nier & Bertaud, 1974). En particulier l'angle Se–O(3)–Se′ égal à 122,4 est très proche de 119,6 (VSe_2O_6) et 121,6° ($ZnSe_2O_5$).

Bien que la coordinence trois du sélénium ait été retenue il faut noter la présence d'un quatrième atome d'oxygène à une distance de 2,831 Å du sélénium [Se–O(13)]. Cette liaison faible assure vraisemblablement la cohésion du réseau (Fig. 1).

Par application de la théorie sur le rôle stéréochimique des paires électroniques non liées, avancée par Galy, Meunier, Andersson & Åström (1975), l'environnement du sélénium peut être décrit par un tétraèdre quasi régulier; les trois atomes d'oxygène O(12), O(2) et O(3) forment la base du tétraèdre, l'atome de sélénium n'occupe pas le centre; il est situé plus près de l'apex que des sommets qui constituent la base.

A la Fig. 4 est schématisée la projection de la structure de $CuSe_2O_5$ sur le plan (010). Les paires E non liées sont pratiquement situées dans des plans parallèles au plan (100) et pointent alternativement dans des directions opposées. La distance paire–paire au sein de ces plans, calculée à partir du modèle proposé par Galy, Meunier, Andersson & Åström, est de 2,38 Å.

Les auteurs remercient les Drs Sten Andersson et Jean Galy pour les nombreuses discussions critiques et fructueuses, qu'ils ont eues avec eux. Ce travail a reçu l'aide financière du Conseil National Suédois de la Recherche Scientifique et du Centre National de la Recherche Scientifique.

Références

ÅSBRINK, S. & NORRBY, L. J. (1970). *Acta Cryst.* B**26**, 8–15.
BERTAUD, M. (1974). Thèse de Doctorat en Chimie, Univ. Bordeaux I.
GALY, J., MEUNIER, G., ANDERSSON, S. & ÅSTRÖM, A. (1975). *J. Solid State Chem.* **13**, 142–159.
HANKE, K., KUPČIK, V. & LINDQVIST, O. (1973). *Acta Cryst.* B**29**, 963–970.
HANSON, H. P., HERMAN, F., LEA, J. D. & SKILLMAN, S. (1964). *Acta Cryst.* **17**, 1040–1044.
LINDGREN, G., LINDQVIST, O. & NYBORG, J. (1970). *Acta Chem. Scand.* **24**, 732–737.
MEUNIER, G. & BERTAUD, M. (1974). *Acta Cryst.* B**30**, 2840–2843.
MEUNIER, G., BERTAUD, M. & GALY, J. (1974). *Acta Cryst.* B**30**, 2834–2839.
MEUNIER, G., BERTAUD, M. & GALY, J. (1976). A paraître.

Acta Cryst. (1976). B**32**, 2667

The Crystal and Molecular Structure of 6-Deoxy-6-azido-14-hydroxydihydroisomorphine, $C_{17}H_{20}N_4O_3$

BY ALAJOS KÁLMÁN AND ZSUZSA IGNÁTH
Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525-Budapest, P.O.B. 17, Hungary

KÁLMÁN SIMON
Chinoin Works for Pharmaceutical and Chemical Products, H-1045-Budapest IV, *Tó utca* 5, *Hungary*

AND REZSÖ BOGNÁR AND SÁNDOR MAKLEIT
Institute of Organic Chemistry, L. Kossuth University, H-4010-Debrecen, Hungary

(*Received* 12 *March* 1976; *accepted* 9 *April* 1976)

$C_{17}H_{20}N_4O_3$ (3,14β-dihydroxy-4,5α-epoxy-6β-azido-17-methylmorphinane) (14-OH-azidomorphine), monoclinic, $P2_1$, $a=7{\cdot}442$ (4), $b=13{\cdot}232$ (8), $c=7{\cdot}920$ (5) Å, $\beta=95{\cdot}41$ (10)°, $Z=2$. The structure was solved by direct methods. An R of 0·134 was obtained for 1250 observed reflexions after least-squares refinement. A comparison with the structure of azidomorphine [Sasvári, Simon, Bognár & Makleit, *Acta Cryst.* (1974), B**30**, 634–641] shows that the substitution of an OH group for the H atom on C(14) does not alter the chair conformation of rings C and D, but the orientation of the azido group is different.

Introduction

The introduction of a C(6)-azido group into dihydroisomorphine increases analgesic activity and considerably decreases tolerance capacity and dependence liability relative to morphine (Knoll, Fürst & Kelemen, 1971). It is known that the introduction of a 14-OH group into morphine decreases toxicity and, because the analgesic activity is usually increased, compounds with a better safety margin are produced (Seki, 1965). With this in mind we synthesized (Bognár, Makleit, Knoll, Berényi & Horváth, 1975; Makleit, Knoll, Bognár, Berényi, Somogyi & Kiss, 1976) 3,14β-dihydroxy-4,5α-epoxy-6β-azido-17-methylmorphinane (14-

OH-azidomorphine) and compared its pharmacological effects with the corresponding parent 14-non-substituted compound (3-hydroxy-4,5α-epoxy-6β-azido-17-methylmorphinane, *i.e.* azidomorphine). 14-Hydroxylation of azidomorphine brought about a favourable change in the pharmacological spectrum and seems to be therapeutically promising (Knoll, Fürst & Makleit, 1975).

Experimental

The colourless, transparent crystals had been obtained from a mixture of water and acetone. The lattice parameters were determined from Weissenberg and precession photographs and the density measured by flotation.

Crystal data

$C_{17}H_{20}N_4O_3$; $M=328{\cdot}38$; monoclinic; $a=7{\cdot}442$ (4), $b=13{\cdot}232$ (8), $c=7{\cdot}920$ (5) Å; $\beta=95{\cdot}41$ (10)°; $V=776{\cdot}43$ Å^3; $D_c=1{\cdot}399$, $D_m=1{\cdot}405$ g cm^{-3}; $Z=2$; $F(000)=342$; space group $P2_1$.

Intensities were collected on a Stoe semi-automatic two-circle (Weissenberg) diffractometer with Ni-filtered Cu $K\bar{\alpha}$ ($\bar{\lambda}=1{\cdot}5418$ Å) radiation. An error, revealed at the end of the measurements, in the Güttinger electronics caused increased deviations in the background intensities, which could not be corrected properly. 124 of the 1374 independent reflexions with $I-2{\cdot}5\sigma(I)<0$ were taken as unobserved with $I_o=\frac{1}{2}\sigma(I)$.

Structure determination and refinement

The phase problem for 237 reflexions with $E_{\min}=1{\cdot}30$ was solved with *MULTAN* (Main, Woolfson & Germain, 1971) applied with some local modifications on an ICL-1903A computer. An unambiguous set of phases (ABSFOM = 0·973, RESID = 37·7) could be obtained when reflexion 095 (selected from the convergence map) was added to the starting reflexions [341, 306, 45$\bar{5}$ ($\varphi=45°$), 20$\bar{4}$ and 513]. The E map computed from this set gave a model which fitted the geometry of the morphine skeleton and from which all non-hydrogen atoms could be obtained [$R=\sum||F_o|-|F_c||/\sum|F_o|=0{\cdot}28$]. Block-diagonal least-squares refinement was terminated at an R of 0·124 for the observed (0·148 for all 1374) reflexions. The H atoms (except

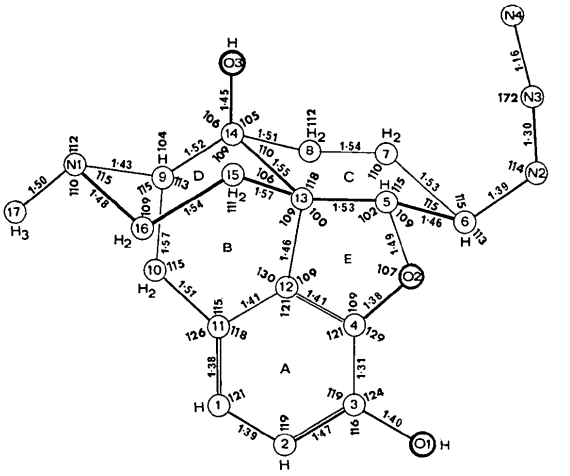

Fig. 1. Bond distances and angles with the atomic and ring numbering for the title compound. The standard deviations for the bond lengths are near 0·02 Å, and for the bond angles 1°. C(5)–C(13)–C(15) 115, C(12)–C(13)–C(14) 107, C(8)–C(14)–C(9) 114, C(13)–C(14)–O(3) 112°.

Table 1. *Fractional coordinates* ($\times 10^4$) *and anisotropic thermal parameters* ($\times 10^3$)

Estimated standard deviations are in parentheses. The anisotropic thermal parameters are in the form $\exp[-(b_{11}h^2+b_{22}k^2+b_{33}l^2+b_{12}hk+b_{13}hl+b_{23}kl)]$.

	x	y	z	b_{11}	b_{12}	b_{13}	b_{22}	b_{23}	b_{33}
C(1)	−2696 (21)	1238 (13)	4409 (18)	254 (29)	51 (31)	55 (42)	74 (9)	−29 (26)	145 (21)
C(2)	−3315 (23)	1913 (13)	3142 (21)	311 (35)	9 (32)	90 (50)	59 (9)	4 (28)	216 (27)
C(3)	−2698 (19)	1790 (12)	1442 (19)	202 (26)	96 (26)	138 (40)	66 (8)	79 (25)	192 (23)
C(4)	−1924 (18)	937 (12)	1069 (17)	178 (23)	108 (24)	161 (34)	71 (9)	43 (25)	149 (20)
C(5)	172 (23)	−127 (12)	45 (16)	279 (30)	62 (30)	33 (35)	67 (9)	5 (22)	88 (14)
C(6)	1913 (24)	374 (13)	421 (19)	276 (35)	21 (31)	194 (45)	65 (9)	52 (26)	181 (22)
C(7)	3279 (19)	−194 (12)	1630 (17)	187 (25)	−15 (26)	87 (37)	59 (8)	−7 (24)	157 (20)
C(8)	2429 (18)	−451 (12)	3278 (16)	171 (25)	16 (27)	−32 (35)	68 (8)	14 (25)	123 (17)
C(9)	−162 (18)	−1355 (12)	4514 (16)	171 (25)	62 (26)	64 (37)	74 (9)	34 (24)	134 (19)
C(10)	−1013 (21)	−399 (14)	5293 (17)	282 (30)	110 (33)	46 (40)	87 (10)	13 (26)	116 (18)
C(11)	−1852 (19)	353 (12)	4022 (16)	193 (27)	9 (25)	45 (35)	65 (8)	−17 (21)	98 (17)
C(12)	−1398 (19)	223 (11)	2346 (14)	176 (26)	46 (24)	37 (33)	58 (7)	9 (20)	90 (15)
C(13)	−569 (16)	−642 (10)	1570 (14)	139 (21)	23 (23)	30 (30)	59 (8)	7 (19)	87 (15)
C(14)	791 (17)	−1124 (11)	2945 (15)	177 (23)	86 (22)	19 (23)	61 (7)	4 (25)	106 (17)
C(15)	−2057 (21)	−1459 (12)	1108 (18)	228 (27)	−17 (29)	−47 (45)	58 (9)	−25 (30)	149 (23)
C(16)	−2877 (21)	−1840 (14)	2697 (20)	190 (27)	−27 (28)	133 (43)	65 (9)	2 (30)	225 (25)
C(17)	−2177 (28)	−2639 (16)	5469 (25)	392 (41)	−8 (41)	268 (59)	87 (12)	142 (36)	300 (33)
N(1)	−1408 (16)	−2146 (10)	3990 (14)	230 (23)	−7 (23)	132 (32)	61 (7)	60 (20)	174 (17)
N(2)	2596 (27)	774 (17)	−1007 (45)	529 (45)	58 (47)	261 (69)	93 (12)	120 (31)	317 (19)
N(3)	3628 (22)	154 (15)	−1751 (20)	355 (33)	2 (35)	145 (49)	111 (11)	73 (40)	249 (26)
N(4)	4630 (28)	−299 (20)	−2484 (24)	515 (46)	64 (56)	340 (65)	149 (18)	27 (49)	269 (34)
O(1)	−3322 (19)	2518 (10)	246 (16)	506 (31)	206 (28)	304 (41)	86 (7)	193 (21)	284 (20)
O(2)	−1222 (14)	658 (9)	−407 (11)	292 (21)	55 (22)	93 (27)	75 (6)	49 (16)	110 (12)
O(3)	1493 (14)	−2076 (8)	2398 (12)	306 (21)	58 (21)	67 (29)	54 (5)	3 (20)	144 (15)

the three methyl H) were located geometrically and checked from a difference map. Scattering factors were taken from *International Tables for X-ray Crystallography* (1962). The final coordinates and thermal parameters for the non-hydrogen atoms are given in Table 1, the parameters of H atoms in Table 2, the bond distances and angles in Fig. 1.*

Discussion

In spite of the limited accuracy of the atomic parameters, due to difficulties in the course of data collection, the analysis established that the saturated carbocyclic ring *C* of the T-shape molecule, as in azidomorphine (Sasvári *et al.*, 1974) and naloxone (Karle, 1974), is in a chair conformation. We pointed out previously (Sasvári *et al.*, 1974) that the chair or boat conformation of ring *C* in azidomorphine, morphine (Mackay & Hodgkin, 1955; Gylbert, 1973) and codeine (Kartha, Ahmed & Barnes, 1962) is not only correlated with the presence or absence of the 4,5-ether bridge (in ring *E*) as had been suggested by Gylbert (1973), but also depends on whether C(7)–C(8) is saturated or not. Nevertheless, the saturated ring *C* may also assume a boat conformation, *e.g.* in dihydrometacodeinone.HCl (Tillack & Kennard, 1973) where the formation of a five-membered *N*-heterocyclic ring alters the configuration of the molecule around the asymmetric C(13) and C(14). The substitution of an OH group for H on C(14) does not alter the chair conformation of rings *C* and *D* either in the title compound or in naloxone. Rings *C* are, however, somewhat flattened and twisted relative to rings *D* as indicated by the torsion angles in Table 3. The orientation of the nearly linear N_3 moiety in the title compound differs from that in azidomorphine as shown by the deviations of N(2), N(3) and N(4) from planes *P*(1) and *P*(2) (Table 4). The analysis of dihedral angles

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31796 (6 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Approximate coordinates for hydrogen atoms* ($\times 10^3$) *(except those of methyl hydrogens) as determined from a difference map*

	x	*y*	*z*	*B* (Å²)
H(1)	−287	140	563	4·9
H(2)	−417	248	338	5·2
H(3)	−240	272	−50	6·4
H(5)	26	−64	−89	4·8
H(6)	172	107	88	5·4
H(7)1	365	−80	107	4·3
H(7)2	438	24	191	4·3
H(8)1	190	10	390	4·3
H(8)2	320	−80	410	4·3
H(9)	90	−170	520	4·4
H(10)1	−220	−60	600	4·9
H(10)2	20	0	580	4·9
H(14)	70	−245	280	3·9
H(15)1	−320	−100	40	4·8
H(15)2	−140	−180	40	4·8
H(16)1	−400	−240	240	5·1
H(16)2	−360	−130	310	5·1

Table 3. *Torsion angles for the rings C (carbocyclic) and D (piperidine) in (a) the title compound, (b) naloxone, and (c) azidomorphine*

Ring *C*	(*a*)	(*b*)	(*c*)
C(5)—C(6)*–C(7)—C(8)	−54·0°	−47·5°	−47·7°
C(6)—C(7)—C(8)—C(14)	61·1	60·6	55·5
C(7)—C(8)—C(14)–C(13)	−53·5	−58·8	−52·3
C(8)—C(14)–C(13)–C(5)	40·3	43·6	41·6
C(14)–C(13)–C(5)—C(6)	−33·8	−28·8	−33·5
C(13)–C(5)—C(6)—C(7)	40·4	31·0	34·9
Average	47·2	45·1	44·3
Ring *D*			
N(1)—C(9)*–C(14)–C(13)	67·7	64·8	61·3
C(9)—C(14)–C(13)–C(15)	−62·7	−64·6	−56·8
C(14)–C(13)–C(15)–C(16)	53·9	58·2	49·9
C(13)–C(15)–C(16)–N(1)	−51·2	−51·7	−48·5
C(15)–C(16)–N(1)—C(9)	59·4	57·2	54·8
C(16)–N(1)—C(9)—C(14)	−66·4	−63·3	−59·1
Average	60·2	60·0	55·1

* Column specifying the origin of the torsion-angle calculations.

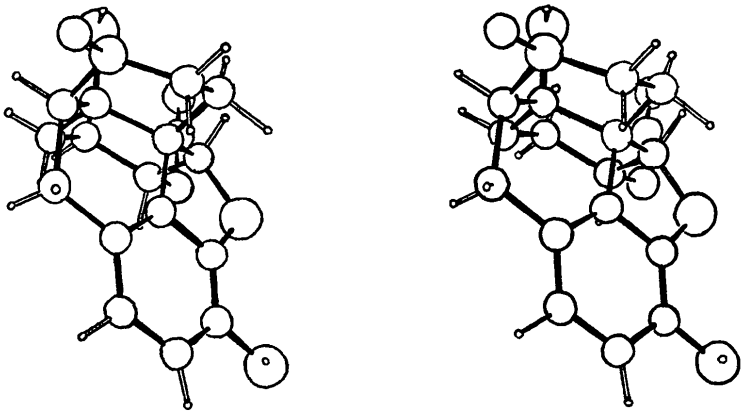

Fig. 2. An *ORTEP* (Johnson, 1965) stereo drawing of the title compound.

Table 4. *Equations of the atomic planes of (a) the title compound, and (b) azidomorphine, and atomic deviations* ($\times 10^3$)

x,y,z are in Å and referred to crystal axes.

	(*a*)	(*b*)
Plane $P(1)$ [for rings A,B,E except atoms C(5) and C(14)]	$0{\cdot}8536x+0{\cdot}4778y+0{\cdot}1262z=-0{\cdot}4979$	$0{\cdot}4072x+0{\cdot}4358y+0{\cdot}8026z=4{\cdot}9132$
Plane $P(2)$ (for ring C)	$-0{\cdot}3132x+0{\cdot}8255y+0{\cdot}4969z=-0{\cdot}0567$	$0{\cdot}9367x-0{\cdot}3444y-0{\cdot}0633z=-1{\cdot}6282$
Plane $P(3)$ (for ring D)	$0{\cdot}4896x-0{\cdot}7955y-0{\cdot}4016z=0{\cdot}2294$	$0{\cdot}8231x-0{\cdot}5459y-0{\cdot}1564z=-2{\cdot}9583$
Plane $P(4)$ [for C(6), C(14), N(2), N(3) and N(4)]	$0{\cdot}7312x+0{\cdot}2844y+0{\cdot}5483z=1{\cdot}3036$	$0{\cdot}5759x+0{\cdot}6812y+0{\cdot}4520z=5{\cdot}6385$

Dihedral angles (°) formed by the least-squares planes given above

	(*a*)	(*b*)		(*a*)	(*b*)
$P(1)/P(2)$	77·2	79·6	$P(2)/P(3)$	12·1	14·3
$P(1)/P(3)$	92·1	91·6	$P(2)/P(4)$	72·7	74·0
$P(1)/P(4)$	27·3	26·6	$P(3)/P(4)$	95·1	91·8

$P(1)$	(*a*)	(*b*)	$P(2)$	(*a*)	(*b*)	$P(3)$	(*a*)	(*b*)	$P(4)$	(*a*)	(*b*)
C(1)*	9	−14	C(5)*	−104	−117	C(9)*	−298	−296	C(6)*	61	−22
C(2)*	−84	−26	C(6)*	185	226	C(13)*	−260	−280	C(14)*	−17	104
C(3)*	60	−16	C(7)*	−278	−316	C(14)*	305	325	N(2)*	−37	−16
C(4)*	−25	−42	C(8)*	288	284	C(15)*	205	205	N(3)*	−32	−21
C(9)*	−11	19	C(13)*	106	98	C(16)*	−199	−188	N(4)*	25	−45
C(10)*	131	100	C(14)*	−196	−176	N(1)*	247	234	C(5)	−1238	−1279
C(11)*	−53	−20	N(2)	−99	−286	C(17)	16	−95	C(7)	1116	1101
C(12)*	−15	−70	N(3)	−1310	531				C(8)	1272	1282
C(13)*	−113	−73	N(4)	−2327	1200				C(13)	−1173	−1212
O(2)*	97	−93									
O(1)*	4	51									
C(5)	531	556									
C(14)	584	674									
N(2)	2535	2619									
N(3)	2725	2948									
N(4)	3002	3298									

* Atom included in the calculation of the plane equation.

formed by $P(1)$, $P(2)$ and $P(4)$, respectively, leads to the conclusion that the N_3 group is twisted by about 140° around the equatorial C(6)–N(2) bond relative to the same moiety in azidomorphine. The T-shape molecule with the upward oriented azido group is depicted in Fig. 2.

The OH group on C(14) results in an infinite chain of hydrogen bonds formed around the 2_1 screw axis, O(1)–H···O(3) (O···O=2·66, H···O=1·73 Å, ∠OH···O=156·6°) which differs from the hydrogen-bond chain found in azidomorphine, O(1)–H···N(1) (O···N=2·79, H···N=1·83 Å, ∠OH···N=169·1°). This means that N(1) of the title compound is unique among the various morphine derivatives with known crystal structure, because it does not take part in any intermolecular hydrogen-bond system. Thus its lone pair which seems to participate only in a weak intramolecular hydrogen bond toward the OH group on C(14) (O···N=2·62, H···N=1·95 Å, ∠OH···N=132·6°) may be responsible for an even more advantageous pharmacological activity in accordance with the conclusions given by Tillack & Kennard (1973).

The authors thank Dr Z. Mészáros, Research Manager of the Chinoin Works for Pharmaceutical and Chemical Products, for his kind interest and for financial support.

References

Bognár, R., Makleit, S., Knoll, J., Berényi, S. & Horváth, G. (1975). *Commun. Dept. Chem. Bulg. Acad. Sci.* **8**, 203–215; *Kém. Közl.* (in Hungarian) **44**, 1–10.

Gylbert, L. (1973). *Acta Cryst.* B**29**, 1630–1635.

International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.

Johnson, C. K. (1965). *ORTEP*. Oak Ridge National Laboratory Report ORNL-3794.

Karle, I. L. (1974). *Acta Cryst.* B**30**, 1682–1686.

Kartha, G., Ahmed, F. R. & Barnes, W. H. (1962). *Acta Cryst.* **15**, 326–333.

Knoll, J., Fürst, S. & Kelemen, K. (1971). *Orvostudomány*, **22**, 265–269.

Knoll, J., Fürst, S. & Makleit, S. (1975). *J. Pharm. Pharmacol.* **27**, 99–105.

Mackay, M. & Hodgkin, D. C. (1955). *J. Chem. Soc.* pp. 3261–3267.

Main, P., Woolfson, M. M. & Germain, G. (1971). *MULTAN. A Computer Program for the Automatic Solution of Crystal Structures*. Univs. of York (England) and Leuven (Belgium).

Makleit, S., Knoll, J., Bognár, R., Berényi, S., Somogyi, G. & Kiss, G. (1976). *Acta Chim. Hung.* In the press.

Sasvári, K., Simon, K., Bognár, R. & Makleit, S. (1974). *Acta Cryst.* B**30**, 634–641.

Seki, I. (1965). *Ann. Sankys Res. Lab.* **17**, 1–34.

Tillack, J. V. & Kennard, C. H. L. (1973). *J. Chem. Soc. Perkin* II, pp. 2044–2046.