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Polymorphism of doxylamine succinate and X-ray structural study of Form I and of doxylamine succinate 0.5 succinic acid

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Summary

Two different polymorphic forms of doxylamine succinate and crystals of doxylamine succinate 0.5 succinic acid (S) were prepared and characterized by means of thermomicroscopy, differential scanning calorimetry, infrared spectrometry and X-ray crystallography. The crystal and molecular structures of both Form I and (S) were determined from three-dimensional X-ray data. The stabilities of Form I and (S) under different storage temperatures were determined.

Introduction

During stability trials on doxylamine succinate tablets received from a pharmaceutical manufacturer the assay results decreased ±20% in 28 weeks under all storage conditions. Tablets stored at 75% relative humidity also turned brown. Dissolution curves revealed a break in the curve indicative of recrystallization. A study on possible polymorphism of doxylamine succinate was undertaken since different crystal forms can exhibit differences in stability and reactivity (Burger, 1983) as well as in compression behavior (Junginger, 1976). Differences in chemical stability of polymorphs of fenretinide (Walkling et al., 1986) and cephalosporins (Pikal et al., 1977) have been reported. The physical stability of the tablets can be influenced by the polymorph they contain. Tablets containing carbochromen hydrochloride crystals II cracked and split in humid conditions but tablets containing Form I remained stable (Yamaoka et al., 1982). Nyqvist and Wadsten (1986) found that the polymorphs of a phosphate salt of a substituted benzamide derivative, precipitated from ethanol and ethanol/water mixtures, differed in water adsorption and light stability. In connection with the increased water adsorption, the rate of discoloration increased upon light exposure. Decreased assay results and discoloration of the doxylamine succinate tablets could be due to polymorphic interconversion during the

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manufacturing process in which polyvinylpyrrolidone in 90% ethanol was used as a granulating agent. Chapman et al. (1968) found that the presence of methanol, methanol vapour or water vapour interconverted the various polymorphs of cephaloridine. Water and water vapour were shown to be important factors in the transformation of Form II of sulphamethoxydiazine at room temperature (Moustafa et al., 1972). Two polymorphs of doxylamine succinate have been observed during thermomicroscopy, namely Form I with a melting point of 100–102° C and a form labelled Form II with a melting point of 78–82° C (Kuhnert-Brandstätter, 1971).

However, during this study crystals with the composition of doxylamine succinate 0.5 succinic acid (S) were also prepared. Crystals of Form II could only be prepared as Kuhnert-Brandstätter (1971) has done on a thermomicroscope slide. Crystals of Form I and of (S) could be prepared by recrystallization and were characterized using thermomicroscopy, differential scanning calorimetry (DSC), infrared spectrometry (IR) and X-ray crystallography. The crystal and molecular structures of Form I and of (S) are described as obtained by single-crystal X-ray diffraction. A stability study on crystals of Form I and (S) was undertaken to ascertain the stability of the two species under various storage conditions.

Materials and Methods

Preparation

The following recrystallization method was used for the preparation of (S) and polymorphic Form I of doxylamine succinate. Commercial doxylamine succinate (Twins-Propan, Johannesburg, R.S.A.) was dissolved in boiling analytical reagent grade solvent under constant stirring. The solution was filtered into a previously warmed conical flask through warm filter paper. The filtered solutions were cooled either by slow cooling at room temperature or rapid cooling in an ice bath. The crystals obtained were collected by filtration through a sintered glass Buchner filter, transferred from one filter paper to another and stored on a watch-glass to remove residual solvent and finally stored in airtight containers.

Doxylamine succinate Form I

Form I was crystallized from a 50% solution of doxylamine succinate in absolute ethanol. The solution was permitted to stand at room temperature until crystallization was complete.

Doxylamine succinate Form II

Form II was only obtained on a thermomicroscope slide. Raw material was heated till it melted and after standing for several hours crystals of Form II and I formed.

Doxylamine succinate 0.5 succinic acid (S)

Crystals were obtained from a 4% solution of doxylamine succinate in ethyl acetate cooled at either room temperature or in an ice bath, a 12 and a 10% solution of doxylamine succinate in isopentanol cooled at room temperature or in an ice bath respectively and from a 30% solution of doxylamine succinate in absolute ethanol cooled in an ice bath.

Characterization of (S) and the polymorphic forms

The crystals obtained by crystallization were identified using data from thermomicroscopy, DSC, IR and X-ray crystallography. Crystals of Form II were identified by thermomicroscopy only.

Thermomicroscopy

The thermal behaviour of the crystals in silicon oil was studied at a heating rate of 4° C per min with a Leitz Laborlux K thermomicroscope connected to a Goerz Metratherm 1200 thermocouple. The thermomicroscope was calibrated with analytical grade acetanilide with a melting point of 115° C.

Differential scanning calorimetry

A Du Pont 910 DSC system equipped with a Du Pont 99 thermal analyzer programmer and a Hewlett-Packard X-Y recorder with a chart speed of 5° C per cm was used. The instrument was calibrated with indium (99.999%) with a melting point of 156.6° C. Samples, varying in mass be-

tween 8.5 and 9.5 mg (Sartorius 4503 microbalance) were measured in Perkin-Elmer aluminum pans. The aluminum pans were sealed with a Du Pont crimping apparatus. An empty sealed aluminum pan was used as reference. The thermal behaviour of the different polymorphic forms was studied under a nitrogen purge at a heating rate of 5 °C/min.

Infrared spectroscopy

IR spectra in Nujol were obtained over a wavenumber range of 4600 to 400 cm^{-1} with a Nicolet 5DX Fourier transform infrared spectrometer, connected to a Nicolet 5DX data processor and a Hewlett-Packard 7470 A printer.

X-ray powder diffraction

Highly crystalline samples were chosen for powder diffraction and their purity established by C, H, N elemental analysis. Samples of Form I and of (S) were finely ground and packed into standard Al holders. Powder patterns were recorded on a Philips PW1050/70 diffractometer using CuK_α radiation ($\lambda = 1.5418$ Å).

X-ray data collection and structure determination

Intensity data were collected on an Enraf-Nonius CAD4 diffractometer in the ω-2θ mode using MoK_α radiation ($\lambda = 0.7107$ Å). Data collection in the range $1° < \theta < 25°$ included variable scan speeds and widths, intensity control at 1-h intervals and orientation control every 200 measured reflections. To reduce uptake of atmospheric water, the crystal of Form I was sealed in a Lindemann capillary. All data were corrected for Lp-effects. Absorption and intensity decay were negligible. Both structures were solved by direct methods using program SHELX76 (Sheldrick, 1976) and refined by full-matrix least-squares. Abnormally high thermal motion for the phenyl rings of the two independent cations in Form I led to their treatment as rigid hexagons throughout refinement. To ensure a reasonable least-squares overdetermination ratio, only the O atoms and atoms N(5) and N(33) were refined anisotropically. For (S) all atoms vibrated anisotropically. H atoms were generally placed in idealized positions. Refinement weights were of the form $w = 1/\{\sigma^2[F] + gF^2\}$. Other programs used were PLUTO79 (Motherwell and Clegg, 1979) and PARST (Nardelli, 1983). Structure factor tables and derived molecular parameters may be obtained from the authors.

Stability study of Form I and (S)

Crystals of Form I and (S) were stored at 20, 37 and 45 °C in closed containers. Samples were assayed at 0, 3, 9 and 12 months using a high-performance liquid chromatographic (HPLC) method (Van Tonder, 1988).

Results and Discussion

Thermomicroscopy

The different polymorphic forms and crystals of (S) melted with the formation of a few small gas bubbles due to small amounts of water adsorbed by the hygroscopic doxylamine succinate and (S). Residual crystals in the partially melted droplets grew into rhomboids, rods and short prisms before finally melting, as previously reported (Kuhnert-Brandstätter, 1971). Crystals of Form I melted at 101.0–106.5 °C, Form II at 79.2–86.0 °C and (S) at 90.1–97.0 °C.

Differential scanning calorimetry

DSC thermograms of Form I and (S) show endothermic peaks with onsets of 102 and 91 °C, respectively. Their maxima occur at 107 and 95 °C, respectively.

Infrared spectroscopy

A comparison of the IR spectra of (S) and Form I (Fig. 1) showed differences in the 408–1740 cm^{-1} region. The main differences are indicated by arrows. The signal at 1680–1740 cm^{-1} occurs as a single peak for Form I. This peak is more intense for (S) and is split, owing to the presence of additional carbonyl groups of the succinic acid moiety.

X-ray powder diffraction

Distinctly different powder patterns were obtained for the two species. The d spacings (in Å) and relative intensities of the three major peaks of

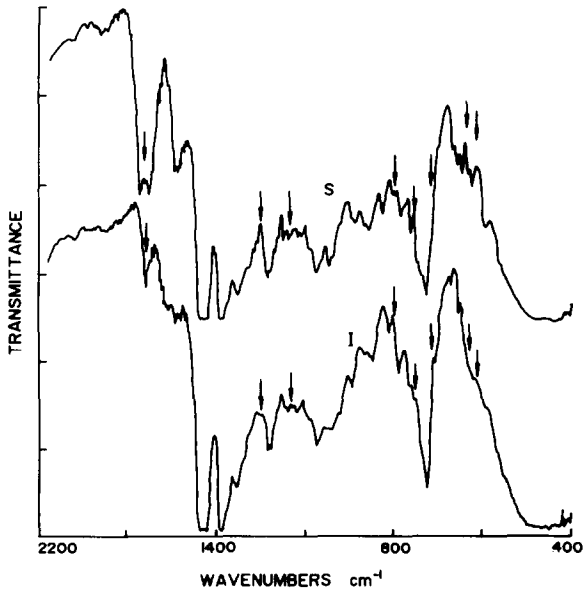

Fig. 1. IR spectra of doxylamine succinate Form I and doxylamine succinate 0.5 succinic acid (S).

Form I were 4.352 (100), 4.832 (69) and 5.331 (53), while for (S) they were 3.813 (100), 4.678 (73) and 4.079 (50).

Molecular and crystal structures

Crystal data and data-collection parameters are listed in Table 1. Tables 2 and 3 list refined atomic coordinates and thermal parameters. Two crystallographically independent doxylamine cations occur in the crystal of Form I. In both, the aminoethyl ether chain adopts a t,t,g conformation (defined by torsion angles C15-C1-O2-C3, C1-O2-C3-C4, O2-C3-C4-N5, respectively, in Fig. 2a and analogous angles in Fig. 2b) which is similar to that observed in carbinoxamine maleate (Bertolasi et al., 1980), a ring-chlorinated member of the aminoethylether class of antihistamines. In (S), Fig. 1c, a t,t,g conformation again obtains but comparison of corresponding torsional parameters for the three conformations shows significant

TABLE 1

Crystal data and data-collection parameters for Form I and (S)

	Doxylamine succinate, Form I	Doxylamine succinate 0.5 succinic acid, (S)
Molecular formula	$[C_{17}H_{23}N_2O]^+[C_4H_5O_4]^-$	$[C_{17}H_{23}N_2O]^+[C_4H_5O_4]^-0.5[C_4H_6O_4]$
Formula mass	388.45	447.51
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
a (Å)	8.955(3)	8.094(1)
b (Å)	21.172(4)	8.923(2)
c (Å)	22.601(3)	16.696(3)
α (°)	90.0	92.56(1)
β (°)	96.61(2)	98.10(1)
γ (°)	90.0	105.81(1)
V (Å^3)	4257(2)	1144(1)
Z	8	2
D_x (g/cm^3)	1.2120	1.2988
μ(MoK$_\alpha$) (cm^{-1})	0.81	0.90
F(000)	1664	478
Crystal size (mm^3)	0.25 × 0.28 × 0.28	0.20 × 0.35 × 0.50
Observed reflections ($I > 2\sigma(I)$)	1925	2648
Final $\Delta\rho$ (e Å^{-3})	0.46	0.24
R	0.091	0.045
R_w	0.086	0.052

TABLE 2

Fractional atomic coordinates [a] and isotropic (or equivalent isotropic) thermal parameters [b] for doxylamine succinate, Form I

Atom	x	y	z	U_{iso}/U_{eq}
C(1)	5336 (14)	4068 (6)	4138 (6)	56 (4)
O(2)	5560 (8)	3506 (4)	4480 (3)	58 (4)
C(3)	6952 (14)	3169 (6)	4451 (5)	64 (4)
C(4)	7052 (13)	2640 (6)	4873 (5)	58 (4)
N(5)	6925 (10)	2826 (5)	5497 (4)	61 (5)
C(6)	7985 (17)	3327 (7)	5706 (6)	91 (5)
C(7)	7062 (17)	2271 (7)	5895 (7)	93 (5)
C(8)	6377 (16)	4586 (7)	4420 (7)	104 (6)
C(9)	5471 (10)	3918 (4)	3501 (5)	69 (4)
C(10)	4731 (10)	3411 (4)	3201 (5)	97 (5)
C(11)	4913 (10)	3297 (4)	2606 (5)	141 (7)
C(12)	5833 (10)	3691 (4)	2310 (5)	126 (7)
C(13)	6572 (10)	4197 (4)	2610 (5)	163 (8)
C(14)	6391 (10)	4311 (4)	3205 (5)	106 (6)
C(15)	3680 (13)	4272 (6)	4182 (5)	48 (4)
C(16)	2849 (13)	3968 (6)	4576 (5)	51 (4)
C(17)	1381 (14)	4191 (6)	4613 (6)	63 (4)
C(18)	871 (14)	4725 (6)	4291 (5)	63 (4)
C(19)	1743 (15)	4993 (6)	3915 (6)	70 (4)
N(20)	3197 (13)	4789 (6)	3846 (5)	84 (4)
C(21)	3863 (17)	3170 (7)	6082 (7)	69 (5)
C(22)	2419 (13)	3395 (6)	6318 (5)	57 (4)
C(23)	2660 (13)	3704 (6)	6920 (5)	62 (4)
C(24)	1264 (14)	3906 (6)	7184 (6)	45 (4)
O(25)	3748 (9)	2847 (4)	5631 (4)	69 (4)
O(26)	5043 (11)	3359 (6)	6350 (5)	154 (7)
O(27)	27 (8)	3890 (4)	6907 (3)	63 (4)
O(28)	1482 (8)	4127 (4)	7727 (3)	65 (4)
H(28)	258 (10)	391 (7)	801 (5)	150 (0) [c]
C(29)	8908 (13)	5776 (6)	8619 (5)	53 (4)
O(30)	8410 (9)	5186 (4)	8335 (3)	68 (4)
C(31)	8052 (16)	4712 (7)	8727 (7)	87 (5)
C(32)	8235 (14)	4048 (6)	8451 (6)	68 (4)
N(33)	6934 (10)	3906 (5)	7990 (4)	50 (4)
C(34)	6800 (14)	4359 (6)	7471 (6)	62 (4)
C(35)	7108 (15)	3257 (6)	7761 (6)	70 (4)
C(36)	7682 (14)	6050 (7)	8941 (6)	79 (5)
C(37)	9151 (14)	6189 (7)	8084 (6)	66 (4)
C(38)	9169 (15)	5990 (7)	7516 (6)	82 (5)
C(39)	9485 (15)	6402 (7)	7056 (7)	91 (5)
C(40)	9777 (14)	7018 (7)	7195 (6)	74 (4)
C(41)	9794 (15)	7196 (7)	7775 (6)	82 (5)
N(42)	9491 (12)	6810 (6)	8227 (5)	84 (4)
C(43)	10382 (11)	5682 (4)	9000 (3)	60 (4)
C(44)	11485 (11)	5308 (4)	8786 (3)	77 (4)
C(45)	12888 (11)	5241 (4)	9119 (3)	97 (5)
C(46)	13187 (11)	5549 (4)	9666 (3)	98 (5)
C(47)	12084 (11)	5923 (4)	9879 (3)	92 (5)
C(48)	10681 (11)	5990 (4)	9546 (3)	64 (4)
C(49)	4116 (15)	3596 (6)	8757 (6)	52 (4)
C(50)	2617 (13)	3372 (6)	8945 (5)	59 (4)
C(51)	2722 (12)	2939 (5)	9468 (5)	51 (4)
C(52)	1171 (15)	2711 (6)	9600 (6)	52 (4)
O(53)	4028 (8)	3938 (4)	8284 (3)	55 (4)
O(54)	5291 (9)	3448 (4)	9043 (4)	82 (5)
O(55)	26 (9)	2829 (4)	9282 (4)	78 (4)
O(56)	1189 (9)	2403 (4)	10097 (4)	61 (4)
H(56)	211 (15)	231 (6)	1036 (6)	98 (55)

[a] Expressed $\times 10^4$; $\times 10^3$ for H atoms,
[b] Expressed $\times 10^3$; U_{eq} of the form $1/3\ \Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$ (Å^2) for all O and N atoms except N(20) and N(42).
[c] Unrefined.

differences, especially among those describing the orientation of the dimethylammonium group. The distance (in Å) between the amino N atom and the centroid of the aromatic ring lying on its vertical in Fig. 2 is (a) 5.92, (b) 6.23 and (c) 6.07. For this parameter, a distance range of 6–6.30 Å has been quoted as relevant to antihistaminic activity (James and Williams, 1974; Bertolasi et al.,

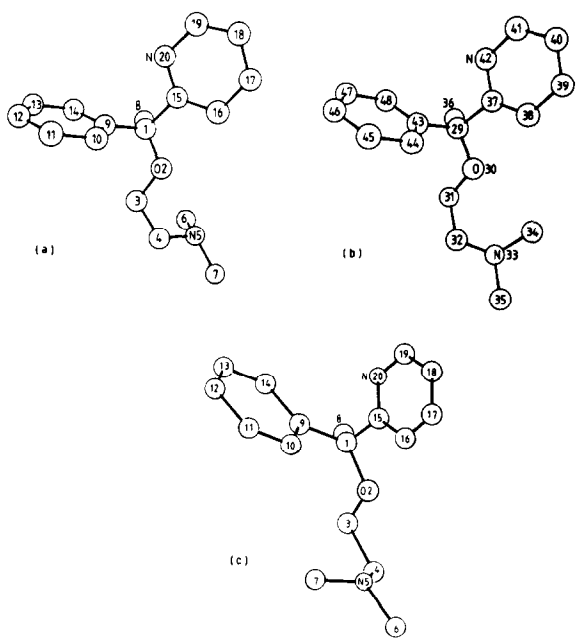

Fig. 2. Observed doxylamine cation conformations: (a) and (b), independent cations in Form I; (c) conformation in (S). Reported coordinates for (c) have been inverted to match the chirality of (a) and (b). H atoms omitted for clarity.

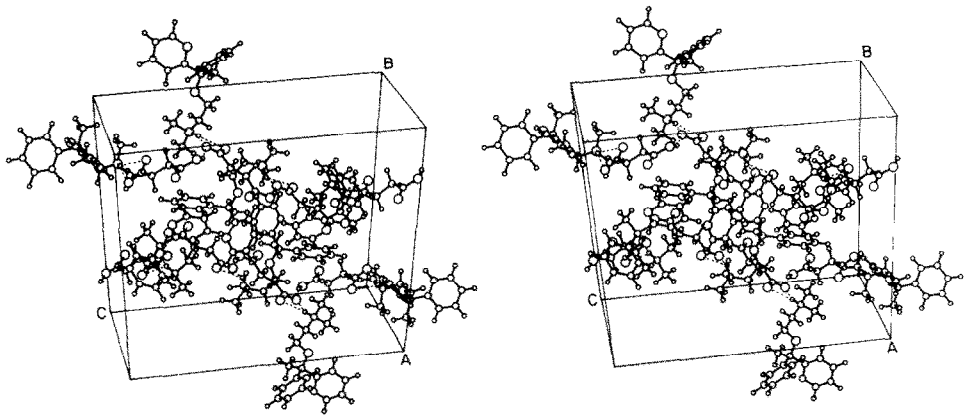

Fig. 3. Stereoscopic packing diagram for doxylamine succinate, Form I. Hydrogen bonds are indicated by dashed lines.

1980). Figs 3 and 4 illustrate the molecular packing in the two species. In Form I, planar hydrogen succinate ions are linked by strong O-H · · · O hydrogen bonds (O . . . O 2.51(1)–2.52(1) Å) in infinite chains parallel to z and the structure is built up by the attachment of doxylamine cations to

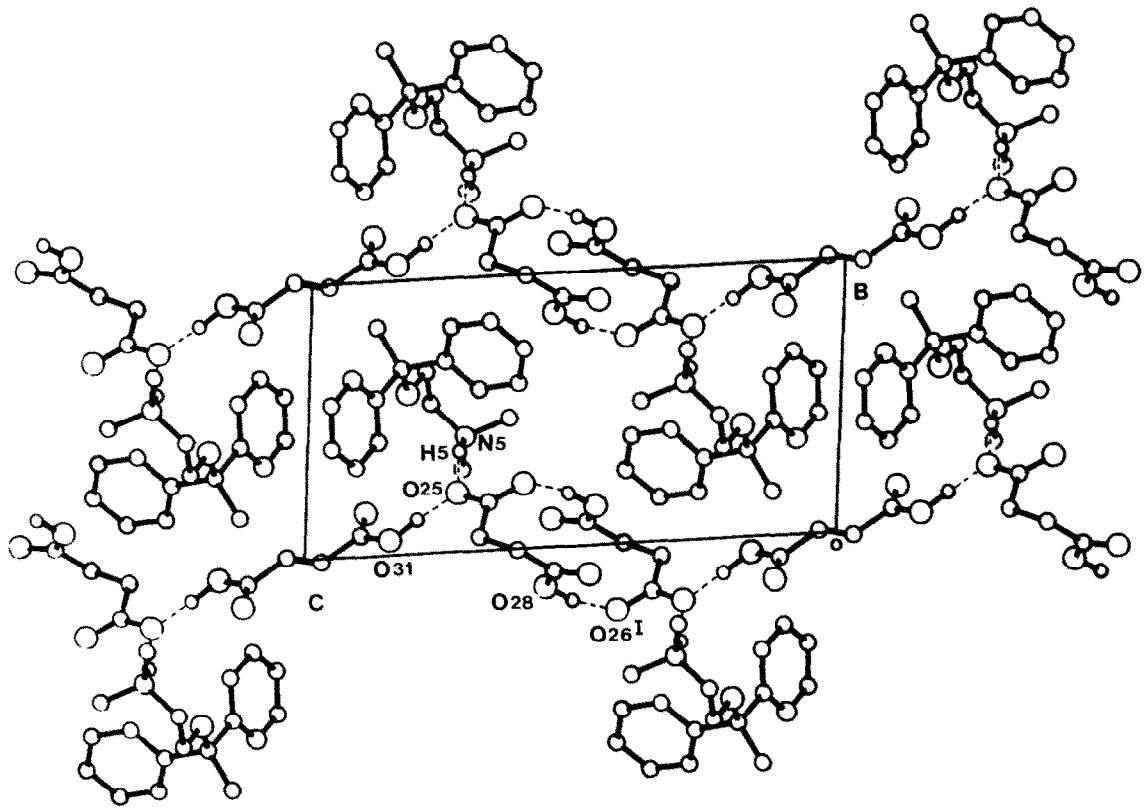

Fig. 4. Molecular packing in (S), doxylamine succinate 0.5 succinic acid, projected down (100). Hydrogen bonds are indicated by dashed lines.

TABLE 3

Fractional atomic coordinates [a] and isotropic (or equivalent isotropic) thermal parameters [b] for doxylamine succinate 0.5 succinic acid (S)

Atom	x	y	z	U_{iso}/U_{eq}
C(1)	4379 (3)	6806 (3)	8276 (2)	43 (1)
O(2)	2575 (2)	5892 (2)	8149 (1)	46 (1)
C(3)	1341 (3)	6656 (3)	7813 (2)	54 (1)
C(4)	−425 (3)	5484 (3)	7711 (2)	55 (1)
N(5)	−761 (3)	4218 (2)	7044 (1)	45 (1)
C(6)	−2461 (4)	3036 (4)	7075 (2)	66 (1)
C(7)	−730 (4)	4818 (4)	6229 (2)	64 (1)
C(8)	4637 (4)	8357 (3)	8763 (2)	57 (1)
C(9)	5037 (3)	7007 (3)	7459 (2)	42 (1)
C(10)	4270 (3)	5920 (3)	6805 (2)	49 (1)
C(11)	4880 (4)	6071 (3)	6070 (2)	57 (1)
C(12)	6280 (4)	7311 (4)	5985 (2)	59 (1)
C(13)	7075 (4)	8372 (3)	6636 (2)	58 (1)
C(14)	6461 (3)	8240 (3)	7371 (2)	51 (1)
C(15)	5322 (3)	5759 (3)	8741 (1)	43 (1)
C(16)	4644 (4)	4163 (3)	8670 (2)	59 (1)
C(17)	5588 (4)	3269 (4)	9075 (2)	67 (1)
C(18)	7157 (4)	3985 (4)	9539 (2)	60 (1)
C(19)	7744 (4)	5585 (4)	9579 (2)	65 (1)
N(20)	6857 (3)	6483 (3)	9188 (1)	59 (1)
C(21)	1818 (3)	1781 (3)	6566 (1)	37 (1)
C(22)	2713 (4)	521 (3)	6717 (2)	51 (1)
C(23)	3394 (3)	−41 (3)	5992 (2)	52 (1)
C(24)	2073 (3)	−880 (3)	5289 (2)	48 (1)
O(25)	1134 (2)	2170 (2)	7155 (1)	49 (1)
O(26)	1813 (2)	2395 (2)	5918 (1)	48 (1)
O(27)	2424 (3)	−1041 (3)	4622 (1)	80 (1)
O(28)	486 (3)	−1446 (3)	5446 (1)	61 (1)
H(28)	−39 (6)	−196 (5)	493 (3)	119 (14)
C(29)	507 (4)	−125 (4)	9673 (2)	53 (1)
C(30)	270 (3)	786 (3)	8955 (1)	43 (1)
O(31)	1225 (3)	566 (2)	8407 (2)	58 (1)
H(311)	112 (5)	127 (4)	789 (2)	104 (12)
O(32)	−681 (3)	1601 (3)	8871 (1)	73 (1)

[a] Expressed $\times 10^4$; $\times 10^3$ for H atoms.

[b] Expressed $\times 10^3$; U_{eq} of the form $(1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$ (Å^2).

one side of an anion chain by bifurcated N–H · · · O=C linkages (N . . . O 2.76(1)–3.09(1) Å). In (S), the hydrogen succinate anions adopt a *gauche* conformation (torsion angle −66.2(3)° for the C–C–C–C backbone) and form dimers by O–H · · · O=C (O . . . O 2.672(2) Å) hydrogen bonds around centres of symmetry. These dimers are linked along the *z*-direction by bridging succinate acid molecules through O–H · · · O hydrogen bonds (O . . . O 2.589(3) Å). The succinic acid molecules lie on centres of symmetry and are thus in the *anti*-conformation. Each doxylamine cation is attached to a hydrogen succinate moiety by a single N–H · · · O=C hydrogen bond (N . . . O 2.684(3) Å).

Up to the stage where single-crystal data revealed the 0.5 succinic acid form, species (S) was believed to be another polymorph, since no succinic acid was added to the recrystallization solution and thin-layer chromatography and HPLC data were the same as that of Form I. The only difference was that (S) was less hygroscopic than Form I (Van Tonder, 1988). Where possible, single-crystal X-ray crystallographic studies should be performed on all crystal forms of a substance in order to rule out new entities that could be mistaken as polymorphs. The reason for the formation of species (S) is not clear and the possibility of its formation from solvents used during manufacturing of dosage forms should be taken into account.

Stability study of Form I and (S)

Assay results of (S) decreased but Form I remained stable during a 12 month storage period at different temperatures (Table 4). The decrease in assay results of the doxylamine succinate tablets could be due to the probable formation of (S) during the manufacturing process as the assay results of (S) stored for 9 months at different temperatures decreased 8.4–11.3%. The colour

TABLE 4

Assay results of Form I and (S) during a stability study

Storage conditions (°C)	Assay results (%) during storage for			
	0 months	3 months	9 months	12 months
Form I				
20	100.6	100.5	100.9	100.9
37	100.6	101.5	100.7	99.7
45	100.6	98.0	97.9	97.8
(S)				
20	96.1	88.8	87.7	85.7
37	96.1	88.2	86.1	82.4
45	96.1	85.9	84.8	82.0

C.V. = 2.8%.

change of the tablets could also be due to the formation of (S) as light stability differs in different crystalline structures especially in the presence of water vapour (Nyqvist and Wadsten, 1986).

The pharmacology of this form should be studied. The possible occurrence of this form may account for the withdrawal of Debendox® and Bendectin® tablets, containing doxylamine succinate, from the market following problems encountered with its use in the treatment of morning sickness (Anonymous, 1984; Grodofsky and Wilmott, 1984). Before the safety of this form is established, care should be taken to prevent its formation during dosage form preparation.

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References

Anonymous., Debendox® settlement for U.S.A. only. *Pharm. J.*, 233 (1984) 79.

Bertolasi, V., Borea, P.A., Gilli, G. and Sacerdoti, M., Crystallographic and conformational studies on histamine H_1 receptor antagonists. I. Structure of carbinoxamine maleate. *Acta Crystallogr. Sect. B*, B36 (1980) 2287–2291.

Burger, A., The relevance of polymorphism. In Breimer, D.D. and Speiser, P. (Eds), *Topics in Pharmaceutical Sciences*, Elsevier, Amsterdam, 1983, pp. 347–358.

Chapman, J.H., Page, J.E., Parker, A.C., Rogers, D., Sharp, C.J. and Staniforth, S.E., Polymorphism of cephalosporidine. *J. Pharm. Pharmacol., 20* (1968) 418–429.

Grodofsky, M.P. and Wilmott, R.W., Possible association of use of Bendectin® during early pregnancy and congenital lung hypoplasia. *N. Engl. J. Med.* 311 (1984) 732. In: *Int. Pharm. Abstr.*, 22 (1985) 2203065.

James, M.N.G. and Williams, G.J.B., Crystal and molecular structure of the antihistaminic drug triprolidine hydrochloride monohydrate (*trans*-1-(*p*-tolyl)-1-(2-pyridyl)-3-(1-pyrrolidino)-prop-1-ene). *Can. J. Chem.*, 52 (1974) 1880–1888.

Junginger, H., Modifikationsumwandlungen durch mechanische Bearbeitung. *Pharm. Ind.*, 38 (1976) 724–728.

Kuhnert-Brandstätter, M., *Thermomicroscopy: The Analysis of Pharmaceuticals*, Pergamon, Oxford, 1971, p. 105.

Motherwell, W.D.S. and Clegg, W., PLUTO79, A program for plotting molecular and crystal structures, University of Cambridge, Cambridge, 1979.

Moustafa, M.A., Khalil, S.A., Ebian, A.R. and Motawi, M.M., Kinetics of interconversion of sulphamethoxydiazine crystal forms. *J. Pharm. Pharmacol.*, 24 (1972) 921–926.

Nardelli, M., PARST: a system of FORTRAN routines for calculating molecular structure parameters from results of crystal structure analyses. Comput. Chem., 7 (1983) 95–98.

Nyqvist, H. and Wadsten, T., Preformulation of solid dosage forms: light stability testing of polymorphs as a part of a preformulation program. *Acta Pharm. Technol.*, 32 (1986) 130–132.

Pikal, M.J., Lukes, A.L. and Lang, J.E., Thermal decomposition of amorphous β-lactam antibacterials. *J. Pharm. Sci.*, 66 (1977) 1312–1316.

Sheldrick, G.M., SHELX76, A program for crystal structure determination, University of Cambridge, Cambridge, 1976.

Van Tonder, E.C., Vastetoestandeienskappe van doksielamiensuksinaat. M.Sc. Dissertation, P.U. for C.H.E., Potchefstroom, R.S.A., 1988, pp. 85–96.

Walkling, W.D., Sisco, W.R., Newton, M.P., Fegely, B.J., Plampin, J.N. and Chrzanowski, F.A., Stability of fenretinide polymorphs. *Acta Pharm. Technol.*, 32 (1986) 10–12.

Yamaoka, T., Nakamachi, H. and Miyata, K., Studies on the characteristics of carbochromen hydrochloride crystals. II: Polymorphism and cracking in the tablets. *Chem. Pharm. Bull.*, 30 (1982) 3695–3700.