A*-2'-3'-3'*A*-4'-5'-5'*A*-6'-7'-8'-8'*A*-8'*B*
    (bicuculline).

In bicuculline plane *A* is approximately parallel to plane *B*, there being a dihedral angle of 14° between the planes and a torsion angle N(2)–C(1)–C(6')–O(7') of 164·1°. In the case of narcotine the planes are inclined at angles of 53 (molecule 1) and 50° (molecule 2) with torsion angles N(2)–C(1)–C(1')–O(2') of −57·6 and −62·8° respectively.

The conformations of the tetrahydropyridine ring in each of the narcotine molecules are almost identical but differ considerably from bicuculline. The narcotine rings are approximately in the sofa conformation, with C(3) occupying the out-of-plane position, whereas the bicuculline ring is a half-chair.

The correct diastereoisomers of bicuculline and narcotine were first determined by proton magnetic

resonance studies (Safe & Moir, 1964). In their studies they made the following assumptions:

(i) the tetrahydroisoquinoline ring is a half-chair;

(ii) the bond joining the two planar moieties is equatorial with respect to the tetrahydroisoquinoline ring;

(iii) the H(1) and H(6′) [or H(1′)] atoms are *gauche*. For bicuculline (i) is seen to be correct while (ii) and (iii) are incorrect. For narcotine (i) and (ii) are incorrect while (iii) is correct.

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Structure of (+)-7β-Acetyl-3-methoxy-N-methyl-6,14-ethenomorphinan-4-ol, C22H27NO3

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Abstract. $M_r = 353.5$, hexagonal, $P6_1$, $a = 11.899$ (2), $c = 22.478$ (6) Å, $V = 2756.2$ Å^3, $Z = 6$, $D_x = 1.28$ Mg m^{-3}, λ(Mo $K\alpha$) = 0.71069 Å, $\mu = 0.091$ mm^{-1}, $F(000) = 1140$, $T = 293$ K, final $R = 0.033$ for 1707 observed reflections. The acetyl substitutent is in the 7β position of the 6,14-ethenomorphinan skeleton. This means that, when the epoxy ring in 4,5-epoxymorphinan-6,8-dienes has first been opened, the Diels–Alder cycloaddition with methyl vinyl ketone takes place at the other side of the molecule as compared to the addition in morphinan-6,8-dienes with a 4,5-epoxy ring. A novel class of potentially interesting 7β-substituted 6,14-etheno-morphinans becomes herewith available.

Introduction. The title compound (2) was prepared by Diels–Alder reaction of 3-methoxy-N-methyl-6,7,8,14-tetradehydromorphinan-4-ol with methyl vinyl ketone. The morphinan-6,8-diene intermediate was obtained by opening of the 4,5-epoxy ring of 6-demethoxythebaine (1) with the aid of zinc and ammonium chloride (Crabbendam, Lie, Linders & Maat, 1984). ^{1}H NMR spectra indicate the cycloaddition takes place in a different way from that observed in 4,5-epoxy-

morphinans, which yield 6,14-ethenoisomorphinans (3) (van Koningsveld, Maat & Lie, 1984). The structure of (2), however, especially the position of the etheno bridge and that of the acetyl substituent, could not be determined unambiguously from ^{1}H NMR data. Therefore, a single-crystal X-ray analysis was started, which proved the structure of (2) to be (+)-7β-acetyl-3-methoxy-N-methyl-6,14-ethenomorphinan-4-ol.