69. Nucleophilic Addition to C,C Double Bonds. III[1]).

Chemical Reactivity of 1*endo*,4*endo*: 5*exo*, 8*exo*-Dimethano-1,2,3,4,4a,5,8,8a-octahydronaphthalen-10*syn*-ol and X-Ray Structure Analysis of its *p*-Nitrobenzoate

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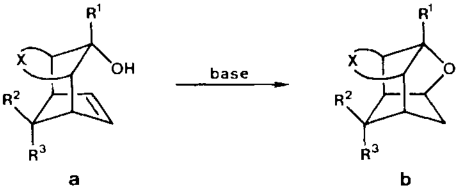
(18.I.80)

Summary

The title compound **1** is a further example of an olefinic alcohol that undergoes ether formation under basic conditions (→**3**) although the double bond is not activated by an electron-attracting group. This unusual reactivity is due to steric compression, which is increased in the 10-methyl analogue **2**. This forms the corresponding ether **7** at a much higher rate. - In a deuteriated medium, base-catalysed cyclization of **1** gives the *exo*-deuteriated ether **6**, corresponding to *trans*-addition. - An X-ray structure analysis of **4**, the *p*-nitrobenzoate of **1**, is presented.

Very recently we reported about the ability of several olefinic alcohols of the general type **a** to undergo ether formation to **b** under basic conditions [2] (see *Scheme 1*). This uncommon reactivity is mainly due to high steric compression, which is more pronounced in compounds with $R^1 = CH_3$ instead of H.

Scheme 1



R^1 = H or alkyl

R^2 and R^3 = H,H, OCH_3,H or =O

X = CH=CH, CH_2-CH_2 or $CH_2-CH_2-CH_2$

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[1]) For Part I, see [1]; for Part II, see [2].

[2]) Chemical Crystallography Research Group.

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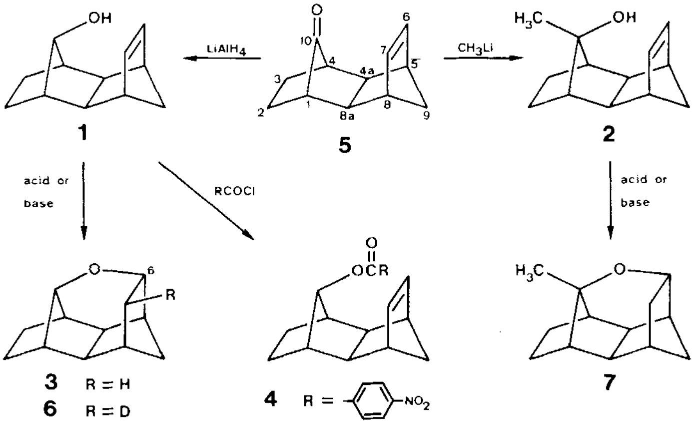
In order to study the applicability of this reaction mode on substrates with skeletons different from that of **a**, we investigated the behaviour in basic media of the known olefinic alcohol **1**[3] [3] [4], as well as of the corresponding methylated novel analogue **2**[4], which promised to be good candidates as well:

Battiste et al. [3], who had synthesized **1** for the first time, did not succeed in isolating it as pure compound. Attempted purification by adsorption chromatography[5] yielded the cyclic ether **3**. In addition they reported attempted esterification of **1** to **4** with *p*-nitrobenzoyl chloride (5 min on a steam bath) to yield a non-olefinic gummy solid. Severe steric compression between the OH-group and the opposing etheno bridge was said to be responsible for the lability of **1**.

Recently *Paddon-Row et al.* [4] were able to purify **1** by chromatography under basic conditions[6]. They chose these conditions after having observed that traces of acid caused rapid formation of **3** and interpreted the ease of cyclization as a result of the close proximity of the hydroxyl group to the double bond. From *Dreiding* models these authors estimated the distance between the oxygen atom and the double bond to be about 1.8 Å, but they pointed out that 'steric interactions should increase this separation'.

For our own studies we have synthesized the secondary alcohol **1** according to the procedure described by *Battiste et al.* [3], and the hitherto unknown tertiary alcohol **2** from the same key intermediate ketone **5** [3] by addition of methyl lithium.

Scheme 2



It is noteworthy that both these alcohols **1** and **2** remained stable during our chromatographic purification under neutral conditions. In contrast to the conditions applied by the above cited authors[5][6] we used silicagel 60 (70-230 mesh ASTM; *Merck*) with benzene/ethyl acetate 12:1 as well as silicagel 60 extra pure (70-230

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[3] 1*endo*,4*endo*:5*exo*,8*exo*-Dimethano-1,2,3,4,4a,5,8,8a-octahydronaphthalen-10*syn*-ol. The designations *syn*/*anti* refer to the steric relation of the substituents at C(10) to the C(6),C(7)-moiety.

[4] 10*anti*-Methyl-1*endo*,4*endo*:5*exo*,8*exo*-dimethano-1,2,3,4,4a,5,8,8a-octahydronaphthalen-10*syn*-ol.

[5] *Woelm* neutral alumina; elution with ether/petroleum ether mixtures.

[6] Neutral alumina pre-treated with a 0.5% solution of triethylamine in petroleum ether; elution with petroleum ether followed by petroleum ether/ether 4:1.

mesh ASTM; *Merck*) with pentane/ether 6:1 or 3:1. Starting from ketone **5**, the yields of chromatographically pure alcohols were 90% **1**[7] and 75% **2**[7], respectively.

Both alcohols cyclized to the corresponding ethers **3** and **7**, respectively, in 1 molal *t*-BuOK in *t*-BuOH at 80°. For the secondary alcohol **1**, reaction was only complete after about 24 hours, but the tertiary analogue **2** needed less than one hour[8]. This result is again in agreement with the idea that steric compression is substantially increased in compounds with a methyl group instead of a hydrogen atom at the carbon atom bearing the hydroxyl group. The higher steric compression in **2** is already manifested by its lower OH stretching vibration at 3530 cm^{-1}[7] in comparison to 3554 cm^{-1} of **1** [4] (CCl_4 as solvent). The ethers were isolated and chromatographically purified on silicagel 60 extra pure (70-230 mesh ASTM; *Merck*): 80% **3**[7] and 95% **7**[7], respectively.

Treatment of the secondary alcohol **1** in deuteriated media with 1 molal *t*-BuOK in *t*-BuOD or with 10% DCl in D_2O led to the mainly monodeuteriated ether **6**[7][9], thus proving that also in the base-catalysed reaction the electrophile enters from the *exo*-side, corresponding to a *trans*-addition to the C,C double bond. An analogous stereochemical course was already observed earlier with compounds of type **a**[10].

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[7] All compounds **1**-**7** were isolated. Their analytical and spectral data - some of them are listed below - are in full agreement with the assigned structures. *General.* Melting points (M.p.) were determined in open capillary tubes in an oil bath (*Büchi* 510 apparatus) and are uncorrected. - *IR. spectra* were recorded in CCl_4 on a *Perkin-Elmer* 297 spectrophotometer; absorption maxima are reported in cm^{-1}. - *^{1}H-NMR. spectra* were measured on a *Varian* HA-100 instrument (100 MHz); chemical shifts are given in ppm relative to TMS (0.00 ppm) as internal standard; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *J* = spin-spin coupling constant (Hz), $w_{1/2}$ = half width (Hz). - *Mass spectra (MS.)* were performed on a *Hitachi* RMU-6M instrument at 70 eV ionizing electron energy, source temp. 180°. The most important ions are listed as *m/z* values with relative intensities (% base peak) in parenthesis.

2. M.p. 67° (after recrystallization from hexane). - IR.: 3530. - ^{1}H-NMR. ($CDCl_3$): 1.0-1.25 and 1.45-1.85 (2 *m*, 2 H and 4 H, 2 H-C(2), 2 H-C(3), H-C(1) and H-C(4)); 1.20 (*d*, *J* = 1.5, *s* after D_2O-exchange, H_3C-C(10)); 1.34 and 1.64 (2 $d \times t$, *J* = 8 and *ca.* 1.5, 2 H-C(9)); 2.39 (*m*, $w_{1/2} \approx 6$, H-C(4a) and H-C(8a)); 2.9-3.05 (*m*, H-C(5), H-C(8) and HO-C(10)); 6.31 (*t*, *J* = 2, H-C(6) and H-C(7)). - MS.: 190 (M^+, 32), 175 (5), 172 (8), 125 (70), 81 (82), 66 (100), 43 (88).

3. ^{1}H-NMR. (CCl_4): 0.7-2.35 (*m*, 14 H); 3.69 (*m*, $w_{1/2} \approx 4$, H-C(10)); 3.98 (*m*, $w_{1/2} \approx 15$, H-C(6)). - MS.: 176 (M^+, 100), 158 (30), 91 (70), 81 (87), 67 (78), 66 (71).

4. M.p. 106.5° (after recrystallization from hexane). - IR.: 1723, 1610, 1532. - ^{1}H-NMR. ($CDCl_3$): 1.05-1.35 (*m*, H-C(2), H-C(3) and H-C(9)); 1.44 ($d \times t$, *J* = 8 and 1.5, H-C(9)); 1.75 (*m*, $w_{1/2} \approx 14$, H-C(2) and H-C(3)); 2.15-2.45 (*m*, H-C(1), H-C(4), H-C(4a) and H-C(8a)); 2.87 (*m*, $w_{1/2} \approx 6$, H-C(5) and H-C(8)); 4.42 (*m*, $w_{1/2} \approx 3$, H-C(10)); 5.74 (*t*, *J* = 2, H-C(6) and H-C(7)); 8.1-8.35 (*m*, *AA'BB'*, 4 arom. H). - MS.: 325 (M^+, 4), 260 (6), 158 (4), 150 (36), 66 (100).

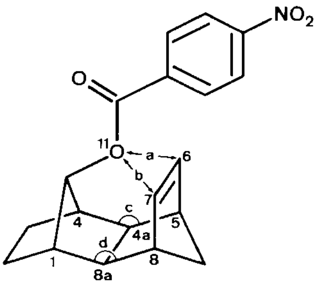
6. IR.: 2173. - ^{1}H-NMR. (CCl_4): 0.7-2.35 (*m*, *ca.* 13 H); 3.67 (*m*, $w_{1/2} \approx 4$, H-C(10)); 3.95 (*m*, $w_{1/2} \approx 9$, H-C(6)). - MS.: 177 (M^+, 100), 159 (28), 91 (58), 81 (79), 68 (57), 67 (68).

7. ^{1}H-NMR. (CCl_4): 0.75-2.3 (*m*, 14 H); 1.13 (*s*, H_3C-C(10)); 4.02 (*m*, $w_{1/2}$ = 15, H-C(6)). - MS.: 190 (M^+, 98), 175 (13), 125 (100), 81 (72), 66 (86), 43 (77).

[8] Alcohol **2** also cyclized at room temperature: 85% of isolated **7** after 5 days.

[9] Deuterium incorporation was determined by MS.: 92% d_1 for the base-catalysed and 94% d_1 for the acid-catalysed reaction. In the ^{1}H-NMR. spectrum of **6** H-C(6) appears as a *m* with $w_{1/2} \approx 9$ Hz instead of a *m* with $w_{1/2} \approx 15$ Hz as in the undeuteriated ether **3**.

[10] See [2] and unpublished results.



4

a 2.76 Å

b 2.83 Å

c 125.9°

d 125.3°

In order to correlate structural features (X-ray data) with reactivity we converted the secondary alcohol **1** to its *p*-nitrobenzoate **4**, which in contradiction to *Battiste et al.* [3] (see above) was found to be easily prepared with *p*-nitrobenzoyl chloride in dry pyridine (room temperature, 20 h). Work-up and chromatography on silicagel with cyclohexane/ethyl acetate 12:1 yielded 93% of **4**[7]).

In view of the cyclization of **1** to **3** the following X-ray data of **4** (for the full structure analysis see below) deserve special attention: The distance of approximately 2.7 Å between O(11) and the double bond (O(11)–C(6) = 2.76 Å and O(11)–C(7) = 2.83 Å) is 0.9 Å longer than the value (1.8 Å) estimated from *Dreiding* models by *Paddon-Row et al.* [4] (see above). The high steric compression between O(11) and the double bond also manifests itself in the strongly widened bond angles C(1)–C(8a)–C(8) and C(4)–C(4a)–C(5) of 125.3 and 125.9°, respectively.

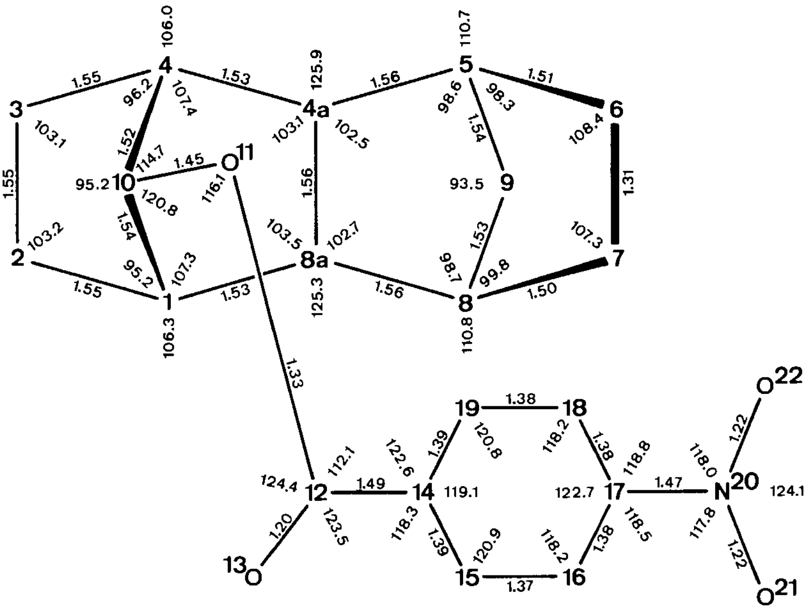


Fig. 1. *Bond lengths (Å) and angles (°) in* **4**. The mean standard deviation for bond lengths is 0.004 Å, for angles 0.2°.

Table. Compound 4: *final positional and thermal parameters* × *10*^{4} *(standard deviations in parantheses)*. The temperature factor expression is $\exp[-2\pi^2(U_{11}h^2a^{*2} + \ldots 2U_{12}hka^*b^*\ldots)]$ for non-hydrogen atoms, $\exp(-8\pi^2 \cdot U \cdot \sin^2\theta/\lambda^2)$ for hydrogen atoms

	x	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	5849 (3)	1586 (1)	−1771 (2)	486 (11)	876 (17)	530 (13)	−150 (12)	48 (11)	− 19 (12)
C(2)	6814 (4)	1345 (2)	−2916 (3)	662 (16)	1158 (26)	716 (17)	−175 (18)	205 (15)	15 (17)
C(3)	5238 (4)	1089 (2)	−3800 (3)	908 (20)	1076 (26)	528 (15)	−153 (18)	219 (15)	− 93 (16)
C(4)	3568 (3)	1198 (1)	−3046 (2)	635 (13)	712 (15)	442 (11)	−172 (12)	36 (11)	− 43 (10)
C(4a)	3234 (4)	1928 (1)	−3061 (2)	761 (16)	749 (16)	549 (14)	−133 (13)	− 57 (13)	153 (12)
C(5)	1569 (4)	2278 (2)	−2568 (3)	822 (19)	726 (18)	1082 (24)	31 (15)	−106 (19)	231 (17)
C(6)	1281 (4)	2071 (1)	−1253 (3)	777 (17)	587 (15)	1175 (23)	185 (14)	219 (18)	62 (16)
C(7)	2621 (5)	2294 (1)	− 521 (3)	1023 (24)	625 (16)	979 (23)	151 (17)	149 (21)	−163 (17)
C(8)	3838 (5)	2661 (1)	−1319 (3)	1105 (23)	537 (15)	1181 (25)	−178 (16)	− 28 (22)	−141 (17)
C(8a)	4814 (4)	2194 (1)	−2190 (3)	724 (15)	664 (15)	761 (17)	−273 (13)	23 (14)	41 (13)
C(9)	2445 (7)	2940 (2)	−2274 (5)	1328 (34)	637 (19)	1539 (39)	54 (23)	65 (31)	208 (24)
C(10)	4485 (3)	1029 (1)	−1783 (2)	489 (11)	600 (13)	471 (11)	− 8 (10)	76 (9)	− 28 (10)
C(12)	4030 (3)	787 (1)	309 (2)	433 (10)	542 (12)	471 (11)	15 (9)	− 7 (9)	21 (9)
C(14)	2678 (3)	713 (1)	1254 (2)	413 (10)	494 (11)	451 (10)	7 (9)	3 (8)	16 (9)
C(15)	3284 (3)	707 (1)	2504 (2)	399 (10)	766 (15)	504 (12)	− 34 (10)	− 48 (9)	20 (11)
C(16)	2093 (3)	660 (1)	3420 (2)	463 (11)	759 (14)	416 (11)	− 20 (11)	− 40 (9)	44 (10)
C(17)	285 (3)	597 (1)	3068 (2)	435 (9)	435 (10)	464 (11)	30 (9)	54 (9)	47 (9)
C(18)	− 365 (3)	584 (1)	1840 (2)	389 (10)	597 (13)	515 (12)	− 8 (10)	− 33 (9)	29 (10)
C(19)	845 (3)	651 (1)	938 (2)	447 (10)	604 (13)	420 (11)	− 3 (10)	− 39 (9)	10 (10)
N(20)	−1004 (2)	558 (1)	4045 (2)	492 (10)	561 (11)	538 (11)	79 (9)	81 (9)	99 (9)
O(11)	3275 (2)	958 (1)	− 796 (1)	424 (7)	570 (8)	421 (7)	26 (6)	49 (6)	36 (6)
O(13)	5623 (2)	705 (1)	528 (1)	410 (7)	1138 (14)	591 (9)	77 (9)	19 (7)	118 (9)
O(21)	− 475 (2)	712 (1)	5100 (1)	733 (11)	872 (12)	490 (9)	30 (9)	125 (8)	− 41 (8)
O(22)	−2525 (2)	373 (1)	3752 (2)	484 (8)	976 (13)	720 (11)	− 34 (9)	104 (8)	132 (10)

	x	*y*	*z*	U(Å^2)
H(1)	6578 (35)	1627 (12)	−1034 (24)	763 (76)
H(2)	7464 (41)	1713 (15)	−3243 (28)	955 (93)
H(2′)	7687 (47)	984 (17)	−2656 (29)	1021 (111)
H(3)	5343 (44)	630 (17)	−4009 (30)	1025 (109)
H(3′)	5139 (43)	1314 (14)	−4574 (29)	920 (92)
H(4)	2566 (33)	940 (11)	−3312 (21)	564 (64)
H(4a)	3309 (36)	2061 (13)	−3900 (25)	791 (79)
H(5)	546 (46)	2249 (16)	−3140 (31)	1072 (112)
H(6)	373 (35)	1767 (13)	−1063 (23)	963 (84)
H(7)	2946 (46)	2155 (16)	373 (34)	1099 (117)
H(8)	4586 (39)	2939 (15)	− 934 (26)	936 (93)
H(8a)	5650 (40)	2462 (14)	−2655 (25)	846 (81)
H(9)	1625 (54)	3227 (20)	−1907 (37)	1374 (154)
H(9′)	2924 (49)	3100 (18)	−3004 (33)	1071 (131)
H(10)	5084 (28)	614 (10)	−1811 (19)	478 (55)
H(15)	4554 (37)	722 (12)	2720 (22)	710 (71)
H(16)	2491 (33)	655 (11)	4270 (22)	701 (70)
H(18)	−1600 (31)	519 (10)	1610 (20)	574 (59)
H(19)	477 (30)	659 (11)	87 (22)	533 (63)

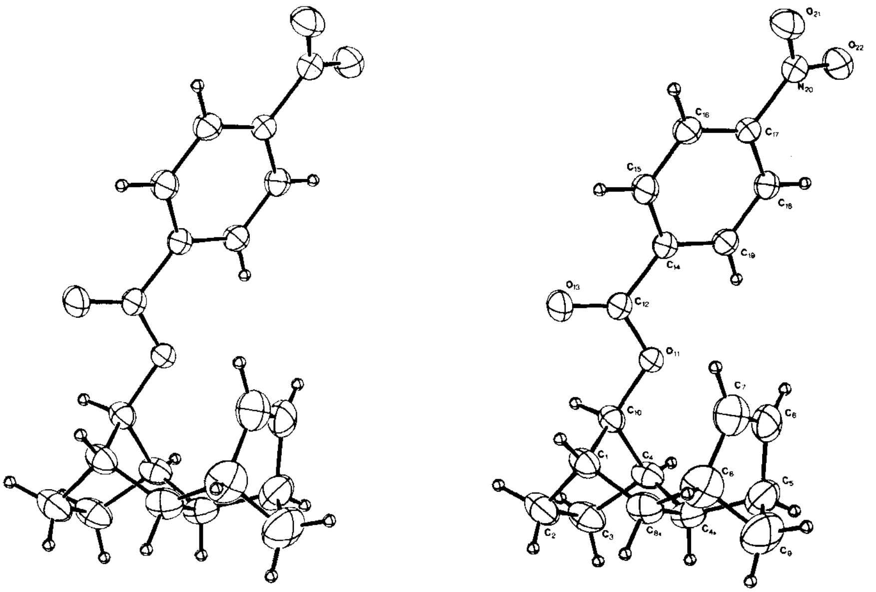


Fig. 2. *Stereoview of molecule* **4**. Vibration ellipsoids for non-hydrogen atoms are drawn at the 30% probability level. Hydrogen atoms are drawn as spheres with radius 0.1 Å.

X-Ray Analysis of 4. - *Crystal data.* $C_{19}H_{19}NO_4$, M = 325.4, monoclinic, $P2_1/n$, a = 7.438 (2), b = 20.711 (17), c = 10.781 (5) Å, β = 93.79 (3)°, Z = 4, D_x = 1.30 g · cm^{-3}.

Structure analysis. Intensities were collected on a CAD-4 *Enraf*-Nonius diffractometer with graphite monochromatized MoK_a radiation (λ = 0.71069 Å, μ = 0.54 cm^{-1}). Of the 3269 unique reflexions measured ($2\theta \leqslant 50°$), 1678 with $I \geqslant 3\sigma$ (I) were used for the refinement. The structure was solved by direct methods [5] and refined by full-matrix least squares [5] [6]. The H-atoms were located from a difference map and included in the refinement (C, N and O with anisotropic, H with isotropic thermal parameters). The weighting scheme applied was: σ^{-2} (F) · exp ($r \cdot \sin^2(\theta)/\lambda^2$) [7], with r = 8. The refinement converged at a R = 0.032 (R_w = 0.040) including extinction correction.

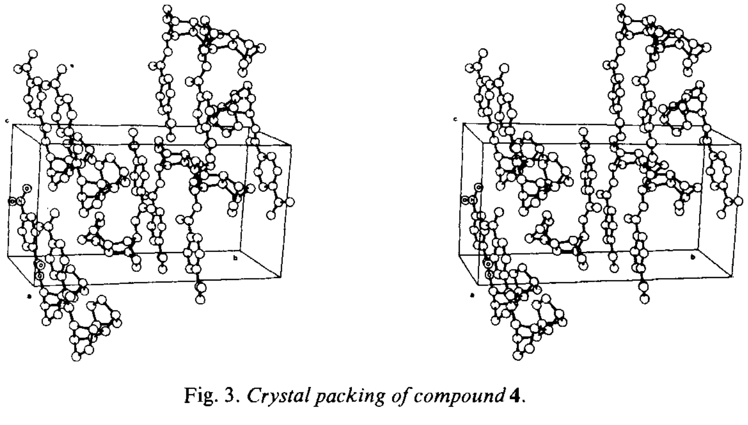
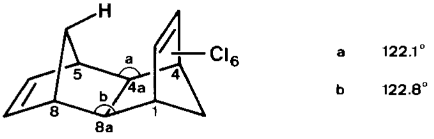


Fig. 3. *Crystal packing of compound* **4**.

Final positional and thermal parameters are listed in the *Table*, bond lengths and bond angles are given in *Figure 1*. *Figure 2* shows a stereoview of the molecule drawn with vibration ellipsoids at the 30% probability level using program ORTEP [8]. The packing diagram *(Fig. 3)* was drawn with program PLUTO [9].

The three fragments (carboxyl group, benzene ring and nitro group) of the nitrobenzoate group are not coplanar (τ: O(11)–C(12)–C(14)–C(19) = 16.4°, C(18)–C(17)–N(20)–O(22) = 14.5°). The plane of the benzene ring is almost perpendicular to the *b*-axis. The typical stacking pattern with the NO_2-group of one nitrobenzoate on top of the carboxyl group of another is not observed in this structure. The only intermolecular contacts closer than 3.2 Å between nonhydrogen atoms are between NO_2-groups: N(20) ... O(21) = 2.97 Å, O(21) ... O(21) = 3.04 Å.



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The repulsion between C(10) and the atoms at the double bond (C(6), C(7); mean distance 3.30 Å) leads to strong angle deformations, mostly at atoms C(4a) and C(8a) (C(1)–C(8a)–C(8) = 125.3°, C(4)–C(4a)–C(5) = 125.9°). Similar angle deformations are found in molecules with the same ring pattern. For example the angles corresponding to C(1)–C(8a)–C(8) and C(4)–C(4a)–C(5) in the structurally related compound **8** [10] are 122.8 and 122.1°, respectively. In this molecule the mean distance (3.05 Å) between the bridge atom and the atoms at the double bond is shorter than in **4**, probably because of the greater repulsion of the O-substituent at C(10) in molecule **4** compared with the H-substituent in molecule **8**. The atom O(11) of **4** does not lie in the local mirror plane of the ring skeleton (O(11)–C(6) = 2.76 Å, O(11)–C(7) = 2.83 Å). An analysis of the vibrational tensors with the program THMB [11] shows that the molecule does not behave as a rigid body ($R = \Sigma(U^{ij}_o - U^{ij}_c)^2 / \Sigma(U^{ij})^2 = 0.153$). Better agreement is obtained when the nitrobenzoate group and the ring skeleton are treated separately ($R = 0.066$ and 0.072, respectively, $\langle \Delta U^2_{ij} \rangle \approx 2 \langle \sigma^2(U_{ij}) \rangle$). For the ring skeleton the largest libration amplitude (5.7°) is roughly about an axis perpendicular to the plane C(1)–C(4)–C(5)–C(8). The two other libration amplitudes are 4.7 and 3.6°. Libration corrections are about the same for all bond lengths (0.007–0.01 Å). For the nitrobenzoate group there is a dominant libration axis about C(14)–C(17) with amplitude of 8.2° (the other two amplitudes are 2.7 and 2.0°). The libration corrections elongate the bonds C(14)–C(15), C(14)–C(19), C(16)–C(17), C(17)–C(18), N(20)–O(21) and N(20)–O(22) by 0.01 to 0.014 Å, whereas the bonds that are parallel to the main libration axis do not change significantly.

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Erratum

Helv. *63*, 406 (1980), Abhandlung Nr. 40 von *A. Brossi, M. Rösner, J. V. Silverton, M.A. Iorio* and *Ch. D. Hufford*

S.410, 1. Zeile von unten, sollte wie folgt ergänzt werden:

$C_{22}H_{25}NO_7$ (415.44) Calc. C 63.60 H 6.07 N 3.37% Found C 63.45 H 5.99 N 3.45%