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Crystal Structure and Absolute Configuration of the Neuroleptic Agent (+)-Isobutaclamol Hydrobromide*

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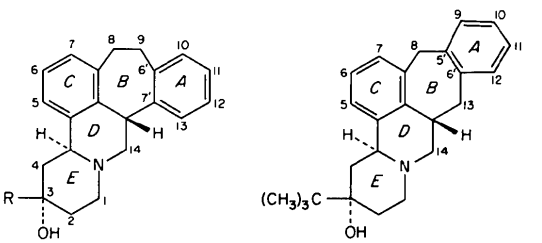
Abstract

(+)-Isobutaclamol, the benzo[5′,6′]cyclohepta analog of (+)-butaclamol, exhibits neuroleptic activity equivalent to (+)-butaclamol. The hydrobromide salt of (+)-isobutaclamol, $C_{25}H_{32}NO^+.Br^-$ forms orthorhombic crystals, $P2_12_12_1$, $a = 10{\cdot}251$ (2), $b = 22{\cdot}841$ (2), $c = 9{\cdot}454$ (3) Å, $Z = 4$. The structure was refined to $R = 0{\cdot}033$ and $R(w) = 0{\cdot}036$ for 2060 observed reflexions. The relative and absolute configurations are found to be the same as those of butaclamol, but the two six-membered rings which share the C—N bond are *cis*-fused in the present structure and *trans*-fused in butaclamol. Consequently, the N lone-pair electrons are facing opposite sides of the two molecules and the *tert*-butyl and hydroxyl substituents occupy different spatial positions. In the present structure, N—H···Br···H—O hydrogen bonds link the molecules into chains parallel to **c**, with N···Br = 3·202 and O···Br = 3·347 Å. Similar hydrogen bonds also occur in (±)-butaclamol.HBr and (+)-dexclamol.HBr.

Introduction

Various chemical and pharmacological studies have been undertaken in recent years at the AYERST Research Laboratories of Canada, in order to determine the topography of the central dopamine receptor and its mode of interaction with neuroleptic agents of the benzocycloheptapyridoisoquinoline series. Some of these studies have been reported by Bruderlein, Humber & Pelz (1974) on synthetic procedures; Humber, Bruderlein & Voith (1975) on the mode of interaction; Humber, Bruderlein, Philipp, Götz & Voith (1979) on the effect of modifications to ring *E* of the neuroleptic butaclamol (I*a*); and Philipp, Humber & Voith (1979) on the effect of modifications to the regions occupied by the *A* and *B* rings of (I*a*). Besides the chemical synthesis and pharmacological evaluation of the compounds, the studies include stereochemical assignments based on NMR interpretations and mechanistic considerations. In addition, the crystal structures of (±)-butaclamol hydrobromide and (+)-dexclamol hydrobromide (I*b*) have been determined (Bird, Bruderlein & Humber, 1976). From these studies, the neuroleptic activity has been established to reside only in the dextrorotatory enantiomers. Consequently, attempts have been made by Humber, Bruderlein, Philipp, Götz & Voith (1979) and Philipp *et al.* (1979) at mapping the central dopamine receptor.



(I*a*) *R* = *tert*-butyl (butaclamol)
(I*b*) *R* = 2-propyl (dexclamol)

(II)

Both butaclamol and dexclamol (I*a*,*b*) contain the benzo[6′,7′]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline nucleus, while the present compound is a benzo[5′,6′]cyclohepta analog of butaclamol (II). Philipp *et al.* (1979) isolated three racemic isomers of (II). One of these, designated (±)-isobutaclamol (AY-23396), was found to be equipotent to (±)-butaclamol as a neuroleptic. Furthermore, resolution studies revealed that (+)-isobutaclamol (AY-26689) was equipotent to (+)-butaclamol. No chemical evidence could be adduced for the relative or absolute configurations of (+)-isobutaclamol; therefore the molecular structure and absolute configuration have been assigned by Philipp *et al.* (1979) on the basis of pharmacological arguments.

Because of the importance of the conclusions made concerning the dopamine receptor topography, it was considered necessary to determine unambiguously the molecular structure and absolute configuration of (+)-isobutaclamol by an X-ray analysis. A summary of the crystallographic, pharmacological and biochemical studies has been reported by Humber, Philipp, Voith, Pugsley, Lippmann, Ahmed & Przybylska (1979).

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Experimental

The hydrobromide salt of (+)-3-*tert*-butyl-1,2,4,-4a,8,13,13a,14-octahydro-3*H*-benzo[5′,6′]cyclohepta-[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol {(+)-isobutaclamol hydrobromide, $[\alpha]_D$ + 221°} forms colourless prismatic crystals. The crystal chosen for the X-ray analysis was 0·20 × 0·22 mm in cross section and 0·20–0·28 mm in length. It was mounted with the prism axis, *c**, parallel to the glass fibre. The space group was determined from precession photographs, and the other measurements were carried out on an automatic Picker diffractometer with Cu radiation and a Ni filter.

Crystal data

$C_{25}H_{32}NO^+.Br^-$, M_r = 442·45, orthorhombic, $P2_12_12_1$, a = 10·251 (2), b = 22·841 (2), c = 9·454 (3) Å, U = 2213·6 Å^3, Z = 4, D_c = 1·327, D_m = 1·329 Mg m^{-3}, $F(000)$ = 928, μ(Cu $K\alpha$) = 2·631 mm^{-1}, $\lambda(K\alpha_1)$ = 1·54050, $\lambda(K\alpha_2)$ = 1·54434 Å.

The density was measured by flotation in carbon tetrachloride and toluene at 296 K. The cell parameters were derived from the $+2\theta$ and -2θ settings of the $K\alpha_1$ and $K\alpha_2$ of five axial reflexions in the range 2θ = 58·5–97·8°, as measured with a narrow slit at a small take-off angle.

Intensity data

The intensities of the *hkl* reflexions within 2θ = 130° were measured with a scintillation counter by the θ–2θ scan method at a 2θ scanning speed of 2° min^{-1} and a take-off angle of 3·3°. The 2θ scan range was 2·0° for 2θ < 80°, 2·4° for 80 ≤ 2θ < 100° and 3·0° for 2θ ≥ 100°. The background was measured for 20 s with a stationary counter at the start and end of each scan. Two reflexions, 400 and 0,12,0, were monitored at frequent intervals for scaling and showed a random variation within ±1·5% throughout. Of the 2160 reflexions measured, 2060 (95%) had significant net intensities and were considered observed. The net intensities were corrected for Lorentz and polarization effects, but not for absorption.

For determination of the absolute configuration, the 22 non-zonal *hkl* reflexions within 2θ = 30° and their corresponding $\bar{h}kl$, $h\bar{k}l$ and $\bar{h}\bar{k}l$ were measured in a similar manner. The intensities of the equivalent reflexions *hkl* and $\bar{h}\bar{k}l$, and similarly of $\bar{h}kl$ and $h\bar{k}l$, showed an overall R of 0·031.

Structure determination

The structure was determined by the heavy-atom method, and refined by block-diagonal least squares minimizing $\sum w(|F_o| - |F_c|)^2$. The Br position was determined from a sharpened Patterson map, then the positions of the 27 non-hydrogen atoms were derived from a Fourier map based on the phases of Br. Refinement of this structure converged at R = 0·06; then the 32 H atoms were located in a difference map with heights of 0·3–0·7 e Å^{-3}. Two more cycles including H with isotropic thermal parameters reduced R to 0·042.

The two possible enantiomorphs were then examined by calculating two cycles for each, including the anomalous dispersion of Br; the resulting R indices were 0·037 and 0·048. The observed and calculated ratios of the low-angle non-zonal reflexions (Table 1) were also in better agreement for the enantiomorph with the lower overall R. The parameters of the correct enantiomorph were refined further, adjusting the constants in the weighting formula to make $\langle w(|F_o| - |F_c|)^2 \rangle$ independent of $|F_o|$. The final weights were calculated from $w = 1/\{1 + [(|F_o| - 25)/20]^2\}$, where 3·1 ≤ $|F_o|$ ≤ 140·0. Three very strong reflexions (020, 140 and 032) showing extinction effects, and the unobserved reflexions, were excluded.

In the final cycle, R = 0·033 and $R(w)$ = 0·036 for the 2060 observed reflexions, mean and maximum (shift/e.s.d.) = 0·13 and 0·95 respectively, and $[\sum w(|F_o| - |F_c|)^2/(m-n)]^{1/2}$ = 0·81. All unobserved reflexions calculated reasonably small, $|F_c|_{max}$ = 5·7 and $|F_{thresh}|$ = 2·7–4·6. The residual electron density distribution in the final difference map was within −0·27 and 0·26 e Å^{-3}.

The atomic parameters are presented in Table 2.* Scattering factors are those of Hanson, Herman, Lea & Skillman (1964) for C, N, O, Br, and of Stewart, Davidson & Simpson (1965) for H. The anomalous

* Lists of anisotropic thermal parameters and structure factors have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34521 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Reflexions with the largest anomalous-dispersion effect*

Observed ratio = $\langle I(hkl), I(\bar{h}\bar{k}l) \rangle / \langle I(\bar{h}kl), I(h\bar{k}l) \rangle$.
Calculated ratio = $|F_c|^2$ of correct enantiomorph/$|F_c|^2$ of opposite enantiomorph.

h k l	Observed ratio	Calculated ratio
2 1 1	1·13	1·11
1 2 1	0·87	0·84
2 2 1	1·29	1·14
3 2 1	1·15	1·12
1 3 1	1·30	1·18
2 5 1	1·16	1·10
2 1 2	0·85	0·86
1 2 2	1·18	1·09
2 3 2	1·15	1·04
1 1 3	1·13	1·08

Table 2. *Fractional coordinates* ($\times 10^4$ *for* Br, N, O, C; $\times 10^3$ *for* H) *and equivalent isotropic temperature factors* (Å^2)

	x	y	z	B(eq.) or B_{iso}
Br	1114 (0)	358 (0)	1651 (0)	3·44
N	1770 (3)	651 (1)	7168 (3)	2·68
O	−400 (3)	85 (1)	4717 (3)	3·43
C(1)	706 (4)	209 (2)	7453 (4)	3·22
C(2)	−625 (4)	433 (2)	7044 (4)	2·99
C(3)	−685 (4)	612 (2)	5477 (4)	2·49
C(4)	406 (4)	1060 (2)	5215 (4)	2·52
C(4a)	1759 (4)	839 (2)	5639 (4)	2·42
C(4b)	2807 (4)	1296 (2)	5384 (4)	2·52
C(5)	3250 (4)	1369 (2)	4011 (4)	3·09
C(6)	4174 (4)	1793 (2)	3704 (4)	3·47
C(7)	4625 (4)	2153 (2)	4758 (5)	3·31
C(7a)	4198 (4)	2089 (2)	6144 (4)	2·81
C(8)	4713 (4)	2476 (2)	7316 (5)	3·54
C(8a)	5635 (4)	2159 (2)	8304 (5)	3·25
C(9)	6851 (5)	2417 (2)	8565 (5)	3·94
C(10)	7793 (5)	2147 (2)	9355 (5)	4·60
C(11)	7551 (5)	1609 (2)	9947 (6)	4·58
C(12)	6339 (5)	1358 (2)	9755 (5)	4·08
C(12a)	5374 (4)	1615 (2)	8936 (4)	3·26
C(13)	4093 (5)	1274 (2)	8799 (5)	3·89
C(13a)	2947 (4)	1541 (2)	8011 (4)	3·01
C(13b)	3292 (4)	1643 (2)	6459 (4)	2·57
C(14)	1737 (4)	1171 (2)	8154 (4)	3·31
C(15)	−2045 (4)	854 (2)	5050 (4)	2·90
C(16)	−3109 (5)	407 (3)	5404 (6)	5·28
C(17)	−2102 (4)	970 (2)	3461 (5)	3·93
C(18)	−2363 (5)	1426 (2)	5799 (6)	4·89
H(N)	242 (4)	53 (2)	731 (4)	2·7 (0·9)
H(O)	−18 (4)	13 (2)	406 (4)	3·2 (0·9)
H(1,1)	72 (4)	12 (2)	848 (4)	2·8 (0·8)
H(1,2)	98 (4)	−11 (2)	698 (4)	2·7 (0·8)
H(2,1)	−96 (4)	80 (2)	766 (4)	3·0 (0·8)
H(2,2)	−126 (4)	12 (2)	727 (4)	2·5 (0·8)
H(4,1)	21 (4)	140 (2)	572 (4)	1·9 (0·7)
H(4,2)	53 (4)	116 (2)	413 (4)	2·9 (0·8)
H(4a)	199 (4)	47 (2)	499 (4)	2·4 (0·7)
H(5)	288 (4)	115 (2)	339 (4)	2·7 (0·8)
H(6)	446 (5)	185 (2)	263 (6)	5·5 (1·3)
H(7)	532 (4)	244 (2)	463 (4)	3·0 (0·9)
H(8,1)	391 (4)	268 (2)	792 (5)	4·1 (1·0)
H(8,2)	518 (4)	282 (2)	684 (4)	2·9 (0·8)
H(9)	703 (4)	279 (2)	800 (4)	3·0 (0·9)
H(10)	867 (5)	234 (2)	936 (5)	5·9 (1·3)
H(11)	823 (5)	131 (2)	1015 (6)	7·5 (1·3)
H(12)	619 (4)	99 (2)	1004 (5)	4·1 (1·0)
H(13,1)	428 (4)	86 (2)	850 (5)	4·0 (1·0)
H(13,2)	365 (6)	127 (3)	982 (7)	8·5 (1·7)
H(13a)	283 (4)	187 (2)	849 (4)	2·9 (0·8)
H(14,1)	86 (3)	142 (1)	781 (4)	2·1 (0·7)
H(14,2)	164 (4)	98 (1)	913 (4)	1·9 (0·7)
H(16,1)	−411 (5)	53 (2)	504 (5)	4·6 (1·1)
H(16,2)	−328 (6)	34 (2)	652 (6)	7·2 (1·5)
H(16,3)	−280 (6)	4 (3)	503 (7)	7·9 (1·6)
H(17,1)	−288 (4)	111 (2)	314 (5)	3·8 (1·0)
H(17,2)	−182 (4)	63 (2)	281 (5)	3·6 (1·0)
H(17,3)	−151 (5)	133 (2)	320 (6)	6·6 (1·3)
H(18,1)	−218 (4)	147 (2)	671 (5)	4·9 (1·1)
H(18,2)	−316 (5)	154 (2)	573 (5)	5·0 (1·1)
H(18,3)	−174 (6)	183 (2)	557 (6)	6·4 (1·5)

dispersion of Br is that in *International Tables for X-ray Crystallography* (1962). All calculations were performed with the NRC program system (Ahmed, Hall, Pippy & Huber, 1973).

Results and discussion

Molecular structure

A view of the molecule showing the conformation and the absolute configuration is presented in Fig. 1. As predicted from pharmacological arguments (Philipp, Humber & Voith, 1979), the relative configurations are 4a,13a-*trans*, and 3(OH),13a(H)-*trans*, similar to dexclamol (Bird *et al.*, 1976), and the absolute configuration is 3*S*, 4a*S* and 13a*S*. The cycloheptane ring is shown to have the geometry of conformer *B* with H(8,1) and H(13a) eclipsed and at a distance of 2·22 Å apart. Conformer *A* of this molecule would have a H atom at position 8 eclipsed with another at position 13 (Philipp *et al.*, 1979).

The only unexpected feature in this structure is the fact that rings *D* and *E* are *cis*-fused at N–C(4a), while they are *trans*-fused in both (±)-butaclamol.HBr and (+)-dexclamol.HBr (Bird *et al.*, 1976). In the predicted structure of (+)-isobutaclamol, Philipp *et al.* (1979) assumed that rings *D* and *E* are *trans*-fused. This significant conformational change at the *D*/*E* junction results in shifting the N lone-pair electrons from one side of the molecule to the other, and considerably changes the relative spatial positions of the substituents at C(3) (Fig. 2).

Bond lengths and angles

Bond lengths and angles are presented on the schematic drawings in Fig. 3(*a*,*b*). Their e.s.d.'s are 0·005–0·007 Å and 0·3–0·5° respectively. The bond lengths are within the expected ranges, with mean values of 1·527 Å for C(sp^3)–C(sp^3), 1·521 Å for

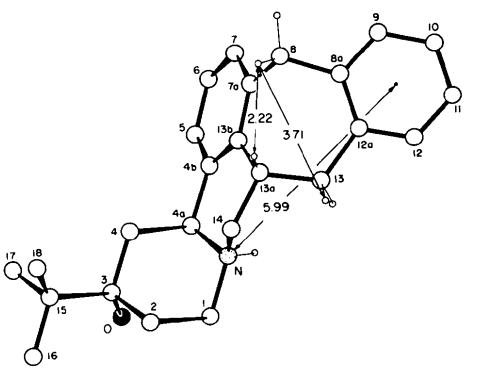
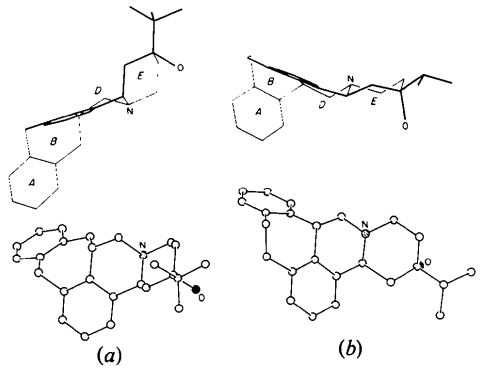
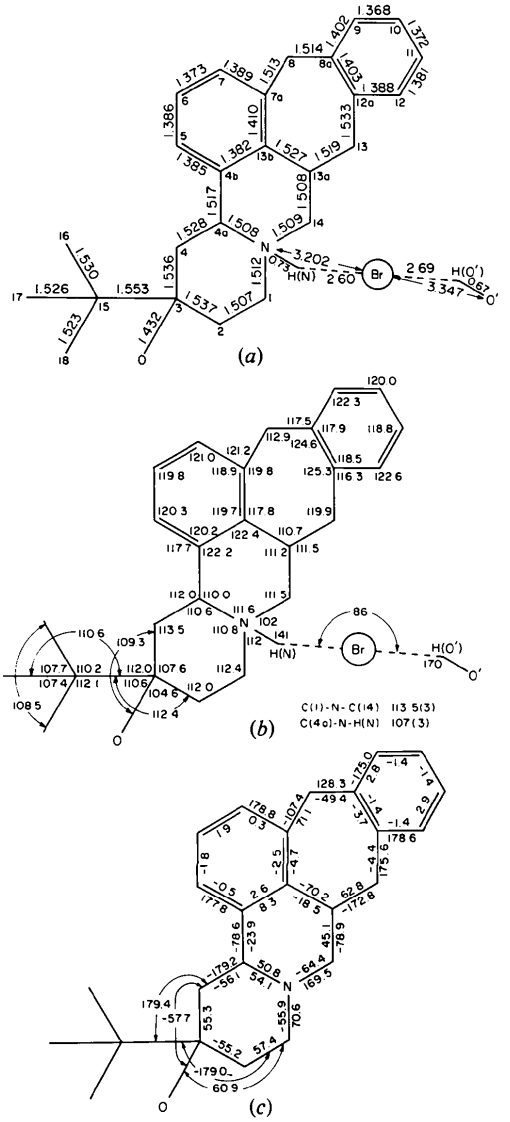


Fig. 1. Perspective view of (+)-isobutaclamol in its absolute configuration. The distances are in Å.



(*a*) (*b*)

Fig. 2. Two orthogonal views of (*a*) (+)-isobutaclamol, and (*b*) (+)-dexclamol, showing the difference in fusion of rings *D* and *E* and its effect on the relative positions of the substituents and the direction of the N lone-pair electrons.



(*a*) (*b*) (*c*)

Fig. 3. (*a*) Bond lengths (Å), (*b*) bond angles (°), and (*c*) torsion angles (°).

C(sp^3)–C(sp^2), 1·387 Å for C(sp^2)–C(sp^2), and 1·510 Å for C(sp^3)–N(sp^3). The C–H are in the range 0·86–1·15 Å (mean = 1·00 Å and e.s.d. = 0·04–0·07 Å), O–H = 0·67 (4) Å and N–H = 0·73 (4) Å.

The bond angles have normal values, except for three endocyclic angles in the cycloheptane ring indicating some strain in the ring. Thus, the angles at C(8a), C(12a) and C(13) are 124·6, 125·3 and 119·9 (4)° which are considerably larger than the values expected for C(sp^2) and C(sp^3).

Molecular conformation

Some torsion angles and mean-plane calculations are presented in Fig. 3(*c*) and Table 3 respectively. The e.s.d.'s are ≤1·0° for the torsion angles, and 0·004–0·006 Å for the displacements from the mean planes. These results indicate very slight non-planarity in the aromatic *A* and *C* rings, with χ^2 values of 42·1 and 50·7, and maximum displacements of 0·015 and 0·017 Å respectively. The angle between their two mean planes is 114·7°. While C(13), C(13a) and C(14) of the phenylpropylamine moiety are within −0·25 Å from the mean plane of ring *A*, N is displaced by 1·06 Å as a

Table 3. *Mean planes*

(*a*) Parameters of the mean planes (expressed in the form $lX + mY + nZ - p = 0$, where *X*, *Y*, *Z* and *p* are in Å)

	l	*m*	*n*	*p*
A	0·3540	−0·4563	−0·8164	−6·6287
B(1)	0·3317	−0·4906	−0·8058	−6·7864
B(2)	−0·7698	0·6293	−0·1072	−0·9120
C	−0·7397	0·6505	−0·1721	−1·0886
D	−0·6394	0·7461	−0·1857	−0·6437
E	0·4312	−0·6325	−0·6435	−4·5214

(*b*) Atomic displacements (× 10³ Å)

A		*B*(1)		*C*	
C(9)	−14	C(8)	40	C(5)	6
C(10)	0	C(8a)	−42	C(6)	−14
C(11)	15	C(12a)	−3	C(7)	6
C(12)	−14	C(13)	47	C(7a)	8
C(12a)	0	C(13a)	−41	C(13b)	−17
C(8a)	15	*B*(2)		C(4b)	9
C(8)*	112			C(4a)*	84
C(13)*	−3	C(8)	10	C(13a)*	−159
C(13a)*	−91	C(7a)	−21	C(8)*	4
C(14)*	−254	C(13b)	21	N*	−452
N*	1060	C(13a)	−10		
D		*E*			
C(13a)	−67	N	2		
C(14)	69	C(1)	−2		
C(4a)	−68	C(3)	2		
C(4b)	67	C(4)	−2		
C(13b)*	152	C(2)*	−665		
N*	−664	C(4a)*	656		

* Atoms not included in the mean-plane calculations.

result of the *D*/*E* *cis*-fusion. Ring *E* has a regular chair conformation, but ring *D* is a flattened chair [at C(13b)] with C(13b) and N at distances of 0·15 and −0·66 Å respectively from the seat formed by the other four atoms. The mean planes of rings *D* and *E* form an angle of 125·1°. The cycloheptane ring *B* is folded along the C(8)···C(13a) diagonal, with C(8), C(8a), C(12a), C(13) and C(13a) forming one approximate plane (within ±0·047 Å), and C(8), C(7a), C(13b) and C(13a) another (within ±0·021 Å). The angle between these two planes is 118·5°. H(8,1) and H(13a) exhibit a flagpole–bowsprit interaction between them, and their parent C atoms are separated by 2·876 Å.

At C(3), OH is axial and the *tert*-butyl is equatorial. The H atoms at O, C(4a) and N are *cis* to each other and *trans* to that at C(13a).

Intermolecular hydrogen-bonding

Each Br is involved in two intermolecular hydrogen bonds of the form N—H···Br···H—O that link the molecules into continuous chains parallel to **c** (Fig. 4). The separate chains do not have linkages between them. The geometrical entities of the hydrogen bonds are presented in Fig. 3(*a*,*b*). Similar N—H···Br···H—O hydrogen bonds are also present in (±)-butaclamol.HBr and (+)-dexclamol.HBr, with N···Br and O···Br distances of 3·245 and 3·245 Å in the former and 3·210 and 3·192 Å in the latter respectively.

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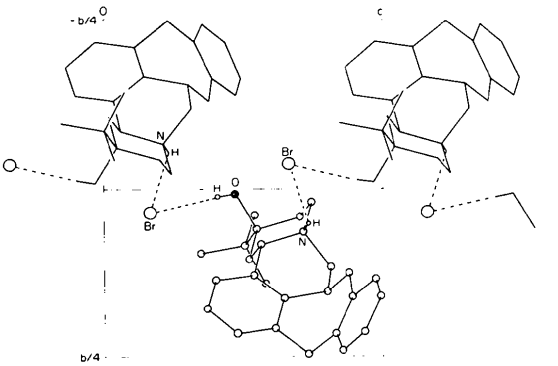

Fig. 4. Projection along **a** of part of the unit-cell contents, showing the intermolecular hydrogen bonding.

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The Structure of an Unknown Triterpane from a Californian (Monterey, USA) Shale Oil, 28,30-Dinor-17α(H),18α(H),21β(H)-hopane, $C_{28}H_{48}$

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Abstract

An unknown triterpane, $C_{28}H_{48}$, extracted from a Californian shale oil, has been identified as 28,30-dinor-17α(H),18α(H),21β(H)-hopane by the determination of its crystal structure. The compound is orthorhombic, space group $P2_12_12_1$, with a = 11·262 (4), b = 7·360 (6), c = 28·378 (11) Å, Z = 4. Refinement

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