Short Communications

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Intermolecular binding in the 1:1 complex between testosterone and *p*-bromophenol.

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In the crystalline state, testosterone and *p*-bromophenol form a 1:1 complex in which steroid molecules which are related by 2_1 axes parallel to **b**, are hydrogen bonded end-to-end, with the 17β-hydroxyl group of one molecule donating a proton to the 3-ketone group of another. This same hydroxyl group also accepts a proton from the phenolic hydroxyl group of an adjacent *p*-bromophenol molecule. Crystal data are: space group $P2_12_12_1$, $a=13{\cdot}104$, $b=22{\cdot}714$, $c=7{\cdot}665$ Å. There are four $C_{19}H_{28}O_2+C_6H_5OBr$ units per unit cell.

In order for a hormone to influence the course of a metabolic process, it must be bound to a receptor in a specific fashion, influenced by the complementary chemical, physicochemical, and stereochemical properties of the hormone and its receptor site (Engel, Stoffyn & Scott, 1964). The study of interactions of steroid hormones with compounds related to coenzymes was initiated by Munck, Scott & Engel (1957) who examined the formation of complexes between steroid hormones and purine bases, purine nucleosides, and purine-containing nucleotides. Their study of the structural requirements for interaction revealed that the α-side of the steroid was involved, probably in the *C* and *D* ring regions, and possibly with part of the *B* ring, but not with the *A* ring. Abelson, Depatie & Craddock (1960) studied the formation of complexes between amino acids and testosterone, but were only able to verify complex formation with tyrosine ethyl ester and tryptophan.

Our original intent was to obtain exact structure analyses of some of these complexes, but we have been quite unsuccessful in our attempts to grow crystals. We have shown, however, that the androgens form stable, crystalline complexes with *p*-bromophenol (Eger & Norton, 1965) and with mercuric chloride (Cooper, Gopalakrishna & Norton, 1968), so that we initiated structure investigations on these complexes to obtain models for future investigations. The structure of the *p*-bromophenol complex is of particular interest in that *p*-bromophenol resembles that portion of the tyrosine molecule which is available for complex formation once this amino acid is incorporated in a protein backbone. It is interesting that the steroid Δ-isomerase that catalyzes interconversion of Δ^5- and Δ^4-3-ketosteroids has been shown to contain ten tyrosyl residues, and Wang, Kawahara & Talalay (1963) have proposed that these tyrosines may be involved in steroid binding or in the catalysis of isomerization.

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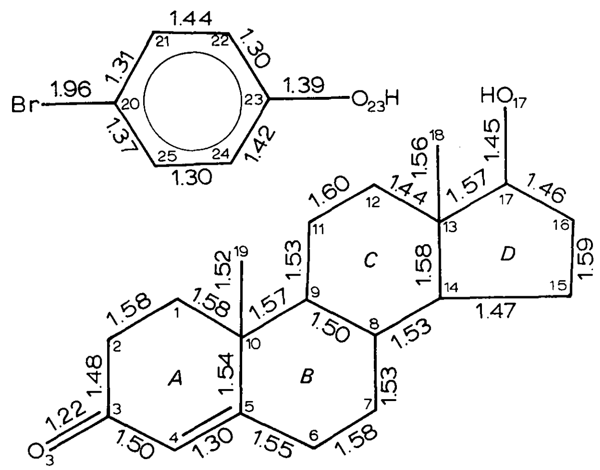

Fig. 1. Summary of the intramolecular bonding distances in the two molecules comprising the complex. Standard deviations are estimated to be about 0·05 Å.

Crystal data

Testosterone: *p*-bromophenol complex (1:1), $C_{19}H_{28}O_2+C_6H_5OBr$. $M=461{\cdot}4$, $a=13{\cdot}104$, $b=22{\cdot}714$, $c=7{\cdot}665$ Å (Cu $K\alpha_1=1{\cdot}54051$ Å). $D_m=1{\cdot}33$, $D_c=1{\cdot}34$ g.cm^{-3} for $Z=4$. Space group $P2_12_12_1$ ($h00$ present for $h=2n$, $0k0$ for $k=2n$ and $00l$ for $l=2n$, only). $F(000)=868$.

Intensity data were collected on a General Electric single-crystal orienter, using Cu $K\alpha$ radiation and the stationary-crystal stationary-counter technique. The bromine atom was located from the three Harker sections of the Patterson synthesis, after which the structure was solved by straightforward application of the heavy-atom method. The positional and isotropic thermal parameters of all atoms were refined by block-diagonal least-squares to an *R* value of 16% (for 2497 reflections).* Refinement was not continued past this point, nor was any attempt made to locate the hydrogen atoms. Table 1 lists the refined parameters.

* A listing of the comparison between the observed and calculated structure factors may be obtained from the last-named author (D.A.N.).

Table 1. *Refined parameters for the atoms*

Atoms C(20)–C(25), O(23) and Br(20) are the *p*-bromophenol molecule. Approximate standard deviations are equivalent to 0·01–0·02 Å foi the positional parameters and are about 0·5 Å^2 from the thermal parameters.

	x/a	y/b	z/c	B(iso)
C(1)	0·0663	0·3302	1·2335	3·2
C(2)	0·0760	0·2611	1·2267	4·5
C(3)	0·0148	0·2366	1·0808	3·5
C(4)	0·0071	0·2718	0·9162	4·6
C(5)	0·0476	0·3241	0·9035	3·0
C(6)	0·0528	0·3541	0·7216	4·3
C(7)	0·0115	0·4190	0·7369	3·4
C(8)	0·0692	0·4512	0·8813	2·4
C(9)	0·0493	0·4217	1·0524	3·0
C(10)	0·0984	0·3584	1·0538	4·1
C(11)	0·0876	0·4562	1·2108	4·1
C(12)	0·0494	0·5230	1·1982	2·8
C(13)	0·0787	0·5514	1·0373	3·3
C(14)	0·0301	0·5146	0·8829	5·0
C(15)	0·0422	0·5538	0·7321	4·1
C(16)	0·0310	0·6185	0·8078	3·3
C(17)	0·0278	0·6122	0·9975	3·6
C(18)	0·1971	0·5549	1·0231	6·4
C(19)	0·2136	0·3580	1·0377	6·3
O(3)	−0·0301	0·1896	1·0912	4·8
O(17)	0·0845	0·6596	1·0789	4·4
C(20)	0·2626	0·1244	0·7870	6·4
C(21)	0·2684	0·1778	0·8485	6·3
C(22)	0·2876	0·2224	0·7183	4·2
C(23)	0·2985	0·2094	0·5541	4·9
C(24)	0·2809	0·1513	0·4939	6·9

Table 1 (*cont.*)

C(25)	0·2658	0·1113	0·6132	6·3
O(23)	0·3149	0·2537	0·4323	5·7
Br(20)	0·2337	0·0615	0·9542	13·7

The intramolecular geometry of the testosterone and the *p*-bromophenol molecules is quite normal (Fig. 1) and the discussion will be confined to the details of the packing of the molecules in the unit cell. Both the steroid and the bromophenol molecules pack almost parallel to (100), making angles of 8° and 10° with this plane, and 91° and 98°, and 98° and 96° with the (010) and (001) planes, respectively. The planes of the bromophenol molecule and of the steroid molecule are themselves almost parallel, lying at an angle of 16° to one another. Steroid molecules which are related by the twofold screw axes parallel to **b** are hydrogen bonded end-to-end, with the 17β-hydroxyl group of one molecule acting as a proton donor to the 3-ketone group of another. This same hydroxyl oxygen also acts as a proton acceptor from the phenolic hydroxyl group of an adjacent *p*-bromophenol molecule. The geometry of this mode of packing is given in Fig. 2, in which it can be seen that the oxygen atom O(17) has adopted almost planar coordination in forming these hydrogen bonds.

In view of the proposed *C*/*D* interactions with complexing molecular moieties, the present structure is quite surprising. There are thirty-three intermolecular distances less than 4·0 Å, and of these, twenty-four involve the *p*-bromophenol molecules. Of these 'complexing contacts', however, thirteen are with the *A* and *B* rings of the steroid, and seven

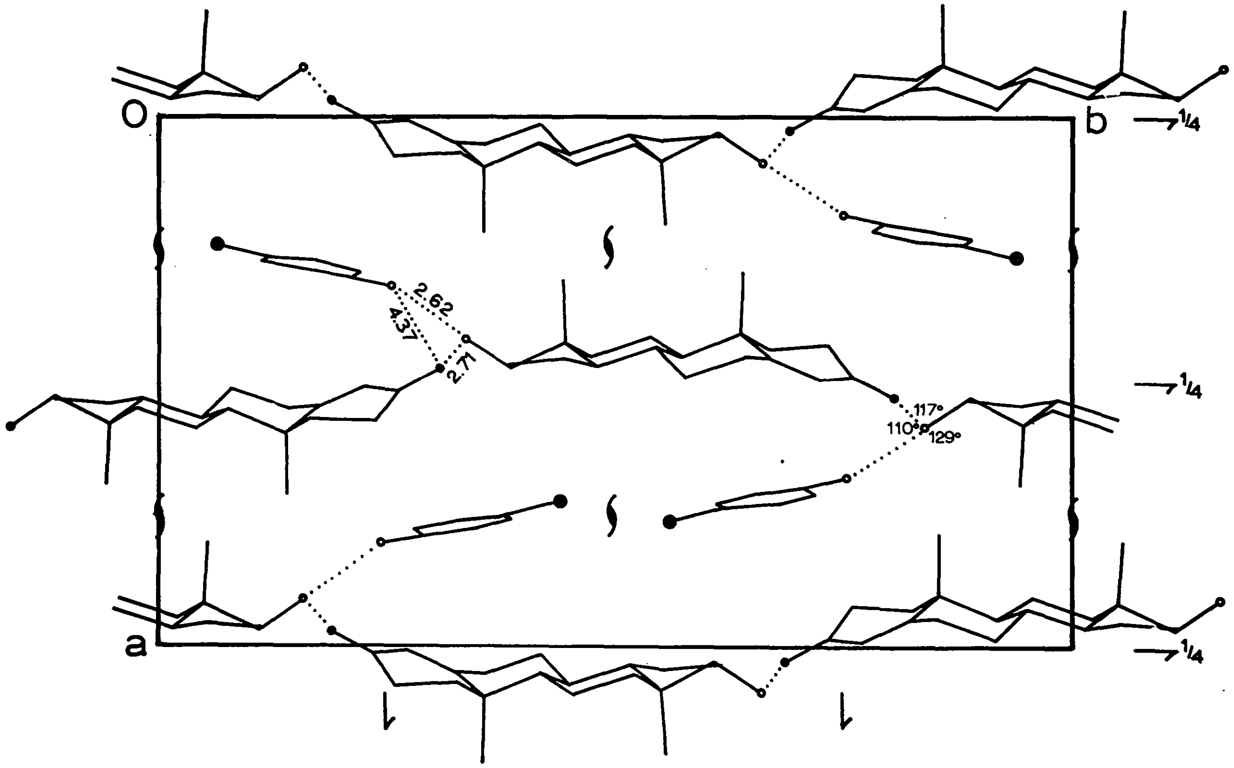

Fig. 2. Projection of the unit-cell contents of the testosterone–bromophenol complex, down the *c* axis. Large solid circles: bromine; small solid circles: carbonyl oxygen; small open circles: hydroxyl oxygen. Hydrogen bonds are indicated by dotted lines. The 4·37 Å distance between the phenolic hydroxyl and the carbonyl groups shows that these are not hydrogen bonded.

are with the D ring. There are no intermolecular contacts between the bromophenol molecules and the C rings of steroid molecules.

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Lattice parameters and space groups of two stilbene substituents.

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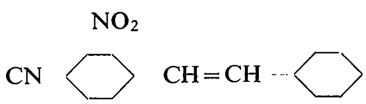
Crystals of 2-nitro-4-cyanostilbene, $C_{15}H_{10}N_2O_2$, are orthorhombic, space group either *Pnam* or $Pna2_1$, with 8 molecules in a unit cell of dimensions $a=13{\cdot}84$, $b=7{\cdot}20$, $c=24{\cdot}88$ Å. 2-Nitro-4-cyano-4′-methoxy-stilbene, $C_{16}H_{12}N_2O_3$, has been crystallized in two forms, one yellow-green and the other orange. The orange crystals are triclinic, with 2 molecules in a unit cell of dimensions $a=8{\cdot}38$, $b=13{\cdot}06$, $c=7{\cdot}25$ Å, $\alpha=97°30'$, $\beta=108°$, $\gamma=71°$.

The compounds 2-nitro-4-cyanostilbene and 2-nitro-4-cyano-4′-methoxystilbene are interesting organic scintillating and conducting materials (Georgescu & Giusca, 1966). The two stilbene substituents were synthesized by condensation of 3-nitro-4-methylbenzonitrile with benzaldehyde and 3-nitro-4-methoxybenzaldehyde in the presence of piperidine as a catalyst, at a temperature of about 140°C (Ullmann & Gschwind, 1908). A few good crystals were obtained by repeated crystallization in absolute ethanol.

X-ray single-crystal and powder diffraction techniques were used, with Ni-filtered Cu radiation, to determine the cell parameters.

(1) 2-Nitro-4-cyanostilbene, structural formula

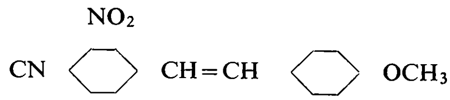


The crystals are thin tablets (001) of a yellow-green colour, and twinning along the c axis is frequently observed. A few monocrystals were selected for single-crystal measurements. From rotation and Weissenberg photographs, the crystals were found to be orthorhombic with the unit-cell parameters:

$a=13{\cdot}841\pm8$, $b=7{\cdot}199\pm6$,
$c=24{\cdot}882\pm30$ (three standard deviations) Å;
$V=2480\pm6$ Å^3;
$Z=8$, $D_m=1{\cdot}26\pm0{\cdot}02$ g.cm^{-3}
and $D_x=1{\cdot}34$ g.cm^{-3}.

The systematic extinctions: reflexions $0kl$ present for $k+1=2n$; reflexions $h0l$ present for $h=2n$, lead to space group $Pna2_1$ or *Pnam*.

(2) 2-Nitro-4-cyano-4′-methoxy stilbene, structural formula



This compound shows two kinds of crystals having yellow-green and orange colour respectively. The powder diffraction data clearly confirm the existence of two structural isomers. The single-crystal study was carried out only on the orange type of crystals. The unit cell is triclinic with:

$a=8{\cdot}377\pm13$,
$b=13{\cdot}065\pm30$ (two standard deviations),
$c=7{\cdot}246\pm10$ Å,
$\gamma=71°14'\pm30'$.
$\alpha=97°30'\pm2°$,
$\beta=108°\pm30'$,
$V=702\pm4$ Å^3;
$Z=2$
and $D_x=1{\cdot}28$ g.cm^{-3}.

Possible space groups are $P1$ or $P\bar{1}$. The value of the β angle is consistent with that obtained by measurement on the optical goniometer.

No further work on these compounds is contemplated at present.

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