

N8—O7—C2	113.3 (1)	N8—C9—C10	114.5 (2)
O7—N8—C9	109.3 (2)	N8—C9—C16	124.9 (2)
O7—C2—N1	122.5 (2)	C9—C10—C11	120.9 (2)

Data collection: CAD-4 diffractometer control software (Enraf-Nonius, 1989). Cell refinement: CAD-4 diffractometer control software. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *TEXSAN LS*. Software used to prepare material for publication: *TEXSAN FINISH*. Literature survey: *CSSR* (1984).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry, including bond distances and angles involving H atoms, have been deposited with the IUCR (Reference: L11120). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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2'-Carbamate Taxol

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Abstract

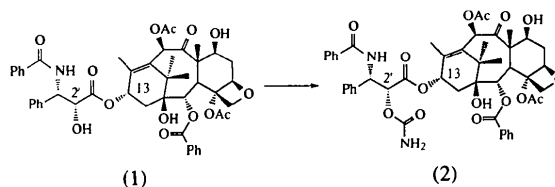
Comparison of the conformation of 2'-carbamate taxol, {2a*R*-[2a*α*,4*β*,4a*β*,6*β*,9*α*,(α*R**,*β*S*),11*α*,-12*α*,12a*α*,12b*α*]}-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-

methano-1*H*-cyclodeca[3,4]benzo[1,2-*b*]oxet-9-yl *β*-(benzoylamino)-*α*-(carbamoyloxy)benzenepropanoate, C₄₈H₅₂N₂O₁₅, with the known X-ray structures of taxotere and methyl (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserinate reveals that the most pronounced differences are in the conformation of the C13 side-chain fragment. The carbamate N atom forms two intermolecular hydrogen bonds with the taxol core and stabilizes the crystal.

Comment

Taxol, (1), a naturally occurring diterpene isolated from the bark of *Taxus brevifolia* (Wani, Taylor, Wall, Coggon & McPhail, 1971), is considered the most exciting lead in the chemotherapy of several malignant solid tumors (Rowinsky & Donehower, 1991). For more than 20 years, attempts to determine the crystal structure for the whole molecule have not been successful due to difficulties in obtaining crystals suitable for X-ray diffraction experiments. To date, detailed structural information on taxol has been restricted to a crystallographic study of taxotere, a semi-synthetic taxol analog with a modified side chain at the 13*R* position (Gueritte-Voegelein, Guénard, Mangatal, Potier, Guilhem, Cesario & Pascard, 1990).

In the course of our SAR program on taxol analogs, we synthesized 2'-carbamate taxol (2) which is, to our knowledge, the simplest crystalline taxol derivative containing both the oxetane ring and the complete taxol-type side chain, and investigated its structure by single-crystal analysis. It was synthesized in two steps, acylation of taxol at the 2' position with chloromethyl chloroformate, followed by treatment of the 2'-chloromethyl carbonate intermediate with ammonia in acetone at room temperature.



The conformation of the tetracyclic ring system in 2'-carbamate taxol is essentially identical to that of taxotere. The slight differences in the conformations of the benzoyl group at C2 and the acetyl group at C4 were also observed in the crystal structures of other taxanes (Appendino *et al.*, 1992; Gunawardana *et al.*, 1992). However, the side chain at C13 possesses a different conformation from that of taxotere. The *N*-benzoyl group at the 3' position is rotated approximately 90° away from the corresponding position of the *tert*-butyl group of taxotere. The

torsion angles about O13—C1', C1'—C2' and C3'—N4' seem to be responsible for the orientation of the side chain relative to the taxol core. In particular, the torsion angle O13—C1'—C2'—C3' is 85.6 (4) in 2'-carbamate taxol but 60.2° in taxotere, and C2'—C3'—N4'—C5' is -100.1 (4) in 2'-carbamate taxol but -141.3° in taxotere. The change in orientation moves the O5' atom of 2'-carbamate taxol 4.03 Å away from the position of O5' in taxotere and the end of the side chain now points away from both the benzoyl group at C2 and the acetyl group at C4; these groups and their interactions with the side chain are believed to be crucial for the biological activity of taxol (Gueritte-Voegelein *et al.*, 1991; Dubois *et al.*, 1993). The distance between O5' and the methyl C atom of the acetyl group at C4 becomes 5.814 Å compared with a corresponding distance of 3.590 Å in taxotere. These notable changes in the side-chain conformation may explain the loss of activity for 2'-carbamate taxol and leads to the suggested importance of O5' in receptor binding. On the other hand, the overall three-dimensional structure of the side chain in 2'-carbamate taxol is similar to that of methyl (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserinate, a taxol-side-chain methyl ester (Peterson, Do & Rogers, 1991). Thus, it seems more sensible to study the conformation of the side chain only when it is coupled to the taxol core.

Dubois *et al.* (1993) showed that the specific orientation of the side chain in taxotere is due mainly to the presence of two intramolecular hydrogen bonds, 2'O—H...1'C=O and 3'N—H...2'O. These two hydrogen bonds no longer exist in (2). The carbamate group points away from the core and the side chain and is not involved in the formation of intramolecular hydrogen bonds. However, it does

form two intermolecular hydrogen bonds which contribute significantly to the stability of the crystal lattice. As shown in Fig. 2 and Table 2, N2' forms one hydrogen bond with O1 through one of its H atoms and a second, weaker, hydrogen bond with O9 through its other H atom. N4' is involved, as donor, in a hydrogen bond with O21 of the benzoate group which is bonded to atom C2 of the core. It was noticed that the interatomic distance O7...O5'(x, y, z-1) is 3.404 Å with the angle O7—H...O5' at 121.1°. The hydrogen bonds between the side chain and core are dominant and only one intermolecular hydrogen bond (O1—H...O7) was observed between core atoms. There is also an intramolecular hydrogen bond, O7—H...O101, between core atoms in this structure.

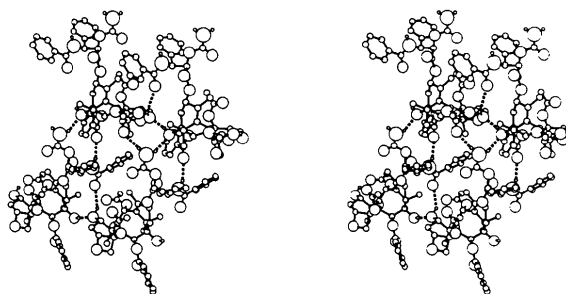


Fig. 2. Stereoscopic view (Motherwell & Clegg, 1978) of the hydrogen-bond scheme in the crystal lattice of 2'-carbamate taxol.

Experimental

Recrystallization from methylene chloride gave chunky plates of m.p. 527–529 K.

Crystal data

C₄₈H₅₂N₂O₁₅
M_r = 896.943
 Orthorhombic
*P*2₁2₁2
a = 19.874 (1) Å
b = 23.935 (2) Å
c = 9.496 (1) Å
V = 4517.1 (5) Å³
Z = 4
D_x = 1.319 Mg m⁻³

Cu Kα radiation
 λ = 1.5418 Å
 Cell parameters from 25 reflections
 θ = 13.73–35.48°
 μ = 0.78 mm⁻¹
T = 290 K
 Fragment cut from a large thick plate
 0.36 × 0.27 × 0.25 mm
 Colorless

Data collection

Enraf–Nonius CAD-4 diffractometer
 θ/2θ scans
 Absorption correction: empirical
T_{min} = 0.962, *T_{max}* = 0.999
 4790 measured reflections
 4790 independent reflections

4104 observed reflections
 [*I* ≥ 3σ(*I*)]
 θ_{max} = 70°
h = -24 → 0
k = -29 → 0
l = 0 → 11
 3 standard reflections
 frequency: 120 min
 intensity decay: 17%

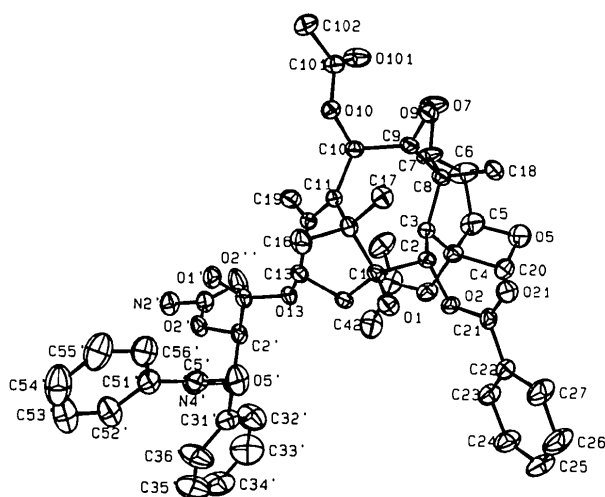


Fig. 1. ORTEP (Johnson, 1976) drawing of 2'-carbamate taxol showing the atomic labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

Refinement

Refinement on F $R = 0.041$ $wR = 0.041$ $S = 1.149$

4104 reflections

586 parameters

H-atom parameters not refined

Unit weights applied

 $(\Delta/\sigma)_{\max} = 0.08$ $\Delta\rho_{\max} = 0.175 \text{ e } \text{\AA}^{-3}$ $\Delta\rho_{\min} = -0.055 \text{ e } \text{\AA}^{-3}$

Extinction correction: none

Atomic scattering factors from *MolEN* (Fair, 1990)

C52'	0.8399 (3)	1.2836 (2)	1.3891 (5)	6.2 (1)
C53'	0.8964 (3)	1.3009 (2)	1.4573 (6)	8.3 (2)
C54'	0.9565 (3)	1.2762 (2)	1.4284 (8)	9.4 (2)
C55'	0.9610 (3)	1.2335 (2)	1.3287 (8)	8.6 (2)
C56'	0.9025 (3)	1.2151 (2)	1.2626 (6)	6.6 (1)
C101	0.9280 (2)	1.0698 (2)	0.3494 (4)	3.92 (8)
C102	1.0017 (2)	1.0760 (2)	0.3228 (5)	5.5 (1)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)

$$B_{\text{eq}} = (8\pi^2/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	x	y	z	B_{eq}
O1	0.7889 (1)	0.9831 (1)	0.9777 (3)	3.94 (5)
O1'	0.7941 (2)	1.2386 (1)	0.8925 (4)	5.19 (8)
O2	0.6747 (1)	0.96641 (9)	0.8457 (3)	3.23 (5)
O2'	0.6876 (1)	1.31172 (9)	0.9427 (3)	4.04 (6)
O2''	0.6391 (2)	1.3094 (1)	0.7295 (4)	8.4 (1)
O4	0.5959 (1)	1.0482 (1)	0.7083 (3)	4.06 (6)
O5	0.5686 (1)	0.9555 (1)	0.4752 (4)	6.00 (8)
O5'	0.7697 (2)	1.1675 (1)	1.2057 (4)	6.08 (8)
O7	0.7497 (2)	1.0269 (2)	0.2387 (3)	6.41 (8)
O9	0.8522 (1)	0.9692 (1)	0.4231 (3)	4.18 (6)
O10	0.9144 (1)	1.0634 (1)	0.4877 (3)	3.41 (5)
O13	0.7192 (1)	1.16848 (9)	0.8679 (3)	3.43 (5)
O21	0.7135 (1)	0.8779 (1)	0.8441 (3)	4.66 (6)
O41	0.6187 (2)	1.1205 (1)	0.5642 (4)	6.9 (1)
O101	0.8851 (1)	1.0708 (1)	0.2605 (3)	5.21 (8)
N2'	0.6640 (2)	1.3902 (1)	0.8360 (4)	4.92 (9)
N4'	0.7332 (2)	1.2568 (1)	1.1870 (4)	4.21 (7)
C1'	0.7378 (2)	1.2210 (1)	0.9004 (4)	3.85 (8)
C1	0.7772 (2)	1.0187 (1)	0.8601 (3)	2.91 (6)
C2'	0.6775 (2)	1.2531 (1)	0.9566 (4)	3.74 (8)
C2	0.7311 (2)	0.9839 (1)	0.7590 (4)	2.87 (6)
C2''	0.6613 (2)	1.3359 (2)	0.8254 (4)	4.32 (9)
C3	0.7035 (2)	1.0127 (1)	0.6227 (4)	2.83 (6)
C3'	0.6708 (2)	1.2419 (1)	1.1171 (4)	4.07 (8)
C4	0.6261 (2)	1.0096 (2)	0.6081 (4)	3.55 (8)
C5	0.5942 (2)	1.0127 (2)	0.4603 (5)	5.4 (1)
C5'	0.7799 (2)	1.2177 (2)	1.2248 (4)	4.53 (9)
C6	0.6385 (2)	1.0211 (3)	0.3304 (5)	6.7 (1)
C7	0.7116 (2)	1.0345 (2)	0.3662 (4)	4.9 (1)
C8	0.7389 (2)	0.9934 (2)	0.4838 (4)	3.38 (7)
C9	0.8157 (2)	1.0035 (2)	0.4777 (4)	3.13 (7)
C10	0.8437 (2)	1.0601 (1)	0.5221 (4)	2.96 (7)
C11	0.8321 (2)	1.0744 (1)	0.6743 (3)	2.87 (6)
C12	0.7992 (2)	1.1219 (1)	0.7058 (4)	3.03 (7)
C13	0.7731 (2)	1.1275 (1)	0.8551 (4)	3.26 (7)
C14	0.7417 (2)	1.0734 (1)	0.9086 (4)	3.34 (7)
C15	0.8468 (2)	1.0317 (1)	0.7908 (4)	3.17 (7)
C16	0.8965 (2)	1.0563 (2)	0.9017 (5)	4.63 (9)
C17	0.8822 (2)	0.9771 (2)	0.7441 (4)	3.95 (8)
C18	0.7272 (2)	0.9310 (2)	0.4499 (5)	5.15 (9)
C19	0.7847 (2)	1.1689 (2)	0.6061 (4)	4.53 (9)
C20	0.5895 (2)	0.9533 (2)	0.6188 (5)	4.6 (1)
C21	0.6746 (2)	0.9122 (1)	0.8880 (4)	3.35 (7)
C22	0.6200 (2)	0.9010 (2)	0.9901 (4)	3.55 (9)
C23	0.5699 (2)	0.9387 (2)	1.0202 (5)	4.42 (9)
C24	0.5205 (2)	0.9244 (2)	1.1160 (6)	5.9 (1)
C25	0.5217 (3)	0.8746 (2)	1.1842 (5)	6.6 (1)
C26	0.5709 (3)	0.8373 (2)	1.1545 (6)	7.7 (1)
C27	0.6203 (3)	0.8500 (2)	1.0562 (6)	6.3 (1)
C31'	0.6116 (2)	1.2729 (2)	1.1824 (5)	5.2 (1)
C32'	0.5521 (3)	1.2782 (3)	1.1137 (7)	8.2 (2)
C33'	0.4972 (3)	1.3063 (3)	1.1751 (8)	10.1 (2)
C34'	0.5040 (3)	1.3297 (3)	1.3021 (7)	9.7 (2)
C35'	0.5625 (4)	1.3259 (3)	1.3685 (8)	11.5 (2)
C36'	0.6178 (3)	1.2971 (3)	1.3132 (6)	9.2 (2)
C41	0.5947 (2)	1.1031 (2)	0.6723 (6)	5.2 (1)
C42	0.5606 (2)	1.1358 (2)	0.7851 (7)	7.0 (1)
C51'	0.8417 (2)	1.2404 (2)	1.2939 (5)	5.0 (1)

Table 2. Selected geometric parameters (\AA , $^\circ$)

O1—C1	1.424 (4)	N4'—C3'	1.450 (5)
O1'—C1'	1.196 (5)	N4'—C5'	1.366 (5)
O2—C2	1.452 (4)	C1'—C2'	1.521 (6)
O2—C21	1.358 (4)	C1—C2	1.567 (5)
O2'—C2'	1.424 (4)	C1—C14	1.557 (5)
O2'—C2''	1.360 (5)	C1—C15	1.564 (5)
O2''—C2''	1.195 (5)	C2'—C3'	1.553 (6)
O4—C4	1.455 (5)	C2—C3	1.565 (5)
O4—C41	1.359 (5)	C3—C4	1.547 (5)
O5—C5	1.467 (6)	C3—C8	1.564 (5)
O5—C20	1.427 (6)	C3'—C31'	1.523 (6)
O5'—C5'	1.232 (5)	C4—C5	1.542 (6)
O7—C7	1.440 (5)	C4—C20	1.534 (6)
O9—C9	1.212 (4)	C5—C6	1.528 (6)
O10—C10	1.443 (4)	C5'—C51'	1.494 (6)
O10—C101	1.350 (5)	C6—C7	1.526 (6)
O13—C1'	1.347 (4)	C7—C8	1.585 (6)
O13—C13	1.458 (4)	C8—C9	1.547 (5)
O21—C21	1.202 (4)	C8—C18	1.546 (6)
O41—C41	1.206 (6)	C9—C10	1.524 (5)
O101—C101	1.199 (5)	C10—C11	1.503 (5)
N2'—C2''	1.303 (5)	C11—C12	1.345 (5)
C11—C15	1.535 (5)	C12—C13	1.515 (5)
C12—C19	1.498 (5)	C13—C14	1.524 (5)
C15—C16	1.559 (6)	C15—C17	1.548 (5)
C41—C42	1.490 (8)	C21—C22	1.481 (5)
C101—C102	1.495 (6)		
C2—O2—C21	116.4 (3)	O2'—C2''—O2''	122.6 (4)
C2'—O2'—C2''	116.2 (3)	O2'—C2''—N2'	110.2 (3)
C4—O4—C41	117.2 (3)	O2''—C2''—N2'	127.2 (4)
C5—O5—C20	91.5 (3)	C2—C3—C4	113.6 (3)
C10—O10—C101	114.9 (3)	C2—C3—C8	114.2 (3)
C1'—O13—C13	116.5 (3)	C4—C3—C8	111.0 (3)
C3'—N4'—C5'	122.3 (3)	N4'—C3'—C2'	109.5 (3)
O1'—C1'—O13	124.8 (4)	N4'—C3'—C31'	110.7 (3)
O1'—C1'—C2'	125.6 (3)	C2'—C3'—C31'	112.5 (3)
O13—C1'—C2'	109.5 (3)	O4—C4—C3	108.7 (3)
O1—C1—C2	104.9 (2)	O4—C4—C5	113.3 (3)
O1—C1—C14	110.2 (3)	O4—C4—C20	108.6 (3)
O1—C1—C15	107.8 (3)	C3—C4—C5	119.2 (3)
C2—C1—C14	111.3 (3)	C3—C4—C20	120.5 (3)
C2—C1—C15	111.4 (3)	C5—C4—C20	84.7 (3)
C14—C1—C15	111.1 (3)	O5—C5—C4	90.5 (3)
O2'—C2'—C1'	110.7 (3)	O5—C5—C6	113.6 (4)
O2'—C2'—C3'	105.9 (3)	C4—C5—C6	120.3 (3)
C1'—C2'—C3'	109.0 (3)	O5'—C5'—N4'	121.1 (4)
O2—C2—C1	104.9 (3)	O5'—C5'—C51'	123.7 (4)
O2—C2—C3	109.0 (3)	N4'—C5'—C51'	115.2 (3)
C1—C2—C3	118.5 (3)	C5—C6—C7	113.3 (3)
O7—C7—C6	106.7 (3)	O13—C13—C14	104.0 (3)
O7—C7—C8	109.5 (3)	C12—C13—C14	112.2 (3)
C6—C7—C8	110.7 (4)	C1—C14—C13	115.4 (3)
C3—C8—C7	104.8 (3)	C1—C15—C11	105.5 (3)
C3—C8—C9	115.4 (3)	C1—C15—C16	110.5 (3)
C7—C8—C18	113.3 (3)	C1—C15—C17	110.8 (3)
C9—C8—C18	107.0 (3)	C11—C15—C16	110.8 (3)
O9—C9—C8	119.9 (3)	C11—C15—C17	116.3 (3)
O9—C9—C10	120.2 (3)	C16—C15—C17	103.0 (3)
C8—C9—C10	119.3 (3)	O5—C20—C4	92.4 (3)
O10—C10—C9	109.9 (3)	O2—C21—O21	123.3 (3)
O10—C10—C11	110.8 (3)	O2—C21—C22	111.6 (3)
C10—C11—C12	118.7 (3)	O21—C21—C22	125.1 (3)
C12—C11—C15	119.7 (3)	C9—C10—C11	114.3 (3)
C11—C12—C19	126.0 (3)	C10—C11—C15	120.8 (3)
O13—C13—C12	112.9 (3)	C11—C12—C13	116.7 (3)
		C13—C12—C19	117.3 (3)
		C3'—C31'—C32'	121.6 (5)

O4—C41—O41	122.7 (4)	O10—C101—O101	123.0 (3)
O4—C41—C42	109.7 (4)	O10—C101—C102	111.8 (3)
O41—C41—C42	127.6 (4)	O101—C101—C102	125.2 (4)
C1'—O13—C13—C12	-92.0 (4)	O1'—C1'—C2'—C3'	-90.9 (5)
C1'—O13—C13—C14	146.1 (3)	C2'—C3'—N4'—C5'	-100.1 (4)
C13—O13—C1'—O1'	15.2 (5)	C2'—C3'—C31'—C32'	38.8 (6)
C13—O13—C1'—C2'	-161.4 (3)	O2'—C2'—C3'—N4'	-63.0 (4)
O13—C1'—C2'—O2'	-158.4 (3)	O2'—C2'—C3'—C31'	60.5 (4)
O13—C1'—C2'—C3'	85.6 (4)	C3'—N4'—C5'—O5'	-2.9 (6)
C1'—C2'—C3'—C31'	179.6 (3)	C3'—N4'—C5'—C51'	179.1 (4)
C1'—C2'—C3'—N4'	56.0 (4)	C31'—C3'—N4'—C5'	135.3 (4)
O1'—C1'—C2'—O2'	25.1 (6)	C32'—C31'—C3'—N4'	161.7 (4)

D—H...A	D—H	H...A	D...A	D—H...A
O1—H1'...O7 ⁱ	1.003	1.851	2.801	156.9
O7—H7'...O10 ⁱ	1.062	1.928	2.896	149.5
N2'—H22'...O1 ⁱⁱ	0.957	2.131	2.991	148.9
N2'—H21'...O9 ⁱⁱⁱ	0.971	2.191	3.120	159.2
N4'—H4'...O2 ⁱⁱ	0.975	2.207	3.101	151.8

Symmetry codes: (i) $x, y, 1+z$; (ii) $\frac{3}{2}-x, \frac{1}{2}+y, 2-z$; (iii) $\frac{3}{2}-x, \frac{1}{2}+y, 1-z$.

The structure was solved by direct methods using *SHELXS86* (Sheldrick, 1985) and refined by full-matrix least-squares techniques using *MolEN* (Fair, 1990). The two hydroxyl H atoms in the molecule were located from difference Fourier maps and the positions of all the other H atoms were calculated from an idealized geometry with standard bond lengths and angles.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: CR1123). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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2-Methyl-2H-1,2-benziselenazol-3-one

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Abstract

The nearly planar molecules of C₈H₇NOSe form chains parallel to [001] with Se...O intermolecular distances of 2.600 (3) Å. The shortest contacts [2.362 (5) Å] occur between the methyl group H atoms of the neighbouring chains.

Comment

Within the last few years selenium has been recognized as an essential component of several biologically important macromolecules (Stadtman, 1990), *e.g.* glutathione peroxidase (GSH-Px), the enzyme which catalyzes reduction of hydroperoxides in the human organism (Parnham & Graf, 1987). An important stage in the enzyme's catalytic cycle is the modification of the selenomethionine at its active centre (Ladenstein, Epp & Wendel, 1983). The anti-oxidant activity of GSH-Px can be mimicked by relatively simple seleno-organic compounds such as 2-methyl-2H-1,2-benziselenazol-3-one (MBS). The best known is ebselen, a 2-phenyl analogue of MBS, which was reported to elicit anti-inflammatory (Dupont, Dideberg & Jacquemin, 1990) and immuno-stimulating (Młochowski & Inglot, 1991) activities. The anti-inflammatory effects of ebselen were suggested to be connected with its stimulating influence on the arachidonic acid metabolism (Leyck & Parnham, 1990). This results in inhibition of 5-lipoxygenase and isomerization of its product LTB₄ to a biologically inactive *trans*-LTB₄, as well as an inhibition of the generation of reactive oxygen species (Cotgreave, Johanson, Westergren, Moldeus & Brattsand, 1988). The nature of the likeness between the antioxidant activity of the seleno-organic compounds and GSH-Px is not yet understood.

A possible explanation might be a similarity between the amide N-atom surrounding of the Se atom in the active selenazoles and in GSH-Px (Wendel, Fausel, Safayhi, Tieg & Otter, 1984).

