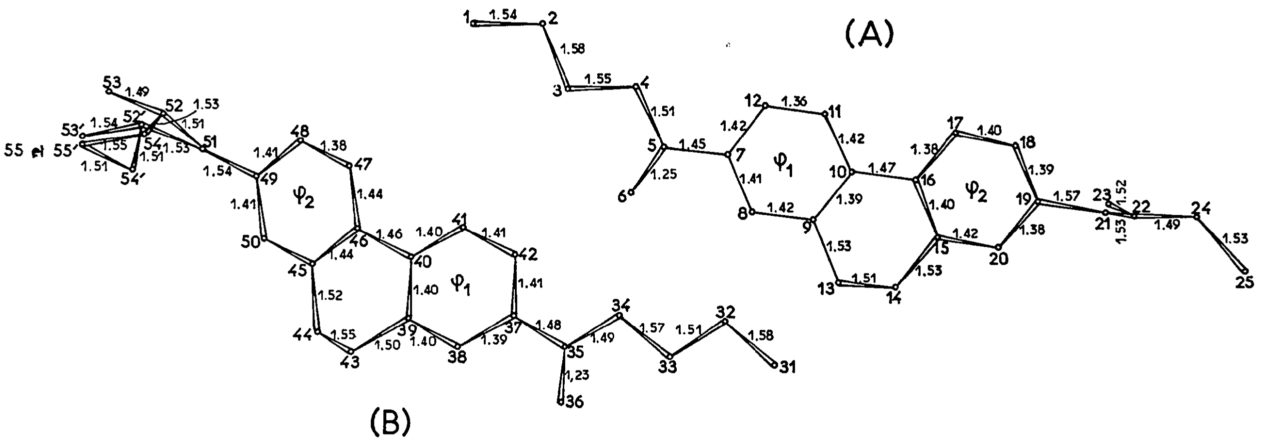

Fig. 2. Projection des molécules *A* et *B* sur le plan moyen de la molécule *A*.

des molécules préfigure déjà une structure de type smectique. La faible densité observée est en faveur d'une cohésion cristalline assurée par des liaisons de van der Waals assez faibles. Il faut noter, en outre, l'absence de fortes interactions entre noyaux.

Nous tenons à remercier, ici, les professeurs J. Billard et J. Jacques (Collège de France) grâce à qui nous avons pu disposer du matériau présenté ici, et avec qui nous avons eu de fructueuses discussions concernant ce travail.

Références

Canceill, J., Jacques, J. & Billard, J. (1974). *Chem. Ind.* n° 15, pp. 615–616.

Destrade, C. & Gasparoux, H. (1975). *Lett. J. Phys.* **36**, 105–107.

Germain, G., Main, P. & Woolfson, M. M. (1971). *Acta Cryst.* **27**, 368–73.

Acta Cryst. (1975). B**31**, 2706

Stereochemical Aspects of Local Anesthetic Action. II.* The Crystal Structure of Cocaine Methiodide

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Abstract. $C_{18}H_{24}NO_4I$, space group $P2_12_12_1$, $a=7\cdot014$ (4), $b=7\cdot416$ (5), $c=37\cdot71$ (3) Å; $Z=4$, $D_x=1\cdot51$, $D_m=1\cdot52$ g cm^{-3}. The structure was solved by the heavy-atom method. The positional and thermal parameters were refined by full-matrix procedures, converging at $R=0\cdot072$ for the observed data. The molecule exists in the piperidine chair conformation.

Introduction. Recent studies suggest a correlation between conformation and local anesthetic potency of procaine (I) and 3-acyloxypiperidine (II) analogs of (I) (Lokhandwala, Patel, Patel, Marker, Shafi'ee & Hite, 1971). This led to the design and synthesis of *pseudo*-4-norcocaine (III) which is equal in local anesthetic potency to its less conformationally rigid analog, cocaine (IV) (Shafi'ee & Hite, 1968). From a consideration of stereochemical superimposability patterns, the local anesthetic action of (III) can be rationalized on the basis of the piperidine boat conformation of (IV).

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* Part I: Lokhandwala, Patel, Patel, Merker, Shafi'ee & Hite (1971).

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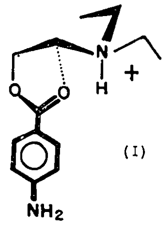
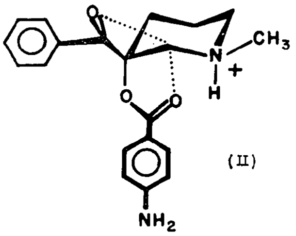
However, in the crystalline state, (IV) hydrochloride exists in the chair conformation (Gabe & Barnes, 1963). The chloride ion is hydrogen bonded and is *cis* to the benzoate unit. This precludes formation of the boat conformation. In solution, the cation is remote from counter ions. Thus, the boat conformation may be stabilized by electrostatic interactions (Craven & Hite, 1973; Ruble, Hite & Soares, 1976, and previous papers in that series) between the benzoate oxygen atoms and the cationic center (< 3·0 Å) particularly in the apolar environment of the nerve membrane where local anesthetics are known to act and where such interactions would be more significant than in water. Thus, since the crystal structure of (IV) hydrochloride may lack biological significance, it was of interest to determine the structures of (IV) methiodide and of normethyl-(IV) salts. In the former, the 1,3-diaxial interaction was visualized as a potential destabilizing influence on the chair conformer and this led to its choice as the model to initiate a search for a cocaine boat conformer.



(I)



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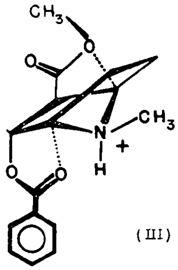
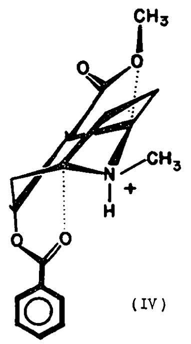


(III)



(IV)

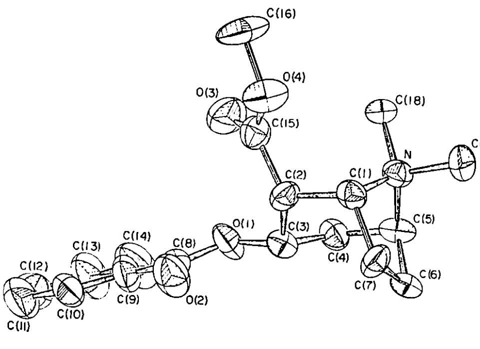


Fig. 1. The conformation and atomic numbering of cocaine methiodide.

A crystal (0·30 × 0·14 × 0·05 mm) of (IV) methiodide (m.p. 168–170°) prepared by treatment of (IV) in ether with methyl iodide and recrystallized from acetone was mounted on a Nonius CAD-IV automatic diffractometer equipped for data collection with graphite-monochromated Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å). Data were collected for 2368 independent reflections with $\theta \leq 75°$ using $\theta/2\theta$ scans. Other than systematic absences, there were 516 unobservably weak reflections $[(I) \leq 2\sigma(I)]$ which were assigned values of $(I) = \sigma(I)/2$. Preliminary data reduction included an absorption correction ($\mu = 132{\cdot}8$ cm^{-1}, Cu $K\alpha$) (Busing & Levy, 1957). The iodide coordinates were determined by the heavy-atom technique. Several cycles of structure factor calculation and Fourier syntheses were required to determine the positions of the remaining non-hydrogen atoms. Full-matrix refinement of all atomic parameters, first with isotropic then anisotropic temperature factors, converged at $R_w = 0{\cdot}082$* ($w = 1/\sigma^2$). No attempt was made to determine H atom positions. The final atomic parameters are listed in Table 1. A table of observed and calculated structure factors and a list of relevant torsion angles and least-squares planes are available.† The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1968), and the anomalous dispersion factors were those of Cromer (1965). Computer programs used in this study were written or modified for the IBM 1130 and DEC 1070 systems by Shiono (1963–1973).

The absolute configuration of (−)-cocaine was previously determined unequivocally by chemical means (Fodor, 1970). Thus (−)-cocaine is (−)-2*R*-methoxycarbonyl-3*S*-benzoyloxytropane (Fig. 1).

Discussion. Cocaine methiodide, like the hydrochloride salt, exists in the piperdine chair conformation (Fig. 1). The C(18) methyl group causes remarkably little distortion in the bond distances and angles (Fig. 2). The methoxycarbonyl and benzoate groups are almost identically situated in both salts (Fig. 1). One significant difference is in the C(1)–C(2)–C(15) bond angle which is wider (115° *vs* 109°) in the methiodide salt. The greatest deviation is found in the orientation of the methoxycarbonyl group. The C(1)–C(2)–C(15)–O(4) torsion angle in the methiodide is increased 29° in magnitude relative to the hydrochloride salt (−46° *vs* −17°).‡ This is due to the presence of the C(18) methyl group, and is implied by the O(4) to C(18) contact of 3·31 Å. Thus the O(4) to C(1) intramolecular distance, governed by electrostatic attraction (Craven

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* $R_w = [\sum w(|F_{\rm obs}| - |F_{\rm calc}|)^2 / \sum w|F_{\rm obs}|^2]^{1/2}$.

† These tables have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31202 (22 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

‡ The absolute configuration of cocaine reported by Gabe & Barnes (1963) was that of 2*S*-methoxycarbonyl-3*R*-benzoyloxytropane, and thus their observed C(1)–C(2)–C(15)–O(4) torsion angles is +17°.

& Hite, 1973; Hite & Craven, 1973; Hite & Soares, 1973) is slightly longer in the methiodide salt (2·63 *vs* 2·84 Å). Packing of the molecules is shown in Fig. 3. Dashed lines indicate possible electrostatic interactions between the oxygens and the cationic center through C(1) and C(18).

Table 1. *Atomic parameters*

Positional parameters are given as fractions of the lattice translations. Anisotropic temperature factors correspond to the expression $T=\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{13}klb^*c^*)]$. Estimated standard deviations are given in parentheses. Positional parameters x and y $\times 10^3$ (except I $\times 10^4$), $z \times 10^4$ (except I $\times 10^5$); thermal parameters $\times 10^3$ (except I $\times 10^4$).

	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	2696 (1)	418 (1)	18300 (2)	430 (4)	419 (4)	704 (7)	61 (4)	−49 (5)	−27 (6)
O(1)	25 (1)	−169 (1)	3938 (2)	81 (7)	34 (6)	56 (6)	−1 (5)	24 (5)	9 (5)
O(2)	230 (2)	−401 (1)	4000 (3)	114 (9)	50 (7)	74 (6)	19 (8)	17 (8)	6 (5)
O(3)	289 (2)	89 (2)	4176 (3)	103 (8)	88 (9)	51 (5)	−23 (8)	12 (7)	−13 (6)
O(4)	554 (1)	116 (2)	3876 (3)	56 (6)	74 (8)	79 (7)	−5 (6)	−1 (5)	−25 (7)
N	227 (1)	183 (1)	3153 (3)	41 (5)	38 (6)	44 (5)	−7 (5)	4 (6)	−2 (5)
C(1)	361 (2)	23 (2)	3239 (3)	41 (5)	31 (8)	49 (8)	6 (6)	−3 (5)	0 (7)
C(2)	319 (2)	−59 (2)	3606 (3)	52 (7)	48 (10)	32 (6)	−2 (8)	0 (5)	−8 (7)
C(3)	108 (2)	−129 (2)	3599 (4)	53 (8)	33 (9)	51 (8)	−2 (7)	−1 (7)	−2 (7)
C(4)	−32 (2)	11 (2)	3446 (3)	42 (6)	39 (10)	54 (7)	0 (6)	−2 (6)	7 (7)
C(5)	41 (2)	86 (2)	3089 (3)	38 (6)	35 (9)	63 (9)	−4 (6)	0 (6)	−12 (7)
C(6)	103 (2)	−69 (2)	2833 (4)	61 (8)	25 (9)	55 (9)	−7 (7)	−6 (7)	−2 (7)
C(7)	315 (2)	−110 (2)	2936 (3)	66 (9)	54 (10)	31 (6)	12 (8)	−9 (6)	−9 (7)
C(8)	90 (3)	−323 (2)	4104 (4)	95 (12)	40 (10)	42 (8)	2 (9)	−9 (8)	−6 (7)
C(9)	−39 (3)	−376 (2)	4404 (4)	127 (16)	43 (10)	39 (8)	0 (11)	15 (9)	7 (8)
C(10)	30 (3)	−521 (2)	4610 (4)	177 (19)	41 (11)	48 (8)	−22 (13)	2 (11)	2 (8)
C(11)	−83 (4)	−571 (3)	4898 (5)	188 (23)	64 (17)	61 (11)	−29 (17)	19 (14)	11 (11)
C(12)	−261 (4)	−484 (3)	4970 (4)	189 (25)	80 (16)	58 (9)	−48 (22)	22 (15)	−9 (10)
C(13)	−324 (3)	−345 (3)	4760 (5)	152 (20)	71 (14)	69 (11)	−8 (14)	48 (13)	11 (10)
C(14)	−209 (3)	−289 (3)	4481 (5)	138 (20)	59 (12)	95 (13)	7 (15)	46 (15)	3 (11)
C(15)	380 (2)	55 (2)	3921 (3)	56 (7)	53 (9)	42 (7)	−1 (9)	6 (6)	1 (8)
C(16)	630 (3)	235 (3)	4148 (5)	94 (13)	101 (17)	91 (13)	−36 (13)	−16 (11)	−48 (13)
C(17)	291 (2)	279 (2)	2816 (3)	74 (10)	58 (10)	43 (7)	−13 (9)	−3 (8)	17 (7)
C(18)	215 (2)	333 (2)	3440 (3)	68 (9)	37 (8)	48 (6)	−13 (8)	−15 (7)	−6 (6)

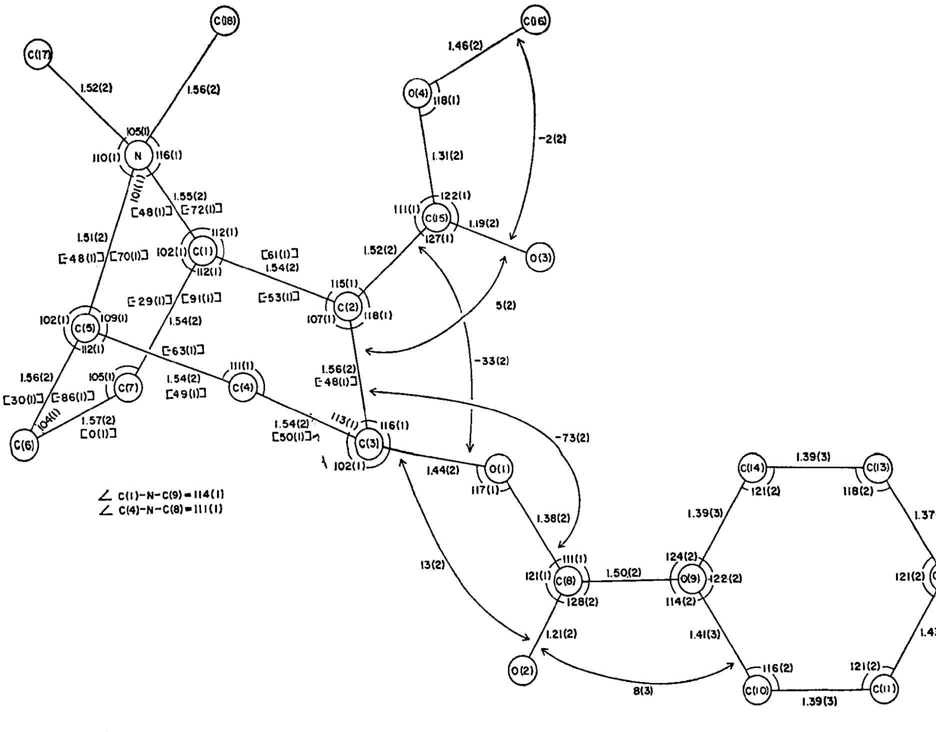

Fig. 2. Bond distances (Å), valency angles (°), and selected torsion angles (°) [tropane internal ring angles in square brackets] for cocaine methiodide. Standard deviations are given in parentheses.

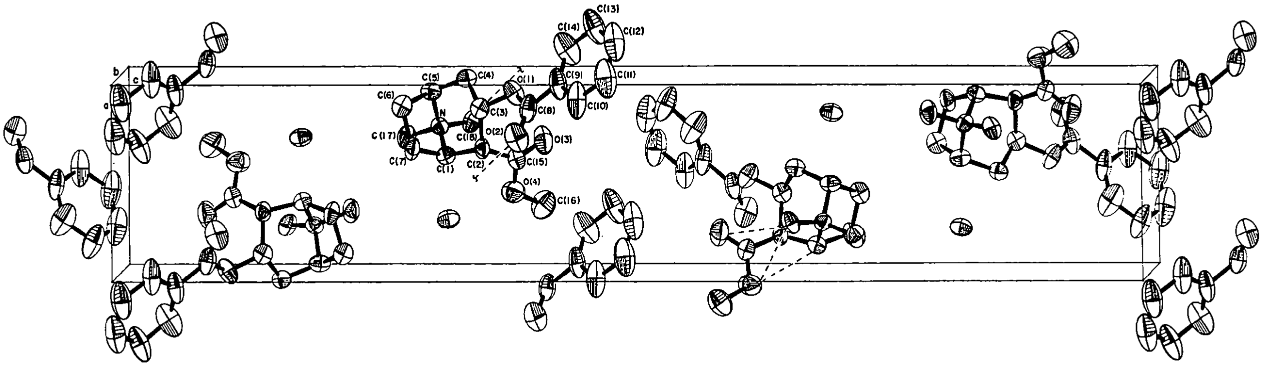

Fig. 3. Unit-cell diagram showing intra- and intermolecular interactions for the methylated cocaine cation. Dashed lines indicate potential electrostatic interactions.

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References

Busing, W. R. & Levy, H. A. (1957). *Acta Cryst.* **10**, 180–182.

Craven, B. M. & Hite, G. (1973). *Acta Cryst.* **B29**, 1132–1136.

Cromer, D. T. (1965). *Acta Cryst.* **18**, 17–23.

Fodor, G. (1970). In *Chemistry of the Alkaloids*, edited by S. W. Pelletier, p. 446. New York: Van Nostrand–Reinhold.

Gabe, E. J. & Barnes, W. H. (1963). *Acta Cryst.* **16**, 796–801.

Hite, G. & Craven, B. M. (1973). *Acta Cryst.* **B29**, 2929–2934.

Hite, G. & Soares, J. R. (1973). *Acta Cryst.* **B29**, 2935–2938.

International Tables for X-ray Crystallography (1968). Vol. III. Birmingham: Kynoch Press.

Lokhandwala, M., Patel, D. B., Patel, H., Merker, P. C., Shafi'ee, A. & Hite, G. (1971). *J. Pharm. Sci.* **60**, 685–689.

Ruble, J. R., Hite, G. & Soares, J. R. (1976). *Acta Cryst.* In the press.

Shafi'ee, A. & Hite, G. (1968). *J. Org. Chem.* **33**, 3435–3440.

Shiono, R. (1963–1973). Techn. Rpts. 48 and 49, Crystallography Department, Univ. of Pittsburgh, Pittsburgh, Pa., and previous reports in this series.

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Die Struktur von Bis-(1,2-benzochinondioximato)palladium(II)

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Abstract. $Pd(C_6H_5N_2O_2)_2$, orthorhombic, *Imcb* (D_{2h}^{26}), $a=6{\cdot}405$ (1), $b=9{\cdot}728$ (1), $c=20{\cdot}649$ (2) Å, $V=1286$ Å^3, $Z=4$, $d_x=1{\cdot}97$ g cm^{-3}. The structure was refined by least-squares methods to $R=8{\cdot}7\%$ for 616 independent counter reflexions. The planar metal complex units form columnar stacks with Pd–Pd distances of 3·202 Å.

Einleitung. Genaue Gitterkonstanten wurden aus den θ-Werten von 18 Reflexen nach einem Ausgleichsverfahren von Berdesinski & Nuber (1966) berechnet. Diffraktometermessungen (5-Wertmessung, $\theta/2\theta$- Abtastung) ergaben mit Mo $K\alpha$-Strahlung bis $2\theta=60°$ 616 unabhängige Reflexe mit $I>2{,}58\sigma(I)$. Die systematischen Auslöschungen sind: hkl für $h+k+l=2n+1$, $h0l$ für $l=2n+1$ ($h=2n+1$) und $hk0$ für $k=2n+1$ ($h=2n+1$). Von den damit möglichen beiden Raumgruppen D_{2h}^{26} (*Imcb*) und C_{2v}^{21} (*I2cb*) konnte die nichtzentrosymmetrische Raumgruppe (C_{2v}^{21}) aufgrund eines statistischen Tests ausgeschlossen werden.

Aus einer 3d-Pattersonsynthese konnten alle Atomlagen entnommen werden, die dann nach der Methode der kleinsten Quadrate verfeinert wurden (Busing, Martin & Levy, 1962). Mit anisotropen Temperaturfaktoren wurde mit allen 616 beobachteten Reflexen ein konventioneller R-Wert von 0,087 erreicht. (Grösste Änderung/Fehler 0,20, mittlere Änderung/Fehler 0,003). Die Positionen der Wasserstoffatome