among the substituents on ring *D* has the net effect of flattening the boat form at C(15) as demonstrated by the smaller torsion angles around C(15) in aconitine: C(13)–C(16)–C(15)–C(8) 18·7 (9) and C(16)–C(15)–C(8)–C(9) −19·9 (8)°. These angles, averaged over the six structures reported in Codding & Kerr (1981) and Kerr & Codding (1982), are 25·4 and 22·8° respectively. Close contacts between C(15) and the axial substituent on C(14), which is an $-OCOC_6H_5$ group in aconitine, may well contribute to the flattening of ring *D*. The torsion angle C(14)–C(13)–C(16)–C(15) is larger in aconitine by *ca* 6°. Acetylation of C(15) or deacetylation of C(8) greatly reduces the toxicity of aconitine (Jacyno, 1981); thus, the positions of these H-bond donors and acceptors are likely important in receptor binding. Another intramolecular hydrogen bond is present between the methoxy O atom on C(16) and the H atom of the hydroxyl group on C(13); O(C16)···O(C13) 2·575 (5), H···O(C16) 1·85 Å, ∠O(C13)–H···O(C16) 136°. No other hydrogen bonds, either intra- or inter-molecular were observed in the structure. The packing of aconitine molecules appears to be determined by van der Waals contacts.

Thus, aconitine and other similar diterpenoids have an inflexible framework with conformational freedom only in the *A* ring and in the free edge of the *D* ring. H-bond formation appears to determine ring conformation and thus the pharmacology of this neurotoxin.

The author wishes to thank the Alberta Heritage Foundation for Medical Research for a Scholarship and Establishment Grant, Dr Patrick van Roey for collecting the data and Dr K. Ann Kerr for use of the diffractometer.

References

BACHELOR, F. W., BROWN, R. F. C. & BÜCHI, G. (1960). *Tetrahedron Lett.* **10**, 1–9.

BIRNBAUM, K. B. (1972). *Acta Cryst.* B**28**, 1551–1560.

CATTERALL, W. A. (1980). *Annu. Rev. Pharmacol. Toxicol.* **20**, 15–43.

CODDING, P. W. & KERR, K. A. (1981). *Acta Cryst.* B**37**, 379–383.

CROMER, D. T. & MANN, J. B. (1968). *Acta Cryst.* A**24**, 321–324.

JACYNO, J. M. (1981). PhD Thesis, Univ. of Calgary, Calgary, Alberta, Canada.

KERR, K. A. & CODDING, P. W. (1982). *Acta Cryst.* B**38**, 1237–1241.

MAIN, P., LESSINGER, L., WOOLFSON, M. M., GERMAIN, G. & DECLERCQ, J. P. (1978). *MULTAN* 78. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

MATSUTANI, T., SEYAMA, I., NARAHASHI, T. & IWARA, J. (1981). *J. Pharmacol. Exp. Ther.* **217**, 812–819.

PELLETIER, S. W., DE CAMP, W. H., FINER-MOORE, J. & ICHINOHE, Y. (1979). *Cryst. Struct. Commun.* **8**, 299–304.

PELLETIER, S. W. & KEITH, L. H. (1970). *Chemistry of the Alkaloids*, edited by S. W. PELLETIER, pp. 503–505. New York: Van Nostrand-Reinhold.

PRZYBYLSKA, M. (1961). *Acta Cryst.* **14**, 429–434.

STEWART, J. M. (1976). XRAY 76. Tech. Rep. TR-446. Computer Science Center, Univ. of Maryland, College Park, Maryland.

Acta Cryst. (1982). B**38**, 2522–2525

Antazoline Hydrochloride*†

BY V. BERTOLASI

Istituto Chimico, Università di Ferrara, Italy

P. A. BOREA

Istituto di Farmacologia, Università di Ferrara, Italy

AND G. GILLI

Centro di Strutturistica Diffrattometrica, Università di Ferrara, Italy

(*Received* 17 *February* 1982; *accepted* 6 *April* 1982)

Abstract. $C_{17}H_{20}N_3^+.Cl^-$, monoclinic, *I*2/*c*, *a* = 25·819 (5), *b* = 5·917 (3), *c* = 21·549 (4) Å, *β* = 104·30 (3)°, *Z* = 8, D_c = 1·26 Mg m^{-3}, *μ*(Cu *K*α) = 1·98 mm^{-1}. The structure was refined to an *R* factor of 0·041 from 2086 observed reflections. Comparison of the present and previous crystal-structure determinations seems to substantiate the idea that a distance of 6·00–6·40 Å between the amino N and the centre of

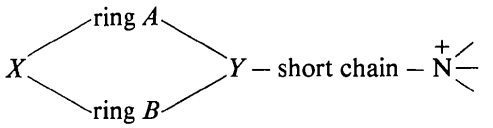
* Crystallographic and Conformational Studies on Histamine H_1 Receptor Antagonists. III.

† 4,5-Dihydro-*N*-phenyl-*N*-(phenylmethyl)-1*H*-imidazole-2-methanamine hydrochloride.

0567-7408/82/092522-04$01.00

gravity of one unsaturated ring is the main requirement to be fulfilled for the molecule to display antihistaminic activity.

Introduction. Histamine H_1 receptor antagonists (briefly antihistamines) are drugs which compete with histamine at its specific H_1 receptor site. From a chemical point of view they belong to several different classes, but it is generally assumed (Horn, 1975; Witiak, 1970) that they can be brought back to the general scheme



where ring A = aryl or heteroaryl, ring B = aryl or arylmethyl, X = –S–, $-CH_2-$, –CH=CH– groups sometimes bridging the *ortho* positions of rings A and B, Y = >N–, >CHO–, >CH–, >C = and (short chain –$\overset{+}{N}$<) can be a linear chain $-CH_2-CH_2-\overset{+}{N}<$ or a cyclic piperidine or piperazine group  .

Our present aim is the identification of a common stereochemical vector of antihistaminic activity which parallels the above chemical scheme. In previous papers of this series (Bertolasi, Borea, Gilli & Sacerdoti, 1980*a*,*b*) we have reported the molecular structures of two antihistamines, carbinoxamine maleate and cyclizine hydrochloride and suggested, on the grounds of the comparison of a few structure determinations and in agreement with early results of James & Williams (1974*b*), that the most active antihistamines are characterized by a distance of 6·00–6·30 Å between the protonated N and the centroid of one of the unsaturated rings. In the present paper we report the crystal structure of antazoline hydrochloride, an antihistamine belonging to the chemical class of ethylenediamines, for which only the structure of histadyl hydrochloride [*N*,*N*-dimethyl-*N'*-2-pyridyl-*N'*-(2-thienylmethyl)-1,2-ethanediamine (Clark & Palenik, 1972)] has so far been reported.

Experimental. Crystals were kindly provided by Ciba–Geigy, Saronno (Varese) and recrystallized from ethanol. Intensities were collected from a crystal of 0·26 × 0·07 × 0·38 mm using a Siemens AED automatic diffractometer (Ni-filtered Cu $K\alpha$ radiation, $\omega/2\theta$ scan and $\theta \leq 60°$). Out of 2376 independent reflections the 2086 having $I_o \geq 3\sigma(I_o)$ were used in the refinement. The structure was solved by direct methods (*MULTAN* 74, Main, Woolfson, Lessinger, Germain & Declercq, 1974). Scattering factors were taken from *International Tables for X-ray Crystallography* (1974) and most computations were carried out with *SHELX* 76 (Sheldrick, 1976). Full-matrix refinement with anisotropic non-H atoms and isotropic H atoms converged to discrepancy values $R = \sum|\Delta|/\sum|F_o| = 0{\cdot}041$ and $R_w = (\sum w|\Delta|^2/\sum w|F_o|^2)^{1/2} = 0{\cdot}049$. Weights for the last cycle were $1/w = \sigma^2(|F_o|) + 0{\cdot}0037|F_o|^2$. Final atomic coordinates and isotropic thermal parameters (Hamilton, 1959) are given in Table 1.*

Table 1. *Positional* (× 10^5, × 10^4 *for* H) *and thermal* (× 10^3) *parameters, with e.s.d.'s in parentheses*

	x	*y*	*z*	U_{eq}/U(Å^2)
Cl(1)	50000	150000	0	54 (1)
Cl(2)	50000	47697 (10)	25000	50 (1)
C(1)	37701 (7)	96006 (29)	16705 (8)	40 (1)
C(2)	33615 (7)	80826 (35)	16834 (9)	48 (1)
C(3)	30074 (8)	84975 (40)	20621 (10)	57 (1)
C(4)	30465 (9)	103993 (41)	24290 (12)	60 (1)
C(5)	34417 (9)	119189 (40)	24155 (10)	61 (1)
C(6)	38042 (8)	115482 (35)	20479 (9)	52 (1)
C(7)	40173 (7)	73438 (33)	8245 (9)	46 (1)
C(8)	35593 (6)	77129 (30)	2376 (8)	42 (1)
C(9)	32391 (8)	96202 (36)	1401 (10)	48 (1)
C(10)	28215 (9)	98395 (40)	−4028 (11)	57 (1)
C(11)	27253 (9)	81700 (43)	−8553 (10)	56 (1)
C(12)	30433 (9)	62750 (45)	−7703 (11)	66 (1)
C(13)	34591 (8)	60455 (36)	−2290 (9)	54 (1)
C(14)	44914 (7)	108851 (34)	11793 (10)	48 (1)
C(15)	50353 (6)	99417 (27)	12085 (8)	40 (1)
C(16)	58559 (8)	95528 (46)	10006 (13)	61 (1)
C(17)	57804 (7)	77390 (42)	14763 (10)	54 (1)
N(1)	41273 (6)	91699 (27)	12919 (7)	42 (1)
N(2)	52520 (6)	82590 (29)	15620 (7)	48 (1)
N(3)	53517 (6)	107867 (32)	8782 (8)	52 (1)
H(N2)	5100 (7)	7432 (31)	1788 (8)	39 (5)
H(N3)	5253 (9)	11918 (44)	622 (11)	61 (6)
H(2)	3325 (8)	6671 (38)	1450 (10)	52 (5)
H(3)	2714 (9)	7348 (39)	2057 (10)	62 (6)
H(4)	2814 (10)	10762 (44)	2676 (12)	74 (7)
H(5)	3487 (10)	13313 (47)	2675 (12)	75 (7)
H(6)	4097 (9)	12734 (40)	2075 (10)	60 (6)
H(71)	4341 (9)	7127 (38)	664 (10)	60 (6)
H(72)	3944 (8)	5921 (42)	1049 (10)	52 (5)
H(9)	3285 (9)	10746 (43)	392 (11)	59 (6)
H(10)	2622 (10)	11139 (47)	−449 (11)	71 (7)
H(11)	2448 (10)	8337 (43)	−1212 (12)	73 (7)
H(12)	3000 (12)	5092 (43)	−1066 (15)	84 (9)
H(13)	3661 (9)	4767 (35)	−164 (10)	49 (6)
H(141)	4373 (9)	11642 (40)	737 (11)	64 (6)
H(142)	4547 (9)	12130 (43)	1547 (11)	69 (6)
H(161)	6136 (10)	10538 (44)	1180 (11)	65 (7)
H(162)	5883 (11)	8897 (47)	574 (14)	81 (7)
H(171)	5785 (8)	6307 (45)	1285 (10)	55 (6)
H(172)	6056 (10)	7825 (42)	1877 (11)	72 (7)

Discussion. A general view of the molecule is reported in Fig. 1. Bond distances and angles and a selection of the relevant torsion angles are given in Table 2. The molecule is protonated at one N of the imidazoline ring

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36854 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

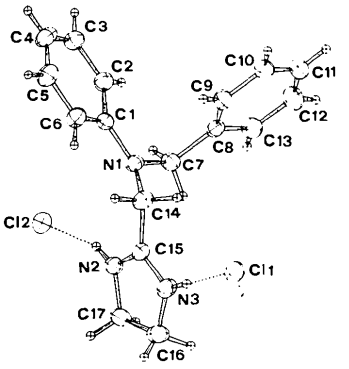


Fig. 1. An *ORTEP* (Johnson, 1965) view of the molecule showing the thermal ellipsoids at 40% probability.

Table 2. *Bond distances* (Å), *bond angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

C(1)–C(2)	1·391 (3)	C(10)–C(11)	1·367 (3)
C(1)–C(6)	1·401 (3)	C(11)–C(12)	1·375 (4)
C(1)–N(1)	1·398 (2)	C(12)–C(13)	1·383 (3)
C(2)–C(3)	1·390 (3)	C(14)–C(15)	1·498 (3)
C(3)–C(4)	1·365 (3)	C(14)–N(1)	1·444 (2)
C(4)–C(5)	1·366 (3)	C(15)–N(2)	1·294 (2)
C(5)–C(6)	1·385 (3)	C(15)–N(3)	1·308 (2)
C(7)–C(8)	1·519 (2)	C(16)–C(17)	1·530 (3)
C(7)–N(1)	1·456 (2)	C(16)–N(3)	1·459 (3)
C(8)–C(9)	1·384 (3)	C(17)–N(2)	1·454 (3)
C(8)–C(13)	1·387 (3)	N(2)–H(N2)	0·85 (2)
C(9)–C(10)	1·387 (3)	N(3)–H(N3)	0·87 (3)

Average C–H 0·97 ±0·06

C(2)–C(1)–C(6)	117·3 (2)	C(8)–C(13)–C(12)	120·6 (2)
C(2)–C(1)–N(1)	120·5 (2)	C(15)–C(14)–N(1)	111·9 (2)
C(6)–C(1)–N(1)	122·2 (2)	C(14)–C(15)–N(2)	125·2 (2)
C(1)–C(2)–C(3)	120·7 (2)	C(14)–C(15)–N(3)	122·7 (2)
C(2)–C(3)–C(4)	121·4 (2)	N(2)–C(15)–N(3)	112·2 (2)
C(3)–C(4)–C(5)	118·6 (2)	C(17)–C(16)–N(3)	102·5 (2)
C(4)–C(5)–C(6)	121·5 (2)	C(16)–C(17)–N(2)	102·4 (2)
C(1)–C(6)–C(5)	120·5 (2)	C(1)–N(1)–C(7)	119·7 (1)
C(8)–C(7)–N(1)	116·6 (2)	C(1)–N(1)–C(14)	121·4 (2)
C(7)–C(8)–C(9)	123·8 (2)	C(7)–N(1)–C(14)	115·4 (1)
C(7)–C(8)–C(13)	118·0 (2)	C(15)–N(2)–C(17)	111·8 (2)
C(9)–C(8)–C(13)	118·2 (2)	C(15)–N(2)–H(N2)	126 (1)
C(8)–C(9)–C(10)	121·0 (2)	C(17)–N(2)–H(N2)	122 (1)
C(9)–C(10)–C(11)	120·0 (2)	C(15)–N(3)–C(16)	111·1 (2)
C(10)–C(11)–C(12)	119·8 (2)	C(15)–N(3)–H(N3)	121 (2)
C(11)–C(12)–C(13)	120·4 (2)	C(16)–N(3)–H(N3)	128 (2)

N(2)–C(15)–C(14)–N(1)	−31·0 (3)	C(14)–N(1)–C(1)–C(6)	−11·2 (3)
N(3)–C(15)–C(14)–N(1)	150·4 (2)	C(14)–N(1)–C(1)–C(2)	168·6 (2)
C(15)–C(14)–N(1)–C(1)	138·8 (2)	N(1)–C(7)–C(8)–C(9)	−2·1 (3)
C(15)–C(14)–N(1)–C(7)	−62·5 (2)	N(1)–C(7)–C(8)–C(13)	177·3 (2)
C(14)–N(1)–C(7)–C(8)	−88·1 (2)		

making N(2) and N(3) atoms indistinguishable. Accordingly, the two bond distances C(15)–N(2) and C(15)–N(3) are intermediate between single and double-bond distances [1·294 (2) and 1·308 (2) Å respectively]. No particular features seem to be associated with the other bond distances and angles with the exception of the distance N(1)–C(1) of 1·398 (2) Å, which is slightly longer than usually observed in a planar $\overset{\diagdown}{\underset{\diagup}{=}}$C–N$\overset{\diagup}{\underset{\diagdown}{}}$ group (Gilli & Bertolasi, 1979, 1981). This is explained by the relevant pyramidalization of the N as expressed by the distance 0·156 (2) Å of N(1) from the plane through C(1)–C(7) and C(14).

The packing in the crystal is shown in Fig. 2. The molecules are linked in infinite chains ···Cl(1)···H(N3)–N(3)–C(15)–N(2)–H(N2)···Cl(2)···H(N2)–N(2)–C(15)–N(3)–H(N3)···Cl(1) in a zig-zag arrangement in the (*yz*) plane at $x = 0$, where the antazoline ions connect non-equivalent Cl^- ions alternately situated at $y = 0$ on crystallographic centres and at $y = \pm 0{\cdot}977$ on twofold axes. On the parallel (*yz*) plane at $x = \frac{1}{2}$ all the chains are shifted by $\frac{1}{2}$ along *y*. This arrangement allows the two half positive charges situated on H(N2) and H(N3) to be saturated by two Cl^- ions located in the two different special positions and having occupancy of $\frac{1}{2}$.

In Fig. 3 the geometry of antazoline is compared with that of histadyl (Clark & Palenik, 1972), the only other antihistamine belonging to the same chemical class (ethylenediamines), and cyproheptadine (Birknes, 1977), an antihistamine having a practically rigid structure. H atoms, including that at the protonated N, are omitted and all molecules are projected onto the plane defined by the amino N and the centres of gravity

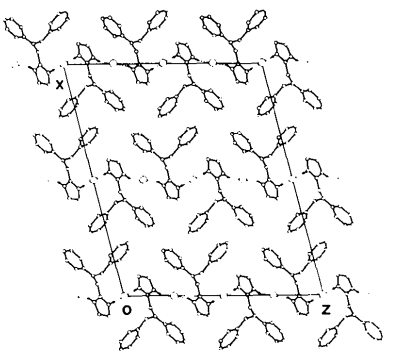


Fig. 2. The packing of the molecules in the crystal.

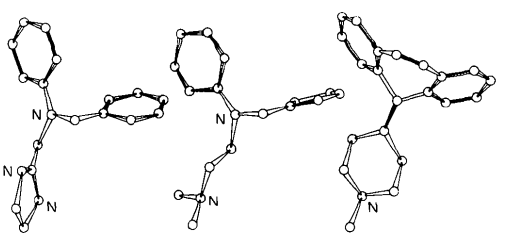


Fig. 3. Comparison of the molecular structures of antazoline (present work), histadyl (Clark & Palenik, 1972) and cyproheptadine (Birknes, 1977) projected on the plane defined by the amino N and the centroids of the unsaturated rings.

of the unsaturated rings. The figure shows the ability of ethylenediamines to mimic the shape of the rigid molecule. In particular the distances $d_{N\text{-}CG}$, between the N atom and the centres of gravity (CG) of the unsaturated rings in cyproheptadine are 6·29 and 6·24 Å, while the corresponding values are N–CG(thenyl) = 6·8 and N–CG(pyridyl) = 5·56 Å in histadyl and N(3)–CG(Ph1) = 6·18 and N(3)–CG(Ph2) = 5·90 Å in antazoline. Thus an N–CG distance of 6·0–6·5 Å is reproduced by the (ring)–CH_2–$\overset{|}{N}$–CH_2–CH_2–$\overset{+}{N}$ or (ring)–$\overset{|}{N}$–CH_2–$\overset{|}{C}$H–$\overset{+}{N}$ arrangements and probably by both if small conformational changes are allowed. This result seems to be of some interest as it has been shown that $d_{N\text{-}CG}$ values of 6·00–6·40 Å can be reproduced by other antihistamines having four-membered propylamino (ring)–$\overset{|}{C}$H–CH_2–CH_2–$\overset{+}{N}$ or propenylamino (ring)–$\overset{|}{C}$=CH–CH_2–$\overset{+}{N}$ chains (James & Williams, 1974*a*, *b*) and also by the five-membered aminoethyl chain (ring)–$\overset{|}{C}$H–O–CH_2–CH_2–$\overset{+}{N}$ present in carbinoxamine (Bertolasi *et al.*, 1980*b*), the correct $d_{N\text{-}CG}$ distance being obtained through a zig-zag planar conformation in the former and a helical one in the latter.

In conclusion, all the data so far collected seem to substantiate the idea that a distance of 6·00–6·40 Å between the amino N and the centre of gravity of an unsaturated ring is the primary stereochemical requirement a molecule must fulfill for showing strong antihistaminic activity, all other factors known to affect the biological response (pK_a values, overall lipophilicity or presence of a second unsaturated ring) being considered mere modulators of the activity itself.

References

BERTOLASI, V., BOREA, P. A., GILLI, G. & SACERDOTI, M. (1980*a*). *Acta Cryst.* B**36**, 1975–1977.

BERTOLASI V., BOREA, P. A., GILLI, G. & SACERDOTI, M. (1980*b*). *Acta Cryst.* B**36**, 2287–2291.

BIRKNES, B. (1977). *Acta Cryst.* B**33**, 687–691.

CLARK, G. R. & PALENIK, G. J. (1972). *J. Am. Chem. Soc.* **94**, 4005–4009.

GILLI, G. & BERTOLASI, V. (1979). *J. Am. Chem. Soc.* **101**, 7704–7711.

GILLI, G. & BERTOLASI, V. (1981). *Acta Cryst.* A**37**, C85.

HAMILTON, W. C. (1959). *Acta Cryst.* **12**, 609–610.

HORN, A. S. (1975). *Handbook of Psychopharmacology*, Vol. 2, edited by L. L. IVERSEN, D. S. IVERSEN & S. H. SNYDER, pp. 179–243. New York: Plenum.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press.

JAMES, M. N. G. & WILLIAMS, G. J. B. (1974*a*). *Can. J. Chem.* **52**, 1872–1880.

JAMES, M. N. G. & WILLIAMS, G. J. B. (1974*b*). *Can. J. Chem.* **52**, 1880–1888.

JOHNSON, C. K. (1965). *ORTEP*. Report ORNL–3794, revised. Oak Ridge National Laboratory, Tennessee.

MAIN, P., WOOLFSON, M. M., LESSINGER, L., GERMAIN, G. & DECLERCQ, J. P. (1974). *MULTAN* 74. *A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

SHELDRICK, G. M. (1976). *SHELX* 76. A program for crystal structure determination. Univ. of Cambridge, England.

WITIAK, D. T. (1970). *Medicinal Chemistry*, 3rd ed., pp. 1643–1668. New York: Wiley–Interscience.

Acta Cryst. (1982). B**38**, 2525–2528

Structures of Radical Anion Salts and Complexes. 5,5-Dimethyldibenzophospholium 7,7,8,8-Tetracyano-*p*-quinodimethanide (1:2)

BY G. J. ASHWELL, D. W. ALLEN, D. A. KENNEDY AND I. W. NOWELL

Department of Chemistry, Sheffield City Polytechnic, Sheffield S1 1WB, England

(*Received* 21 *December* 1981; *accepted* 6 *April* 1982)

Abstract. $C_{14}H_{14}P^+.2C_{12}H_4N_4^{1/2-}$, (DMDBP)$(TCNQ)_2$, $M_r = 621·6$, monoclinic, space group $P2_1/m$, $a = 7·547$ (4), $b = 30·19$ (2), $c = 7·863$ (5) Å, $\beta = 115·86$ (7)°, $U = 1612·1$ Å^3, $Z = 2$, $D_m = 1·30$, $D_c = 1·28$ Mg m^{-3}, $F(000) = 642$, μ(Mo $K\alpha$, $\lambda = 0·71069$ Å) $= 0·09$ mm^{-1}. The structure was solved by direct methods and refined to $R = 0·095$ for 1081 observed reflexions. The radical anions stack plane-to-plane in columns parallel to **c**, each column consisting of a series of TCNQ dimers. The columns are arranged in sheets parallel to the *ac* plane, with successive sheets being interleaved along **b** by the DMDBP cations.

Introduction. The crystal structure of (DMDBP)$(TCNQ)_2$ has been determined as part of a series of studies on conducting TCNQ salts (Ashwell, 1978, 1981, 1982). A common feature of these materials is a

0567-7408/82/092525-04$01.00