rule that the best proton donors and acceptors remaining after intramolecular hydrogen-bond formation form intermolecular bonds to one another (Etter, 1990). Analogous intermolecular hydrogen bonds were observed in [Cd(biuret)$_2$]Cl$_2$ and biuret.0.6H$_2$O, suggesting that the overall hydrogen-bonding scheme (both inter- and intramolecular) in biuret derivatives is hardly influenced by the surroundings (for example, substituents on the N atoms or complexation to metals). It is also worth noting that the N1—HN1 and N2—HN2 bonds, which adopt an *anti* relationship with respect to their neighboring carbonyl groups, behave as in the studied diaryl ureas in which no intramolecular interaction is observed between the O atom and the N-bonded H atoms (Etter & Panunto, 1988).

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Structural Aspects of the 6,11-Dihydro-11-oxodibenz[b,e]oxepin Skeleton

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Abstract. (I) 6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid, C$_{16}$H$_{12}$O$_4$, $M_r = 268.27$, monoclinic, $P2_1/n$, $a = 11.004$ (1), $b = 12.6209$ (9), $c = 9.6920$ (8) Å, $\beta = 108.224$ (7)°, $V = 1278.5$ (3) Å^3, $Z = 4$, $D_m = 1.39$, $D_x = 1.39$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1.54184$ Å, $\mu = 7.9$ cm^{-1}, $F(000) = 560$, $T = 295$ K, $R = 0.041$ for 2422 observed reflections. (II) Methyl 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetate, C$_{17}$H$_{14}$O$_4$, $M_r = 282.30$, monoclinic, $P2_1/c$, $a = 13.644$ (1), $b = 8.878$ (1), $c = 13.000$ (2) Å, $\beta =$

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117.10 (1)°, $V = 1401.9$ (4) Å^3, $Z = 4$, $D_m = 1.33$, D_x = 1.34 g cm^{-3}, Cu $K\alpha$, $\lambda = 1.54184$ Å, μ = 7.5 cm^{-1}, $F(000) = 592$, $T = 295$ K, $R = 0.046$ for 2592 observed reflections. (III) Ethyl 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetate, $C_{18}H_{16}O_4$, M_r = 296.33, triclinic, $P\bar{1}$, $a = 10.177$ (1), $b = 10.630$ (1), c = 7.776 (1) Å, $\alpha = 103.72$ (1), $\beta = 100.70$ (1), $\gamma = $ 107.85 (1)°, $V = 746.72$ (8) Å^3, $Z = 2$, $D_m = 1.35$, D_x = 1.32 g cm^{-3}, Cu $K\alpha$, $\lambda = 1.54184$ Å, μ = 7.2 cm^{-1}, $F(000) = 312$, $T = 295$ K, $R = 0.048$ for 2688 observed reflections. These three compounds have anti-inflammatory activities. The inherent structures of the 6,11-dihydro-11-oxodibenz[b,e]oxepin system, the conformational variability, and the relationships to their pharmacological activities are discussed.

Introduction. A series of 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-acetic acids were synthesized and the anti-inflammatory activities evaluated (Aultz, Helsley, Hoffman, McFadden, Lassman & Wilker, 1977). 6,11-Dihydro-11-oxodibenz[b,e]oxepin-2-acetic acid (oxepac) is one of the non-steroidal anti-inflammatory agents which are applied clinically today. The activities must be closely related to the characteristic skeleton. The three-dimensional structure of the skeleton, however, has not yet been disclosed. We have undertaken X-ray analyses of oxepac, the methyl ester and the ethyl ester to determine the inherent structural aspects and consider the structure–activity relationships.

Experimental. Colourless crystals of (I) and (III) were obtained from ethyl acetate solution, and those of (II) from chloroform solution, at 295 K. All crystals are prismatic. Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Cu $K\alpha$ radiation, ω–2θ scan technique, $2 \leq \theta \leq 75°$. Intensity and orientation standards were measured periodically to check decomposition or movement of the crystals. No significant changes were observed for each crystal. Corrections were made for Lorentz and polarization but not for absorption effects. A secondary-extinction correction (Zachariasen, 1963) was applied. Experimental and refinement details are listed in Table 1.

Structures were solved by direct methods using MULTAN11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Refinement used the SDP package (Frenz, 1983); full-matrix least-squares refinement on F, with non-H atoms having anisotropic temperature factors. H atoms were located from difference syntheses and refined isotropically. Unit weight was applied. Atomic scattering factors from International Tables for X-ray Crystallography (1974, Vol. IV). Computers used: VAX 11/750 and VAX 8550.

Table 1. *Experimental and refinement details*

	(I)	(II)	(III)
Crystal size (mm)	0.4 × 0.3 × 0.3	0.4 × 0.4 × 0.3	0.5 × 0.4 × 0.3
No. of reflections for cell	25	25	25
determination [2θ range (°)]	[34 ≤ 2θ ≤ 49]	[35 ≤ 2θ ≤ 48]	[34 ≤ 2θ ≤ 47]
Range of h	−13 to 13	−17 to 17	−12 to 12
k	0 to 15	0 to 11	−12 to 12
l	0 to 12	0 to 16	0 to 9
No. of unique reflections	2613	2999	2974
No. of data with $I > 3\sigma(I)$	2422	2592	2688
R_{int}	0.024	0.023	0.025
Empirical isotropic extinction coefficient	1.07 × 10^{-5}	3.77 × 10^5	1.50 × 10^5
Final R	0.041	0.046	0.048
wR	0.039	0.045	0.047
S	0.501	0.510	0.418
Max. Δ/σ	0.01	0.03	0.01
$\Delta\rho_{max}$ (e Å^{-3})	0.16 (4)	0.34 (3)	0.23 (3)
$\Delta\rho_{min}$ (e Å^{-3})	−0.71 (3)	−0.56 (5)	−0.54 (2)
No. of parameters	230	247	261

Discussion. Atomic parameters are given in Table 2* and bond lengths, angles and selected torsion angles in Table 3. The structural formulae with the atomic numbering schemes are shown in Fig. 1. ORTEP (Johnson, 1976) drawings of the compounds are shown in Fig. 2.

The bond lengths in the molecules are in the range expected. Most the corresponding bond lengths in the three compounds agree within experimental error. In (II), however, C(12)—C(13) is significantly shorter and C(8)—C(11) significantly longer than the corresponding distances in (I) and (III). This means that the conjugation system of the B ring in (II) is different from those in the other two compounds.

The torsion angles around the seven-membered rings in (I) and (II) are similar. The angles in (III) are quite different from the corresponding values in (I) and (II). Angles α, γ, δ, ε, η, θ_1 and θ_2, in particular, differ significantly. This implies that the seven-membered ring is very flexible and changes its conformation relatively easily depending on the circumstances. The pattern of the torsion angles around the seven-membered ring in 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (Reboul, Soyfer, Cristau, Darbon, Oddon & Pèpe, 1983), which lacks the ring O atom in the seven-membered ring, is significantly different from those in these three compounds, indicating that the effect of the ring O on the conformation is large. The exocyclic torsion angle χ_1 in (I) differs from the corresponding values in (II) and (III).

It is noteworthy that the planarity of the A rings is much higher than that of the B rings in these three compounds. The planarity of the B ring in (II) is

Table 2. *Positional parameters* ($\times 10^4$) *and equivalent isotropic temperature factors of the non-H atoms with e.s.d.'s in parentheses*

$$B_{eq} = (4/3)\Sigma_i\Sigma_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	Compound (I)				Compound (II)				Compound (III)			
	x	y	z	B_{eq} (Å²)	x	y	z	B_{eq} (Å²)	x	y	z	B_{eq} (Å²)
O(1)	8746 (1)	5665 (1)	7754 (1)	4.27 (3)	6 (1)	5116 (1)	2174 (1)	4.43 (3)	6559 (2)	8751 (1)	6323 (2)	4.38 (3)
O(2)	7053 (1)	3978 (1)	3722 (1)	4.98 (3)	−1183 (1)	1193 (2)	−30 (1)	4.99 (3)	4831 (2)	6783 (2)	10063 (2)	6.21 (4)
O(3)	9661 (1)	1193 (1)	5457 (1)	3.81 (2)	3911 (1)	1867 (2)	2157 (1)	7.29 (4)	9811 (2)	4861 (2)	7629 (3)	7.58 (5)
O(4)	11488 (1)	666 (1)	5152 (1)	4.01 (2)	4165 (1)	1070 (2)	694 (1)	6.49 (4)	8877 (1)	2748 (1)	7863 (2)	4.34 (3)
C(1)	5847 (2)	6869 (2)	6086 (2)	4.33 (4)	−2615 (1)	4398 (2)	1837 (2)	5.06 (5)	3792 (2)	9791 (2)	6950 (3)	4.78 (5)
C(2)	5101 (2)	7278 (2)	4774 (2)	5.08 (5)	−3674 (2)	4081 (3)	1005 (2)	6.06 (6)	2340 (3)	9249 (3)	6776 (3)	5.83 (6)
C(3)	5104 (2)	6769 (2)	3491 (2)	4.83 (4)	−3853 (1)	3239 (3)	53 (2)	5.70 (5)	1757 (2)	8086 (3)	7277 (3)	5.63 (6)
C(4)	5850 (2)	5921 (2)	3530 (2)	3.97 (4)	−2966 (1)	2679 (2)	−75 (2)	4.52 (4)	2641 (2)	7448 (2)	7978 (3)	4.62 (5)
C(5)	6633 (1)	5512 (1)	4838 (2)	3.10 (3)	−1891 (1)	3001 (2)	749 (1)	3.54 (3)	4103 (2)	7966 (2)	8115 (3)	3.54 (4)
C(6)	6620 (2)	5994 (1)	6135 (2)	3.30 (3)	−1716 (1)	3859 (2)	1709 (1)	3.76 (4)	4685 (2)	9145 (2)	7602 (3)	3.69 (4)
C(7)	7406 (2)	5557 (2)	7560 (2)	3.95 (4)	−575 (1)	4178 (2)	2620 (1)	4.15 (4)	6244 (2)	9662 (2)	7749 (3)	4.20 (5)
C(8)	9298 (2)	4882 (2)	7174 (2)	3.22 (3)	509 (1)	4365 (2)	1626 (1)	3.62 (4)	6609 (2)	7526 (2)	6552 (2)	3.41 (4)
C(9)	8708 (1)	4345 (1)	5864 (2)	2.92 (3)	129 (1)	3062 (2)	970 (1)	3.29 (3)	6023 (2)	6877 (2)	7745 (2)	3.23 (4)
C(10)	7430 (2)	4566 (1)	4767 (2)	3.26 (3)	−984 (1)	2334 (2)	555 (1)	3.54 (3)	5016 (2)	7223 (2)	8774 (3)	3.83 (4)
C(11)	10546 (2)	4646 (2)	7991 (2)	3.85 (4)	1496 (1)	5033 (2)	1772 (2)	4.56 (4)	7348 (2)	6937 (2)	5471 (3)	4.21 (5)
C(12)	11214 (2)	3853 (2)	7573 (2)	3.68 (3)	2115 (1)	4362 (2)	1312 (2)	4.62 (4)	7565 (2)	5749 (2)	5603 (3)	4.11 (5)
C(13)	10655 (2)	3284 (1)	6291 (2)	3.06 (3)	1794 (1)	3023 (2)	704 (1)	3.85 (4)	7040 (2)	5096 (2)	6832 (3)	3.38 (4)
C(14)	9427 (2)	3546 (1)	5468 (2)	3.07 (3)	809 (1)	2391 (2)	541 (1)	3.55 (3)	6287 (2)	5668 (2)	7865 (2)	3.34 (4)
C(15)	11406 (2)	2430 (1)	5836 (2)	3.44 (3)	2490 (1)	2264 (2)	222 (1)	4.58 (4)	7249 (2)	3779 (2)	7000 (3)	3.67 (4)
C(16)	10753 (1)	1380 (1)	5480 (2)	3.01 (1)	3587 (1)	1750 (2)	1146 (1)	4.31 (4)	8789 (2)	3902 (2)	7537 (3)	4.04 (5)
C(17)					5226 (2)	474 (3)	1517 (2)	7.07 (7)	10309 (2)	2706 (3)	8337 (4)	6.28 (7)
C(18)									10207 (3)	1393 (3)	8688 (5)	7.62 (8)

Table 3. *Bond distances* (Å), *bond angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

	(I)	(II)	(III)
O(1)—C(7)	1.433 (2)	1.440 (2)	1.443 (3)
O(1)—C(8)	1.369 (2)	1.368 (2)	1.370 (3)
O(2)—C(10)	1.220 (3)	1.222 (3)	1.223 (3)
O(3)—C(16)	1.314 (2)	1.185 (2)	1.190 (2)
O(4)—C(16)	1.218 (3)	1.325 (3)	1.335 (3)
O(4)—C(17)		1.452 (2)	1.453 (3)
C(1)—C(2)	1.380 (3)	1.383 (3)	1.379 (3)
C(1)—C(6)	1.386 (3)	1.395 (3)	1.389 (3)
C(2)—C(3)	1.384 (3)	1.369 (3)	1.378 (4)
C(3)—C(4)	1.370 (3)	1.386 (3)	1.391 (4)
C(4)—C(5)	1.390 (2)	1.397 (2)	1.392 (3)
C(5)—C(6)	1.401 (2)	1.387 (2)	1.396 (3)
C(5)—C(10)	1.496 (2)	1.493 (2)	1.490 (3)
C(6)—C(7)	1.487 (2)	1.492 (2)	1.483 (3)
C(8)—C(9)	1.406 (3)	1.391 (2)	1.396 (3)
C(8)—C(11)	1.387 (2)	1.403 (3)	1.392 (3)
C(9)—C(10)	1.501 (2)	1.506 (2)	1.491 (4)
C(9)—C(14)	1.407 (2)	1.415 (3)	1.411 (3)
C(11)—C(12)	1.376 (2)	1.373 (3)	1.371 (3)
C(12)—C(13)	1.400 (2)	1.383 (3)	1.399 (4)
C(13)—C(14)	1.378 (3)	1.382 (2)	1.372 (3)
C(13)—C(15)	1.506 (2)	1.513 (3)	1.511 (4)
C(15)—C(16)	1.495 (2)	1.501 (3)	1.500 (3)
C(17)—C(18)			1.461 (5)
C(7)—O(1)—C(8)	116.6 (1)	115.4 (1)	117.9 (2)
C(16)—O(4)—C(17)		115.8 (1)	116.4 (2)
C(2)—C(1)—C(6)	120.7 (2)	120.0 (2)	120.1 (2)
C(1)—C(2)—C(3)	119.7 (2)	120.7 (2)	121.0 (3)
C(2)—C(3)—C(4)	119.9 (2)	119.8 (2)	119.9 (2)
C(3)—C(4)—C(5)	121.4 (2)	120.3 (2)	119.7 (2)
C(4)—C(5)—C(6)	118.7 (2)	119.5 (2)	120.2 (2)
C(4)—C(5)—C(10)	117.4 (2)	116.9 (2)	118.8 (2)
C(6)—C(5)—C(10)	123.9 (1)	123.6 (1)	121.0 (2)
C(1)—C(6)—C(5)	119.7 (1)	119.8 (1)	119.5 (2)
C(1)—C(6)—C(7)	120.0 (2)	119.7 (2)	121.8 (2)
C(5)—C(6)—C(7)	120.4 (2)	120.6 (2)	118.8 (2)
O(1)—C(7)—C(6)	111.2 (2)	110.9 (1)	110.7 (1)
O(1)—C(8)—C(9)	125.4 (1)	126.1 (2)	126.4 (2)
O(1)—C(8)—C(11)	114.2 (1)	113.8 (1)	113.6 (2)
C(9)—C(8)—C(11)	120.6 (2)	120.1 (2)	120.2 (2)
C(8)—C(9)—C(10)	128.0 (1)	127.7 (2)	127.4 (2)
C(8)—C(9)—C(14)	116.8 (1)	117.6 (2)	117.1 (2)
C(10)—C(9)—C(14)	115.0 (1)	114.4 (1)	115.1 (2)
O(2)—C(10)—C(5)	118.1 (1)	117.9 (1)	119.1 (3)
O(2)—C(10)—C(9)	118.4 (1)	118.8 (2)	120.2 (3)
C(5)—C(10)—C(9)	123.3 (1)	123.2 (1)	120.4 (2)
C(8)—C(11)—C(12)	120.9 (2)	120.0 (2)	121.1 (3)
C(11)—C(12)—C(13)	120.5 (1)	121.6 (2)	120.5 (3)
C(12)—C(13)—C(14)	118.1 (2)	118.0 (2)	118.1 (2)
C(12)—C(13)—C(15)	119.8 (1)	121.6 (2)	121.7 (2)

Table 3 (*cont.*)

	(I)	(II)	(III)
C(14)—C(13)—C(15)	122.1 (1)	120.4 (2)	120.3 (2)
C(9)—C(14)—C(13)	123.1 (1)	122.5 (2)	123.1 (2)
C(13)—C(15)—C(16)	115.8 (1)	113.0 (1)	114.8 (1)
O(3)—C(16)—O(4)	122.7 (1)	122.4 (2)	123.0 (3)
O(3)—C(16)—C(15)	112.1 (1)	126.3 (2)	126.4 (2)
O(4)—C(16)—C(15)	125.1 (2)	111.3 (1)	110.6 (2)
O(4)—C(17)—C(18)			109.1 (2)
C(6)—C(5)—C(10)—C(9) α	−31.4 (3)	−31.6 (2)	−47.1 (3)
C(7)—C(6)—C(5)—C(10) β	−1.5 (3)	0.4 (3)	−0.9 (3)
C(5)—C(6)—C(7)—O(1) γ	66.3 (2)	66.2 (2)	72.8 (2)
C(8)—O(1)—C(7)—C(6) δ	−85.1 (2)	−85.4 (2)	−77.4 (2)
C(7)—O(1)—C(8)—C(9) ε	36.0 (2)	34.0 (2)	18.4 (3)
O(1)—C(8)—C(9)—C(10) ζ	6.1 (3)	10.8 (3)	11.4 (3)
C(8)—C(9)—C(10)—C(5) η	7.6 (3)	3.7 (2)	22.9 (3)
C(4)—C(5)—C(10)—O(2) θ_1	−26.4 (2)	−24.7 (2)	−41.5 (3)
C(14)—C(9)—C(10)—O(2) θ_2	7.9 (2)	5.2 (2)	22.7 (3)
C(12)—C(13)—C(15)—C(16) χ_1	128.8 (2)	64.3 (2)	59.0 (2)
C(13)—C(15)—C(16)—O(4) χ_2	177.4 (1)	179.0 (2)	172.7 (2)

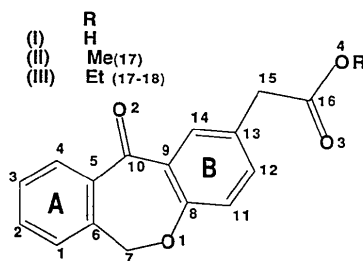|	R
(I)	H
(II)	Me(17)
(III)	Et (17-18)

Fig. 1. Chemical structures and the atomic numbering scheme.

exceptionally low and must be related to its conjugated system. The dihedral angles between the *A* and *B* rings are very similar in (I) and (II) (31.5 and 34.2°, respectively), but the angle in (III) is significantly larger (49.0°). The variability of the dihedral angle together with the above-mentioned conformational flexibility of the central seven-membered ring suggest that the 6,11-dihydro-11-oxodibenz[b,e]oxepin ring system could change its conformation easily
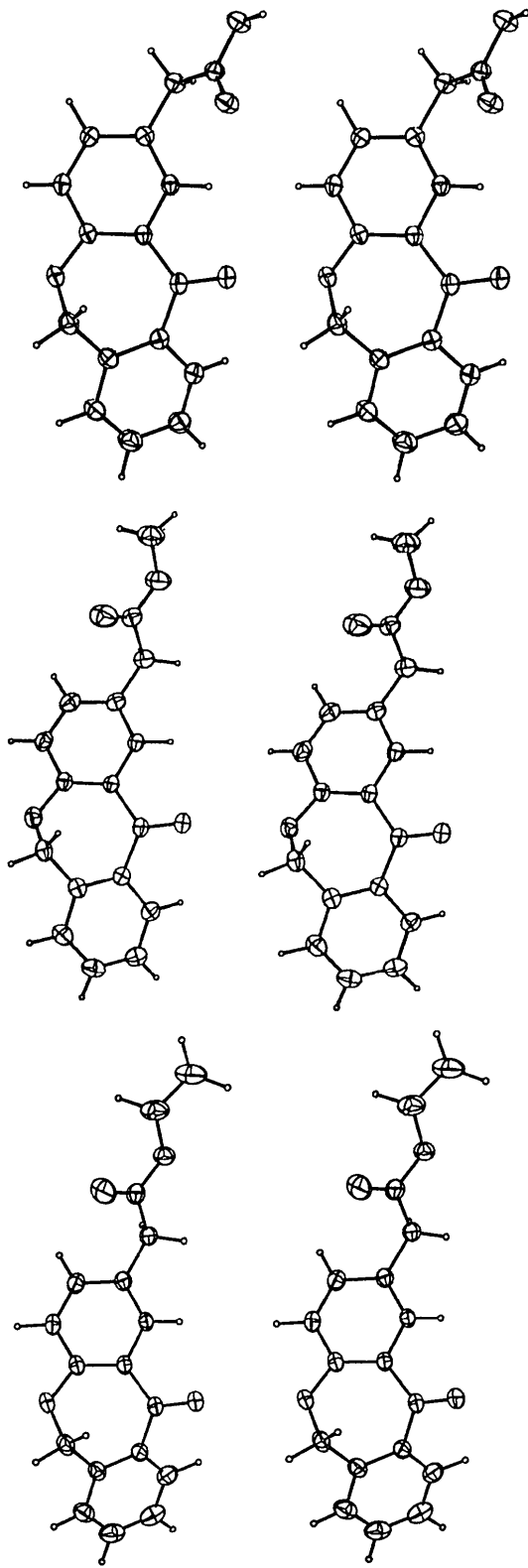
Fig. 2. Stereoscopic drawings of (I) (top), (II) (middle) and (III) (bottom).

through subtle differences of the substituents and the environmental changes around the molecules. This means that the skeleton could become one of the versatile spare parts for drug design because the regulation of the relative disposition of pharmacophores is indispensable for the molecular design of drugs. In indometacin, which is a well known potent non-steroidal anti-inflammatory agent, the corresponding dihedral angle between the two phenyl-ring planes is 67.4° (Kistenmacher & Marsh, 1972) and much larger than those in the oxepac derivatives. Although the dihedral angles in (I), (II), (III) and indometacin differ markedly, the distances between the centres of gravity of the two rings are similar, i.e. 5.21, 5.20, 5.03 and 4.98 Å, respectively.

In the crystal structure, (I) forms a centrosymmetric dimer through hydrogen bonds between the carboxyl groups [O···O 2.643 (2), H···O 1.69 (2) Å, ∠O—H···O 174 (2)°]. Ring A and part of ring B stack face to face in the crystals of (I) and (III), but in the crystal of (II) they stack almost perpendicular to each other.

The anti-inflammatory activities evaluated in carrageenan paw edema assay [ED_{50} (mg kg^{-1})] for (I), (II), (III) and indomethacin are 6.36, 31.04, 6.85 and 4.35, respectively (Aultz, Helsley, Hoffman, McFadden, Lassman & Wilker, 1977). To consider the reason for the low activity of (II) from the stereochemical point of view is interesting. The present analysis clearly shows that the electron distribution and the planarity concerning the B ring in (II) are notably different from those in (I) and (III). It is possible that this stereochemical feature could cause the difference of the packing mode. Therefore, we can speculate that the B ring might play an important role in the interaction with the receptor and in this case the planar conjugated system might be preferable.

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