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Structure of *cis*-1-{[4-(1-Imidazolylmethyl)cyclohexyl]methyl}imidazole–Succinic Acid Complex

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Abstract. CGS 14796C, $C_{14}H_{20}N_4.C_4H_6O_4$, M_r = 362·43, monoclinic, $C2/c$, a = 28·148 (4), b = 9·722 (1), c = 19·200 (2) Å, β = 133·06 (1)°, V = 3838·88 Å^3, Z = 8, D_x = 1·26 Mg m^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ = 0·702 mm^{-1}, $F(000)$ = 1552, T = 294 K, R = 0·075 for all 3285 reflections. The structure is composed of linear chains of alternating CGS 14796C and succinic acid molecules. The CGS 14796C molecule is in an extended conformation.

Introduction. *cis*-1-{[4-(1-Imidazolylmethyl)cyclohexyl]methyl}imidazole–succinic acid [CGS 14796C, (I)] is an active non-steroidal aromatase inhibitor (Schiavo, Green, Triana, Spaet & Zaidi, 1988; Bullion, Osawa & Braun, 1990). Compound (I) is structurally unrelated to the natural substrates of the enzyme or to the clinically used inhibitor aminoglutethimide (II) (Santen, Santner, Davis, Veldhuis, Samojlik & Ruby, 1978; Shaw, Nicholls & Smith, 1988). However, (I) has the imidazole group in common with other potent aromatase inhibitors, CGS 16949A (III) and CGS 18320B (IV) (Steele, Meller, Sawyer & Brown, 1987), as shown in Fig. 1. The crystal structures of these compounds are being determined as part of on-going structure–activity studies of non-steriodal aromatase inhibitors (Van Roey, Bullion, Osawa, Browne, Bowman & Braun, 1990; Van Roey, Bullion, Osawa, Bowman & Braun, 1991).

Experimental. The sample was provided by the Ciba–Geigy Corporation. Crystals were obtained by slow evaporation over a period of about 6 weeks of a 3 ml methanol solution containing approximately 20 mg of compound. The sample was kept in a glass vial, sealed with a plastic cap and placed in a walk-in hot room at 310 (1) K. Very slow evaporation at high temperature yields excellent quality crystals for all compounds in this series and many other compounds. However, the benefits or effects of crystallization at the elevated temperature over room temperature have not been further evaluated. The crystal used for data collection had approximate dimensions 0·30 × 0·35 × 0·35 mm. Oscillation and Weissenberg photographs were used to determine the crystal system and preliminary cell dimensions. Systematic absences (hkl, $h+k \neq 2n$; $h0l$, $h,l \neq 2n$) are consistent with the space groups $C2/c$ or Cc. A body-centred orthorhombic cell was also consistent with the orientation angles but not with the diffraction pattern observed on the photographs. Equivalent reflections (hkl and $\bar{h}kl$) of the orthorhombic cell had different intensities. The highest symmetry monoclinic space group was selected for the first structure determination attempt and proved to be correct. Enraf–Nonius CAD-4 diffractometer, Cu $K\alpha$ radiation (λ = 1·5418 Å), Ni filter, $\theta/2\theta$ scan method. Unit-cell dimensions and orientation matrix

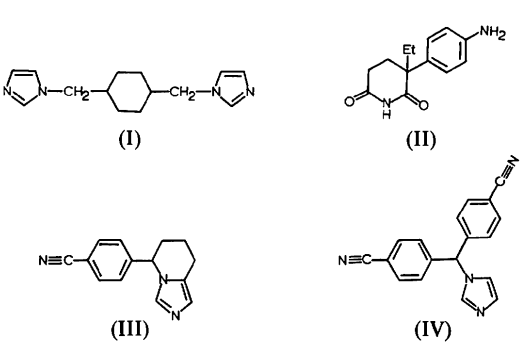

Fig. 1. Schematic diagrams of the structures of the non-steroidal aromatase inhibitors: (I), CGS 14796C, the title compound; (II), aminoglutethimide; (III), CGS 16949A; and (IV), CGS 18320B.

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0108-2701/91/051015-04$03.00

were determined from 25 reflections with $41{\cdot}66 < 2\theta < 58{\cdot}76°$. 5373 total data with $3{\cdot}0 < 2\theta < 154{\cdot}0°$, $-35 < h < 35$, $0 < k < 12$, $-1 < l < 24$. Intensities of six standard reflections ($\bar{3}19$, $\bar{1}1,1,2$, 912, 533, $\bar{1}3,3,9$, 261) were monitored every 3 h but did not decline significantly. Orientation checks were made after every 400th intensity measurement. Lorentz and polarization corrections were applied but an absorption correction was not considered necessary. Of the 3992 unique data ($R_{int} = 0{\cdot}025$), 3290 had $F > 3\sigma(F)$. $\sigma(F)$ was calculated according to Stout & Jensen (1968): $\sigma^2(F) = (k/4\mathrm{Lp}I)[\sigma^2(I) + (0{\cdot}01I)^2]$. The structure was determined by direct methods using the program *MULTAN* (Germain, Main & Woolfson, 1971) and refined by full-matrix least squares, minimizing $\sum[w(F_o - F_c)^2]$ where $w = 1/\sigma^2(F)$ for the data with $F > 3\sigma(F)$. Coordinates for all H atoms, except the one bonded to O(25), were determined from difference maps and refined with the non-H atoms after the anisotropic refinement had converged. The maximum value of the shift/e.s.d. during the last cycle of refinement was 0·04. Two reflections were considered mismeasurements on the basis of a δR plot (Abrahams & Keve, 1971) and not included in the refinement during the last cycles. Final R values are $R = 0{\cdot}067$, $wR = 0{\cdot}078$ for the 3285 data included in the refinement (335 parameters) and $R_{all} = 0{\cdot}075$ for all 3992 data; $S = 3{\cdot}091$. The R values are somewhat higher than expected because of the higher thermal motion or disorder of the succinic acid molecule and because of high correlations caused by the large β angle. 45 correlation coefficients were greater than 0·75. O(26) has the highest thermal parameter and the two largest positive (0·520 and 0·379 e Å^{-3}) and the most negative ($-0{\cdot}664$ e Å^{-3}) peaks in the final difference map are within 1·5 Å from it. The remaining maximum and minimum densities of the map are 0·301 and $-0{\cdot}303$ e Å^{-3}. Atomic scattering factors and dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 71–147). Other programs used include Blessing's (1987) data reduction package, locally modified refinement and structure analysis programs based on programs in the Enraf–Nonius *SDP* package (1979), and the plotting program *ORTEP*II (Johnson, 1976).

Discussion. Atomic coordinates and equivalent isotropic thermal parameters are listed in Table 1.* Fig. 2 shows the molecular conformation of (I) and the numbering scheme used. Selected bond lengths, bond angles and torsion angles are listed in Table 2. The structure is described as the complex of (I) with succinic acid, rather than the ion pair because H(19) is closer to O(19) than to N(16). The hydrogen bonds between the molecules are very strong. The hydrogen bond geometry is as follows: O(19)—H(19)···N(16) (x, y, z): O···N 2·610 (5), O—H 1·28 (7), H···N 1·35 (7) Å, O—H···N 167 (3)°; and O(25)···N(4)(x, y, $-1+z$): O···N 2·648 (4) Å. The long O(19)—H(19) bond length may be a result of the strength of the hydrogen bond. The H atom of the other bond, O(25)···N(4), could not be located. A complex of neutral molecules was also observed in the structure of (IV) which was also determined as the complex with succinic acid (Van Roey, Bullion, Osawa, Browne, Bowman & Braun, 1990).

Table 1. *Atomic coordinates* ($\times 10^4$ *for non*-H *atoms;* $\times 10^3$ *for* H *atoms*) *and equivalent isotropic thermal parameters* (Å$^2 \times 10$) *for the succinic acid complex of* (I); *e.s.d.'s are given in parentheses*

$$B_{eq} = (1/3)\sum_i\sum_j B_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
C(2)	7487 (2)	2190 (3)	3426 (2)	56 (2)
C(3)	7804 (2)	2308 (4)	4359 (3)	67 (2)
C(5)	8273 (1)	3683 (4)	4125 (2)	60 (2)
C(6)	7675 (2)	3250 (3)	2429 (2)	56 (2)
C(7)	7851 (1)	1978 (3)	2188 (2)	45 (1)
C(8)	7742 (1)	2228 (4)	1305 (2)	55 (1)
C(9)	7894 (1)	960 (3)	1022 (2)	56 (1)
C(10)	8569 (1)	395 (3)	1831 (2)	47 (1)
C(11)	8693 (2)	223 (3)	2733 (2)	56 (2)
C(12)	8549 (1)	1521 (3)	3010 (2)	48 (1)
C(13)	9098 (1)	1269 (3)	2024 (2)	48 (1)
C(15)	9141 (1)	2033 (3)	813 (2)	53 (1)
C(17)	9329 (2)	129 (4)	487 (2)	61 (2)
C(18)	9267 (1)	−170 (3)	1106 (2)	53 (2)
N(1)	7795 (1)	3077 (2)	3293 (1)	49 (1)
N(4)	8297 (1)	3255 (3)	4792 (2)	67 (1)
N(14)	9145 (1)	1056 (2)	1315 (1)	43 (1)
N(16)	9248 (1)	1508 (3)	302 (2)	60 (1)
C(20)	9471 (1)	3515 (3)	−954 (2)	50 (1)
C(22)	9888 (2)	4073 (4)	−1116 (2)	65 (2)
C(23)	9527 (2)	4902 (3)	−2014 (2)	56 (2)
C(24)	9173 (1)	4055 (3)	−2889 (2)	57 (2)
O(19)	9759 (1)	2544 (2)	−315 (1)	71 (1)
O(21)	8945 (1)	3972 (2)	−1330 (1)	66 (1)
O(25)	8898 (1)	4749 (3)	−3650 (2)	85 (2)
O(26)	9144 (3)	2841 (3)	−2905 (2)	115 (3)
H(2)	717 (1)	180 (3)	302 (2)	54 (7)
H(3)	769 (1)	185 (3)	468 (2)	80 (8)
H(5)	855 (1)	437 (3)	417 (2)	76 (8)
H(6*a*)	794 (2)	400 (4)	258 (2)	94 (10)
H(6*b*)	718 (2)	348 (3)	187 (2)	85 (8)
H(7)	751 (1)	121 (2)	198 (2)	51 (5)
H(8*a*)	729 (2)	253 (3)	74 (2)	95 (9)
H(8*b*)	802 (1)	299 (3)	146 (2)	61 (7)
H(9*a*)	755 (2)	27 (3)	79 (2)	87 (9)
H(9*b*)	779 (1)	118 (3)	39 (2)	68 (7)
H(10)	858 (1)	−45 (2)	165 (2)	45 (5)
H(11*a*)	843 (1)	−59 (3)	262 (2)	80 (8)
H(11*b*)	908 (2)	−5 (3)	326 (2)	80 (9)
H(12*a*)	886 (1)	231 (3)	323 (2)	52 (6)
H(12*b*)	861 (1)	130 (2)	356 (2)	41 (5)
H(13*a*)	898 (1)	231 (3)	196 (2)	51 (5)
H(13*b*)	949 (1)	108 (3)	260 (2)	59 (6)
H(15)	902 (1)	299 (3)	79 (2)	69 (7)
H(17)	941 (2)	−44 (3)	20 (2)	77 (8)
H(18)	927 (2)	−99 (3)	139 (2)	83 (9)
H(O19)	944 (2)	210 (4)	−10 (3)	131 (12)
H(22*a*)	1008 (2)	334 (3)	−114 (2)	78 (9)
H(22*b*)	1024 (2)	489 (5)	−47 (3)	139 (14)
H(23*a*)	919 (2)	558 (4)	−210 (3)	107 (11)
H(23*b*)	983 (1)	559 (3)	−196 (2)	71 (7)

* Lists of structure factors, anisotropic thermal parameters, full bond lengths and angles, and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53492 (36 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Selected bond lengths* (Å), *bond angles* (°) *and torsion angles* (°) *for the succinic acid complex of* (I)

C(2)—N(1)	1·336 (6)	C(2)—C(3)	1·354 (6)
C(3)—N(4)	1·373 (5)	C(5)—N(1)	1·331 (3)
C(5)—N(4)	1·304 (6)	C(13)—N(14)	1·467 (5)
C(6)—N(1)	1·459 (6)	C(15)—N(14)	1·348 (5)
C(15)—N(16)	1·310 (6)	C(17)—N(16)	1·366 (4)
C(17)—C(18)	1·344 (7)	C(18)—N(14)	1·375 (4)
C(20)—O(19)	1·301 (3)	C(23)—C(24)	1·486 (4)
C(20)—O(21)	1·205 (4)	C(24)—O(25)	1·282 (4)
C(20)—C(22)	1·506 (7)	C(24)—O(26)	1·182 (4)
C(22)—C(23)	1·504 (5)		
N(1)—C(2)—C(3)	105·3 (3)	C(13)—N(14)—C(18)	126·3 (2)
N(1)—C(5)—N(4)	111·7 (2)	N(14)—C(15)—N(16)	111·6 (2)
C(2)—C(3)—N(4)	109·8 (3)	N(16)—C(17)—C(18)	110·0 (3)
C(2)—N(1)—C(6)	127·0 (2)	C(15)—N(16)—C(17)	105·7 (2)
C(3)—N(4)—C(5)	105·4 (3)	C(13)—N(14)—C(15)	127·0 (2)
C(2)—N(1)—C(5)	107·8 (2)	C(15)—N(14)—C(18)	106·4 (2)
C(5)—N(1)—C(6)	125·0 (2)	N(14)—C(18)—C(17)	106·3 (2)
O(19)—C(20)—O(21)	123·4 (2)	O(19)—C(20)—C(22)	112·7 (2)
C(23)—C(24)—O(25)	114·4 (3)	O(21)—C(20)—C(22)	123·8 (2)
C(23)—C(24)—O(26)	124·3 (3)	O(25)—C(24)—O(26)	121·2 (3)
C(7)—C(6)—N(1)—C(5)	108·1 (4)	C(11)—C(10)—C(13)—N(14)	158·9 (3)
C(7)—C(6)—N(1)—C(2)	−65·4 (4)	C(9)—C(10)—C(13)—N(14)	−76·2 (3)
N(1)—C(6)—C(7)—C(8)	−177·9 (3)	C(10)—C(13)—N(14)—C(15)	128·4 (3)
N(1)—C(6)—C(7)—C(12)	−54·8 (4)	C(10)—C(13)—N(14)—C(18)	−58·8 (4)
O(19)—C(20)—C(22)—C(23)	164·1 (3)	C(22)—C(23)—C(24)—O(25)	−175·7 (3)
O(21)—C(20)—C(22)—C(23)	−20·2 (5)	C(22)—C(23)—C(24)—O(26)	3·3 (6)
C(20)—C(22)—C(23)—C(24)	−79·5 (4)		

Both imidazole rings are very planar with r.m.s deviations from planarity of 0·025 and 0·026 Å for the rings containing N(1) and N(14), respectively. The cyclohexyl ring has a nearly perfect chair conformation with no torsion angle differing by more than 4·8° from the average value of 54·4 (7)°. One of the imidazolylmethyl substituents, C(6), is equatorial and the other, C(13), is axial. The links between the cyclohexyl ring and the imidazolylmethyl substituents are in extended conformations, especially at the side of the equatorial substitution. The C(6)—N(1) bond is *trans* to the endocyclic C(7)—C(8) bond, while the N(14)—C(13) bond deviates by about 20° from coplanarity with C(10)—C(11). The angle between the planes of the imidazole rings is 120·1 (7)°.

The C(23)—C(24), C(24)—O(25) and C(24)—O(26) bond lengths appear significantly shortened, owing to the high thermal motion of that part of the succinic acid molecule. The angle between the two planar carboxyl groups is 92·2 (9)°.

Fig. 3 shows the crystal packing. The structure is composed of helical chains along the *c* axis of alternating molecules of (I) and succinic acid connected by strong hydrogen bonds as described earlier. No other intermolecular contacts shorter than 3·45 Å are observed.

Banting *et al.* (1988) proposed that imidazole-containing non-steroidal aromatase inhibitors bind in the active site in the place of the *A* ring of the steroid and that this would position the imidazole ring in a plane perpendicular to the steroid location and allow for interaction of the imidazole nitrogen with the haem group in the active site of the enzyme. It is conceivable that compound (I) could bind in the place of the steroid molecule but the observed conformation is not consistent with the required imidazole orientation.

The analysis of the structures of the more rigid compounds (III) and (IV) (Van Roey, Bullion, Osawa, Browne, Bowman & Braun, 1990) showed that both compounds have N atoms at the extreme ends of the molecules that are between 8·5 and 9·0 Å apart. This arrangement may be important for the interaction of the inhibitors with the enzyme. The distance between the two free imidazole N atoms in (I) is 10·77 (1) Å. However, distance map calculations using *SYBYL* (Tripos Associates, Inc., 1988) have shown that conformations that have N(4)···N(16) distances between 8·25 and 9·0 Å are accessible without obvious increases in molecular energy (P. Van Roey, unpublished work). Therefore, although (I) differs substantially in structure from other inhibitors, it could bind in a similar manner as (III) and (IV).

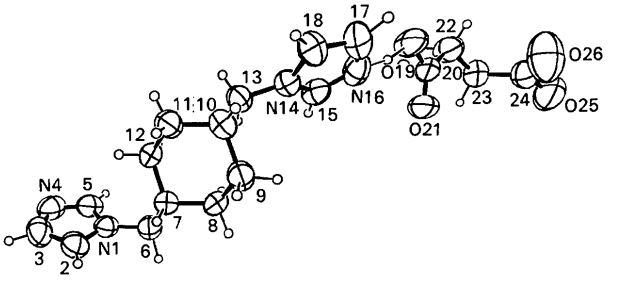

Fig. 2. Structure of the succinic acid complex of (I), showing the numbering scheme used in the text. Thermal ellipsoids are shown at 50% probability levels.

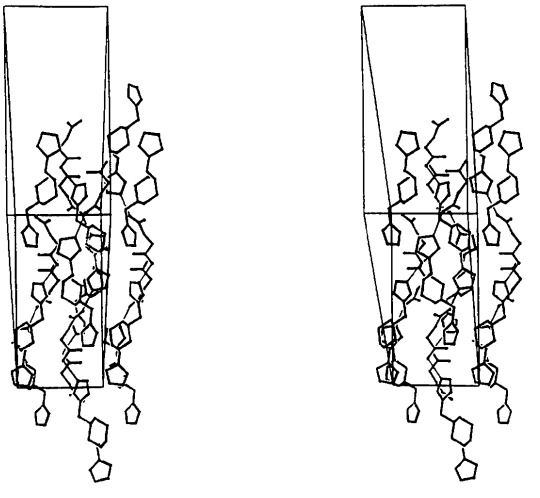

Fig. 3. Stereo packing diagram of the succinic acid complex of (I) viewed approximately down the *a* axis. The *c* axis is vertical and the *b* axis is horizontal. Note the helical strings of alternating donor and acceptor molecules parallel with the *c* axis.

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References

ABRAHAMS, S. C. & KEVE, E. T. (1971). *Acta Cryst.* A27, 157–165.

BANTING, L., SMITH, H. J., JAMES, M., JONES, G., NAZARETH, W., NICHOLLS, P. J., HEWLINS, M. J. E. & ROWLANDS, M. G. (1988). *J. Enzyme Inhib.* **2**, 215–229.

BLESSING, R. H. (1987). *Crystallogr. Rev.* **1**, 3–57.

BULLION, K. A., OSAWA, Y. & BRAUN, D. G. (1990). *Endocrinol. Res.* **16**, 255–267.

Enraf–Nonius (1979). *Structure Determination Package*. Enraf–Nonius, Delft, The Netherlands.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A27, 368–376.

JOHNSON, C. K. (1976). *ORTEPII*. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

SANTEN, R. J., SANTNER, S., DAVIS, B., VELDHUIS, J., SAMOJLIK, E. & RUBY, E. (1978). *J. Clin. Endocrinol. Metab.* **47**, 1257–1265.

SCHIAVO, D. M., GREEN, J. D., TRIANA, V. M., SPAET, R. & ZAIDI, I. (1988). *Fundam. Appl. Toxicol.* **10**, 329–334.

SHAW, M. A., NICHOLLS, P. J. & SMITH, H. J. (1988). *J. Steriod Biochem.* **31**, 137–146.

STEELE, R. E., MELLER, L. B., SAWYER, W. K. & BROWN, L. J. (1987). *Steroids*, **50**, 147–161.

STOUT, G. H. & JENSEN, L. H. (1968). *X-ray Structure Determination*, pp. 457. New York: Macmillan.

Tripos Associates, Inc. (1988). *SYBYL*. A molecular modeling program. Tripos Associates, Inc., St Louis, Missouri, USA.

VAN ROEY, P., BULLION, K. A., OSAWA, Y., BOWMAN, R. M. & BRAUN, D. G. (1991). *Acta Cryst.* C47, 829–832.

VAN ROEY, P, BULLION, K. A., OSAWA, Y., BROWNE, L. J., BOWMAN, R. M. & BRAUN, D. G. (1990). *J. Enzyme Inhibit.* In the press.

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Structure of Sodium 1,2,3,4-Thiatriazole-5-thiolate Dihydrate and 5-Benzoylthio-1,2,3,4-thiatriazole

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Abstract. Sodium 1,2,3,4-thiatriazole-5-thiolate (*A*) dihydrate, $Na^+.CS_2N_3^-.2H_2O$, $M_r = 177{\cdot}18$, monoclinic, $P2_1/n$, $a = 5{\cdot}821\ (2)$, $b = 18{\cdot}494\ (7)$, $c = 6{\cdot}786\ (3)$ Å, $\beta = 114{\cdot}84\ (3)°$, $V = 663{\cdot}0$ Å^3, $Z = 4$, $D_x = 1{\cdot}77$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 7{\cdot}6$ cm^{-1}, $F(000) = 360$, $T = 173\ (1)$ K, $R = 0{\cdot}024$ for 1160 observed reflections. 5-Benzoylthio-1,2,3,4-thiatriazole (*B*), $C_8H_5N_3OS_2$, $M_r = 223{\cdot}28$, triclinic, $P\bar{1}$, $a = 7{\cdot}420\ (3)$, $b = 11{\cdot}115\ (2)$, $c = 5{\cdot}642\ (1)$ Å, $\alpha = 91{\cdot}50\ (2)$, $\beta = 98{\cdot}42\ (2)$, $\gamma = 79{\cdot}68\ (2)°$, $V = 452{\cdot}8$ Å^3, $Z = 2$, $D_x = 1{\cdot}64$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 5{\cdot}3$ cm^{-1}, $F(000) = 228$, $R = 0{\cdot}026$ for 1435 observed reflections. The structure of the reaction product of sodium azide and carbon disulfide is unequivocally established as (*A*). The exocyclic C—S bond length is 1·704 (1) Å in contrast with the bond length of 1·580 Å predicted by MNDO methods [Conti, Franco & Trsic (1986). *Inorg. Chim. Acta*, **113**, 71–74]. Benzoylation of (*A*) is established to occur at the exocyclic S atom rather than at an N atom of the thiatriazole ring, yielding (*B*).

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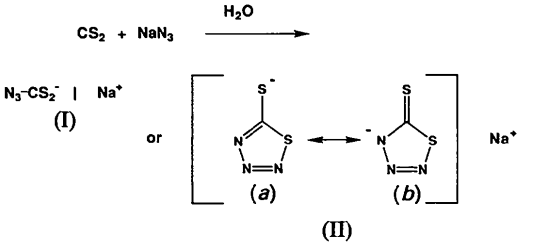
Introduction. Brown & Hoel (1922) reported the reaction of carbon disulfide and sodium azide to give what was thought to be an azidodithiocarbamate (I). From infrared spectroscopic measurements Lieber, Pilli, Ramachandran & Hites (1957) concluded that the reaction product was actually the 1,2,3,4-thiatriazole-5-thiolate anion (II). Discussion has continued concerning the structure of (II) and its protonated form as to whether the thiol (II*a*) or the thione (II*b*) structure is the major resonance contributor (Lieber, Oftedahl & Rao, 1961; Christopherson & Holm, 1971); L'abbe, Toppet, Willocx & Mathys, 1977). Recently the MNDO method has been applied to the problem and Conti, Franco &



(II)