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On the Isostructural Molecular Compound Formation of a Steroid with α- and β-Naphthols

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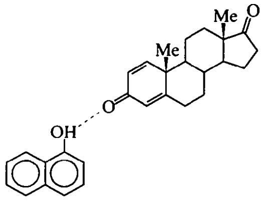
Abstract

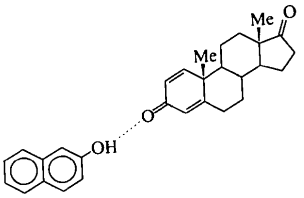
The crystal structures of the molecular compounds androsta-1,4-diene-3,17-dione–1-naphthol (1/1) and androsta-1,4-diene-3,17-dione–2-naphthol (1/1), two isomers of $C_{19}H_{24}O_2.C_{10}H_8O$, are described. The degree of isostructurality is characterized and an explanation for the preservation of a mutual crystal structure is established. Correlation is made between the chemical properties and the properties found in the crystals.

Comment

Since the late 1950's androsta-1,4-diene-3,17-dione, (I), has been used as a key intermediate in the synthesis of estrone (Dryden, Webber & Wieczorek, 1964). Industrial production of (I) by microbial transformation of progesterone with *Fusarium* species (Fried, Thoma & Klingsberg, 1953) and by microbial side-chain cleavage of natural sterols with *Arthrobacter simplex* (Nagasawa, Bae, Tamura & Arima, 1969) and *Mycobacteria* (Wix, Büki, Tömörkény & Ambrus, 1968) as well as the mutants of the latter (Marsheck, Kraychy & Muir, 1972) has been developed. In the course of experiments on the isolation of (I) from the fermentation broth it was found that β-naphthol (m.p. 395–396 K) and (I) form a 1:1 molecular compound, BENA, in several solvents (m.p. 442–443 K) (Pauncz, Wix, Rados & Alföldi, 1961). A similar molecular compound, ALNA (m.p. 436–438 K), was obtained with α-naphthol (m.p. 369 K) and (I). Since the solubilities of the molecular compounds are considerably different from those of the starting materials and the by-products of fermentation [*e.g.* androst-4-ene-3,17-dione, (II)], the formation of the molecular compound with β-naphthol proved to be useful in the purification of (I). In this study we report the crystal structures of the compounds ALNA and BENA and try to explain their properties on a crystallographic basis.



ALNA



BENA

It was established that the two crystals are highly isostructural (see Tables 1, 2, 3 and 4, and Figs. 3 and 4), although the hydrogen-bond data given below show that the complex formed between β-naphthol and the steroid is clearly stronger than that formed by α-naphthol. It is also worth mentioning that the more stable molecular compound is easier to prepare in the form of good quality single crystals, a fact which is also reflected by the quality of our data and results.

The only important difference between the two crystal structures is in the position of the naphthol OH group, which is linearly hydrogen-bonded to the conjugated carbonyl group in position 3 of a neighbouring steroid molecule in both compounds [ALNA: O1N—H1ON 0.95, H1ON···O1 1.87, O1N···O1 2.76 (2) Å, O1N—H1ON···O1 156°; BENA: O1N—H1ON 1.14, H1ON···O1 1.58, O1N···O1 2.684 (6) Å, O1N—H1ON···O1 161°]. To characterize the degree of isostructurality between the two compounds we calculated the unit-cell similarity (Π) as well as the isostructurality indices [$I_i(n)$ and $I_i(n^*)$] as defined by Kálmán, Párkányi & Argay (1993). All point to a very high degree of isostructurality, with $\Pi = 4.94 \times 10^{-4}$, $I_i(31) = 92\%$ and $I_i(31^*) = 93\%$. In addition, this particular case seems to add a new subclass, or at least an

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exception, to the classification introduced by Kálmán, Párkányi & Argay (1993). This is because in this case we seem to have isometric molecules differing in one substituent only (A1 subclass), but we also have crystals of molecular associates (class A/B). These crystals are not host–guest complexes in the classical sense, in which guest species are accommodated in holes within a lattice formed by the host, since the constituent molecules in ALNA and BENA are of similar size and the naphthol molecules in each actively contribute to the scaffold of the lattice.

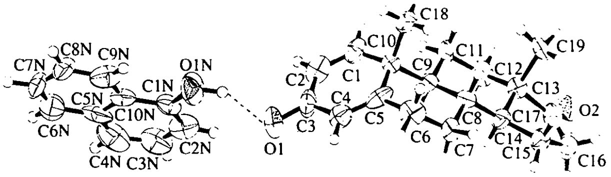

Fig. 1. Molecular structure and atomic numbering for a hydrogen-bonded pair of molecules in ALNA. Displacement ellipsoids are plotted at the 50% probability level.

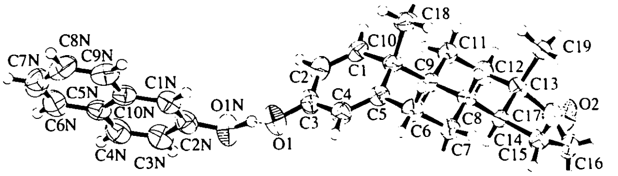

Fig. 2. Molecular structure and atomic numbering for a hydrogen-bonded pair of molecules in BENA. Displacement ellipsoids are plotted at the 50% probability level.

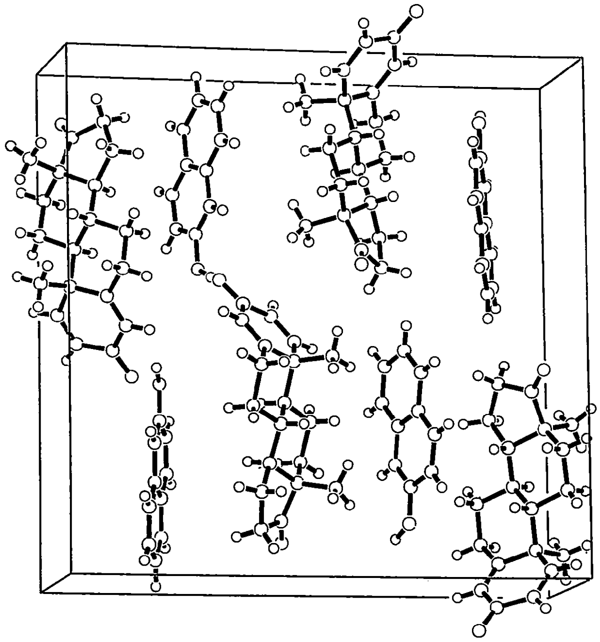

Fig. 3. Packing diagram for ALNA.

The mean plane of the steroid molecule positioned above the β-naphthol moiety is, not surprisingly, parallel with the β-naphthol molecule. This observation does not support our former idea that the interaction between the delocalized π system of the naphthol molecule and the *A* ring of the steroid would be responsible for the formation of a stable molecular compound. It is tempting to speculate on the reason why compound (I) forms molecular compounds with the naphthols, while (II) does not, even though the difference between (I) and (II) is only the presence of an additional conjugated double bond in (I). We suggest that this phenomenon could be due to the higher basicity of the 3-oxo group in the 1,4-diene-3-ones.

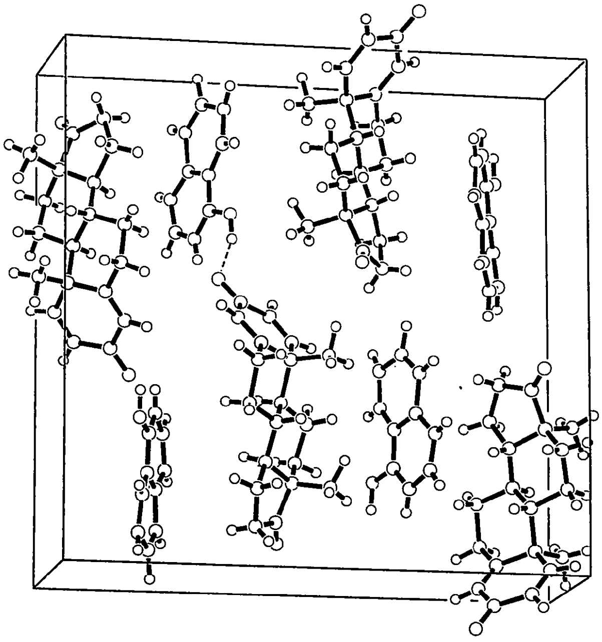

Fig. 4. Packing diagram for BENA.

Experimental

ALNA

Crystal data

$C_{19}H_{24}O_2.C_{10}H_8O$
$M_r = 428.6$
Orthorhombic
$P2_12_12_1$
$a = 19.158$ (3) Å
$b = 19.029$ (3) Å
$c = 6.377$ (2) Å
$V = 2324.9$ (8) Å^3
$Z = 4$
$D_x = 1.225$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 21 reflections
$\theta = 40.05–47.88°$
$\mu = 0.6615$ mm^{-1}
$T = 296$ K
Plate
0.2 × 0.2 × 0.08 mm
Transparent
Crystal source: crystallized from ethanol–water

Data collection

AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2734 measured reflections
2734 independent reflections
1302 observed reflections $[I > \sigma(I)]$
$\theta_{\max} = 75°$
$h = 0 \rightarrow 24$
$k = -13 \rightarrow 0$
$l = -6 \rightarrow 0$
3 standard reflections monitored every 150 reflections intensity decay: none

Refinement

Refinement on F
$R = 0.088$
$wR = 0.062$
$S = 1.320$
1302 reflections
289 parameters
H-atom parameters not refined
Weighting scheme based on measured e.s.d.'s
$(\Delta/\sigma)_{\max} = 0.3250$
$\Delta\rho_{\max} = 0.405$ e Å^{-3}
$\Delta\rho_{\min} = -0.396$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* ALNA

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O1	0.3207 (3)	−0.0804 (3)	0.991 (1)	0.096 (5)
O2	0.4435 (5)	0.4207 (4)	1.144 (2)	0.094 (6)
O1N	0.3519 (4)	−0.2158 (4)	1.115 (1)	0.092 (5)
C1N	0.3257 (5)	−0.2342 (6)	1.299 (2)	0.050 (7)
C1	0.4642 (5)	0.0381 (5)	0.996 (2)	0.054 (6)
C2N	0.3022 (6)	−0.1889 (6)	1.442 (2)	0.064 (8)
C2	0.4234 (6)	−0.0142 (5)	1.057 (2)	0.062 (7)
C3N	0.2773 (6)	−0.2131 (8)	1.638 (2)	0.082 (9)
C3	0.3606 (6)	−0.0327 (5)	0.937 (2)	0.065 (7)
C4N	0.2721 (6)	−0.2832 (10)	1.686 (3)	0.102 (10)
C4	0.3442 (5)	0.0097 (5)	0.758 (2)	0.054 (6)
C5N	0.2953 (5)	−0.3309 (7)	1.535 (3)	0.071 (10)
C5	0.3846 (5)	0.0640 (5)	0.690 (2)	0.050 (6)
C6N	0.2935 (6)	−0.4056 (7)	1.578 (2)	0.085 (9)
C6	0.3647 (5)	0.1070 (5)	0.507 (2)	0.060 (6)
C7N	0.3168 (7)	−0.4510 (5)	1.426 (3)	0.086 (10)
C7	0.3538 (4)	0.1837 (5)	0.574 (1)	0.041 (5)
C8N	0.3445 (6)	−0.4277 (6)	1.237 (3)	0.091 (10)
C8	0.4143 (4)	0.2132 (5)	0.707 (2)	0.042 (6)
C9N	0.3441 (5)	−0.3582 (7)	1.195 (2)	0.077 (8)
C9	0.4344 (4)	0.1632 (5)	0.894 (2)	0.041 (6)
C10N	0.3233 (5)	−0.3098 (6)	1.340 (2)	0.050 (7)
C10	0.4487 (4)	0.0845 (5)	0.812 (2)	0.042 (5)
C11	0.4938 (5)	0.1935 (5)	1.027 (2)	0.052 (6)
C12	0.4774 (5)	0.2684 (5)	1.112 (2)	0.049 (6)
C13	0.4595 (4)	0.3161 (5)	0.930 (2)	0.038 (5)
C14	0.3987 (4)	0.2858 (5)	0.805 (2)	0.047 (6)
C15	0.3736 (5)	0.3462 (5)	0.659 (2)	0.049 (6)
C16	0.3802 (5)	0.4084 (4)	0.812 (2)	0.066 (7)
C17	0.4304 (6)	0.3886 (5)	0.995 (2)	0.059 (7)
C18	0.5136 (4)	0.0834 (5)	0.659 (2)	0.056 (6)
C19	0.5242 (4)	0.3315 (5)	0.788 (2)	0.061 (6)

Table 2. *Selected geometric parameters* (Å) *for* ALNA

O1—C3	1.234 (10)	C2—C3	1.47 (1)
O2—C17	1.16 (1)	C3—C4	1.43 (1)
O1N—C1N	1.32 (1)	C4—C5	1.36 (1)
C1—C2	1.33 (1)	C5—C6	1.48 (1)
C1—C10	1.50 (1)		

BENA

Crystal data

$C_{19}H_{24}O_2.C_{10}H_8O$
$M_r = 428.6$
Orthorhombic
$P2_12_12_1$
$a = 19.058$ (2) Å
$b = 19.209$ (2) Å
$c = 6.275$ (1) Å
$V = 2297.1$ (6) Å^3
$Z = 4$
$D_x = 1.239$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.5418$ Å
Cell parameters from 25 reflections
$\theta = 40–50°$
$\mu = 0.5670$ mm^{-1}
$T = 298$ K
Needle
0.80 × 0.40 × 0.25 mm
Transparent
Crystal source: crystallized from ethanol–water

Data collection

AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2754 measured reflections
2754 independent reflections
2022 observed reflections $[I > 3\sigma(I)]$
$\theta_{\max} = 75°$
$h = 0 \rightarrow 23$
$k = 0 \rightarrow 24$
$l = 0 \rightarrow 0$
3 standard reflections monitored every 150 reflections intensity decay: 0.17%

Refinement

Refinement on F
$R = 0.0513$
$wR = 0.0456$
$S = 4.581$
2022 reflections
289 parameters
Only H-atom U's refined
Weighting scheme based on measured e.s.d.'s
$(\Delta/\sigma)_{\max} = 0.0001$
$\Delta\rho_{\max} = 0.267$ e Å^{-3}
$\Delta\rho_{\min} = -0.171$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* BENA

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
O1	0.3207 (2)	−0.0832 (2)	0.9932 (7)	0.073 (2)
O2	0.4452 (3)	0.4136 (2)	1.1268 (8)	0.081 (2)
O1N	0.3047 (2)	−0.1248 (2)	1.3987 (7)	0.072 (2)
C1	0.4649 (3)	0.0337 (3)	0.9917 (10)	0.048 (2)
C1N	0.3238 (3)	−0.2420 (3)	1.284 (1)	0.053 (2)
C2	0.4248 (3)	−0.0191 (3)	1.0512 (10)	0.053 (2)
C2N	0.3040 (3)	−0.1935 (3)	1.429 (1)	0.053 (2)
C3	0.3603 (3)	−0.0359 (3)	0.937 (1)	0.052 (2)
C3N	0.2788 (3)	−0.2147 (3)	1.632 (1)	0.060 (2)
C4	0.3452 (3)	0.0053 (3)	0.7461 (10)	0.049 (2)
C4N	0.2744 (3)	−0.2834 (4)	1.681 (1)	0.062 (2)
C5	0.3855 (3)	0.0579 (3)	0.6838 (9)	0.040 (2)
C5N	0.2948 (3)	−0.3355 (3)	1.535 (1)	0.051 (2)
C6	0.3651 (3)	0.1027 (3)	0.4977 (10)	0.048 (2)
C6N	0.2918 (4)	−0.4074 (4)	1.584 (1)	0.071 (3)
C7	0.3537 (3)	0.1774 (3)	0.5726 (9)	0.041 (2)
C7N	0.3131 (4)	−0.4569 (3)	1.437 (1)	0.078 (3)
C8	0.4153 (3)	0.2061 (3)	0.6969 (9)	0.034 (2)
C8N	0.3384 (4)	−0.4341 (4)	1.241 (1)	0.077 (3)
C9	0.4361 (3)	0.1570 (3)	0.8833 (9)	0.036 (2)
C9N	0.3409 (3)	−0.3652 (4)	1.188 (1)	0.068 (2)
C10	0.4499 (3)	0.0808 (3)	0.8041 (9)	0.039 (2)

C10N	0.3204 (3)	−0.3140 (3)	1.332 (1)	0.049 (2)
C11	0.4966 (3)	0.1870 (3)	1.0184 (9)	0.045 (2)
C12	0.4813 (3)	0.2607 (3)	1.0988 (10)	0.050 (2)
C13	0.4620 (3)	0.3081 (3)	0.9151 (9)	0.040 (2)
C14	0.3994 (2)	0.2767 (3)	0.7914 (9)	0.034 (2)
C15	0.3741 (3)	0.3365 (3)	0.6497 (9)	0.047 (2)
C16	0.3811 (3)	0.4012 (3)	0.795 (1)	0.058 (2)
C17	0.4332 (4)	0.3786 (3)	0.973 (1)	0.054 (2)
C18	0.5166 (3)	0.0767 (3)	0.660 (1)	0.055 (2)
C19	0.5275 (3)	0.3232 (3)	0.776 (1)	0.060 (2)

Table 4. *Selected geometric parameters* (Å) *for* BENA

O1—C3	1.234 (7)	C2—C3	1.459 (9)
O2—C17	1.201 (8)	C3—C4	1.464 (9)
O1N—C2N	1.333 (8)	C4—C5	1.328 (8)
C1—C2	1.324 (8)	C5—C6	1.501 (8)
C1—C10	1.511 (8)		

For both compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1992). Program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990) for ALNA; *SIR*88 (Burla *et al.*, 1989) for BENA. For both compounds, program(s) used to refine structures: *TEXSAN LS*; software used to prepare material for publication: *TEXSAN FINISH*.

Thanks are due to Chinoin Pharmaceuticals for supporting the project with manpower and instrumentation. The authors are grateful to Professor A. Kálmán for helpful discussions on problems of isostructurality.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, bond distances and angles involving non-H atoms for ALNA and complete geometry for BENA have been deposited with the IUCr (Reference: KA1098). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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DL-4-Hydroxy-3-methoxymandelic Acid

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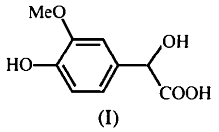
Abstract

In the title compound, DL-2-(4-hydroxy-3-methoxyphenyl)-2-hydroxyacetic acid, $C_9H_{10}O_5$, the acetic acid side chain adopts a roughly perpendicular orientation with respect to the phenyl ring. The molecules are linked together through hydrogen bonds of the type O—H···O.

Comment

The crystal structures of the catecholamines dopamine (Bergin & Carlström, 1968; Giesecke, 1980), adrenaline (Andersen, 1975*a*), noradrenaline (Andersen, 1975*b*; Carlström & Bergin, 1967) and their analogues (Barlow, Johnson, Howard, Walton & Koellner, 1989; Seiler, Markstein, Walkinshaw & Boelsterli, 1989) have been determined. It is also important to clarify the detailed structure of catecholamine metabolites in order to study catecholamine action as well as metabolism. In this respect the structures of the dopamine metabolites 3-methoxytyramine (Okabe, Mori & Sasaki, 1991; Okabe & Mori, 1992) and homovanillic acid (Okabe, Hatanaka & Sasaki, 1991), and the noradrenaline metabolite normetanephrine (Pattanayek, Dattagupta, Bhattacharyya & Saha, 1984) have been reported. We report here the crystal structure of the title compound, (I), which is the principal metabolite of adrenaline and noradrenaline (Grodsky, 1983).



(I)

The acetic acid side chain is oriented roughly perpendicularly to the phenyl ring [torsion angle C(2)—C(1)—C(7)—C(8) −63.8 (2)°]. This conformational feature of the molecule resembles that observed for catecholamines and the corresponding amines (Barlow, Johnson, Howard, Walton & Koellner, 1989) as well as the catecholamine metabolites normetanephrine (Pattanayek, Dattagupta, Bhattacharyya & Saha, 1984), homovanillic acid (Okabe, Hatanaka & Sasaki, 1991) and 3-methoxytyramine (Okabe & Mori, 1992). Two hydroxyl groups and the carboxyl group participate