THE SYNTHESIS AND X-RAY STRUCTURE OF 3,7-DIIODODIBENZOSUBERONE. SYNTHESIS OF 3,7-DIIODOAMITRIPTYLINE

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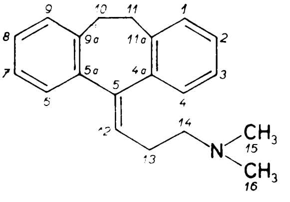
The preparation of iodinated tricyclic antidepressive drug amitriptyline as the substrate for isotopic exchange labelling is described. Direct iodination of 10,11-dihydro-5*H*-dibenzo[*a,d*]-cycloheptene-5-one leads mainly to 3,7-diiododerivative (*III*). Its structure was confirmed by means of single crystal X-ray diffraction analysis: monoclinic, $P2_1/c$, $a = 13{\cdot}315(2)$, $b = 7{\cdot}852(1)$, $c = 13{\cdot}584(2)$ Å, $\beta = 103{\cdot}67(2°)$, $Z = 4$, $R = 0{\cdot}064$ for 2 474 observed independent reflections. Iodinated ketone was transformed to 3,7-diiodo-5-(3-N,N-~~dim~~ethylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (diiodoamitriptyline), by the reaction with dimethylaminopropylmagnesiumchloride and dehydration of the resulting alcohol. The product was isolated as hydrogen oxalate salt.

Among antidepressive drugs, one of the recently most popular compounds is 5-(3-N,N-dimethylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene (*I*) (Amitriptylin Spofa, Laroxyl Roche, Saroten Lundbeck). For pharmacological studies labelled derivative was needed. Because of high achievable specific activity and simplicity of measurement we decided to use iodine ^{125}I as the label. As neither direct nor indirect (thallation) radioiodination methods were succesful, we prepared nonradioactive iodinated derivative by analogy to the preparation of the noniodinated one[1-6] and then tried the isotope exchange labelling. The isotope exchange study will be published elsewhere.



I

EXPERIMENTAL

10,11-Dihydro-3,7-diiodo-5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (*III*)

A three-necked flask equipped with a mechanical stirrer, a reflux condenser and a dropping funnel was charged by 10·5 g (50 mmol) of dibenzosuberone (*II*), 17·7 g (70 mmol) of iodine and 100 ml of acetic acid. After dissolution, the mixture of 4 ml of concentrated nitric acid and 10 ml of sulfuric acid was added followed by about 5 ml of carbon tetrachloride. The reaction mixture was refluxed for 12 hours. The cold reaction mixture was diluted with 500 ml water. The crude solid product was filtered and dissolved in dichloromethane. The dichloromethane solution was washed with 10% solution of sodium sulfite, then with 10% solution of sodium hydrogencarbonate, water and dried. The solvent was evaporated and the product was crystalized from ethanol or an ethanol-isopropanol mixture. Yield of the pure product (m.p. 166—167°C) was 9 g (52%). For $C_{15}H_{10}I_2O$ (459·9) calculated 39·16% C, 2·19% H, 55·11% I; found 39·20% C, 2·22% H, 54·84% I. ^1H NMR (C^2HCl_3, 300 MHz, tetramethylsilane as internal standard): 3·12 s, 4 H (H-10, H-11); 6·97 d, 2 H (H-1, H-9, $J(1, 2) = J(8, 9) = 8, 1$); 7·74 d, 2 H (H-2, H-8, $J(8, 9) = J(2, 1) = 8{\cdot}0$); 8·28 s, 2 H (H-4, H-6). ^{13}C NMR (C^2HCl_3): 34·3 (C-10, C-11); 91·7 (C-3, C-7); 131·3 (C-1, C-9); 139·3 (C-4, C-6); 139·6 (C-4a, C-5a); 141·3 (C-11a, C-9a, C-2, C-8).

X-Ray Analysis

Single crystals were obtained by slow cooling of a hot saturated solution of *III* in acetone/hexane (1 : 4). The density was measured by flotation in aqueous ZnI_2 solution. A crystal fragment of 0·30 × 0·30 × 0·35 mm was mounted on a Hilger and Watts difractometer (MoK_α radiation, $\lambda = 0{\cdot}71073$ Å); 46 precisely centered reflections in the 4—15 Θ-range gave, after least-squares refinement, the following cell parameters: $a = 13{\cdot}315(2)$, $b = 7{\cdot}852(1)$, $c = 13{\cdot}584(2)$ Å, $\beta = 103{\cdot}67(2)°$, $V = 1\,380{\cdot}0(4)$ Å^3, for the $P2_1/c$ space group and $\varrho_x = 2{\cdot}214$ g cm^{-3} for $Z = 4$ in accordance with $\varrho_m = 2{\cdot}19(1)$. Intensities were recorded in the intervals $h \in \langle 0, 18 \rangle$, $k \in \langle 0, 10 \rangle$ and $l \in \langle -18, 18 \rangle$ respectively using the $\Theta - 2\Theta$ scan mode. Two standard reflections monitored after every 30 reflections showed no significant intensity fluctuation. From 3 678 total measured reflections, 2 474 fulfilling the $I > 1{\cdot}96\sigma(I)$ criterion were used in subsequent data treatment. The intensities were corrected for absorption[7] ($\mu = 4{\cdot}45$ mm^{-1}) assuming a spherical sample of 0·16 mm diameter ($2{\cdot}60 < A^* < 2{\cdot}75$). The structure was solved by the heavy-atom method[8]. All hydrogen atoms were found in the difference map. Coordinates, displacement parameters (anisotropic for non-H, isotropic for H-atoms) and scale factors were then refined[9] simultaneously by full matrix least-squares to $R = 0{\cdot}064$, $wR = 0{\cdot}075$. The function minimized was $w = \sum(|F_o| - |F_c|)^2$ where $w = 2{\cdot}20/(\sigma_F^2 + 0{\cdot}0016F^2)$. As a probable consequence of imperfect sphericity of the sample, the final difference map exhibits a number of "ripples" close to both iodine atoms with the largest absolute value of 1·95 e Å^{-3}. Full details of crystal structure determination are given in Table I.

3,7-Diiodo-5-(hydroxy-5-dimethylaminopropyl)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (*IV*)

To the suspension of 230 mg (6·4 mmol) magnesium in 10 ml of dry tetrahydrofuran was added 1·1 g (8·5 mmol) of freshly prepared N,N-dimethylaminopropylchloride and two drops of 1,2-dibromoethane. The reaction mixture was stirred and refluxed until most of magnesium reacted (about 2 hours). To the filtered solution of Grignard reagent cooled to 0°C, a solution of 3,7-diiododibenzosuberone in 60 ml of tetrahydrofuran (2 g, 4·3 mmol) was added with stirring.

The reaction mixture was allowed to warm to room temperature and then refluxed for three hours. The cold mixture was treated with 100 ml 10% solution of ammonium chloride in water and extracted with ether (3 × 50 ml). The combined extracts were dried, the solvents evaporated and the solid obtained was recrystallized from ethanol–ether (1 : 1). Yield 1·6 g (70%), m.p. 221–223°C. For $C_{20}H_{29}I_2NO$ (547·2) calculated 43·89% C, 4·20% H, 2·56% N, 36·41% I; found 43·47% C, 4·16% H, 35·97% I, 2·46% N. Mass spectrum, *m*/*z* (relative intensity, %): 547 (M^+, 2·4), 461 (1·4), 334 (1·8), 257 (0·8), 229 (0·9), 217 (2·2), 207 (2·0), 202 (1·4), 189 (1·7), 87 (17), 58 (100).

3,7-Diiodo-5-(3-dimethylaminopropylidene)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (3,7-diiodoamitriptyline) (*V*)

Hydroxyderivative *IV* 1 g (1·8 mmol) was dissolved in 10 ml of cold 85% sulfuric acid and allowed to stand at 4°C for 2 hours. The mixture was then diluted with water and sodium hydroxide solution was added to a slightly alkaline reaction. After 2 hours of stirring at room temperature a solid material was formed which was extracted with ether. After addition of a solution of

Table I

Crystal data, measurement and refinement details

Formula	$C_{15}H_{10}I_2O$
Molecular weight	459·9
Space group	$P2_1/c$
a, b, c, Å; β, °	13·315(2), 7·852(1), 13·584(2), 103·67(2)
Cell volume, Å^3	1 380·0(4)
Z	4
D_m, D_c; g cm^{-3}	2·19(1), 2·214
Radiation	MoK$_\alpha$, $\lambda = 0·71073$ Å
Absorption correction	Empirical, $\mu = 4·45$ mm^{-1}
$F(000)$	856
Temperature; K	295
Crystal dimensions, mm	0·30 × 0·30 × 0·35
No. of reflections for lattice parameter determination	46 ($4 < \Theta < 15$)
Diffractometer	Hilger and Watts
Scan mode	$\Theta - 2\Theta$
$(\sin \Theta/\lambda)_{max}$, Å^{-1}	0·7
Standard reflections (variation)	2 after every 30 (2·7%)
Interval h, k, l	$\langle 0, 18\rangle, \langle 0, 10\rangle, \langle -18, 18\rangle$
No. of reflections measured	3 678
No. of reflections used ($I > 1·96\sigma(I)$)	2 474
Residual electron density, e Å^{-3}	1·82, −1·95
(Δ/σ_{max}) for non-H atoms	0·139
Function minimized	$\sum w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Weight	$2·20/(\sigma^2(F_0) + 0·0016F^2)$
R, wR	0·064, 0·075

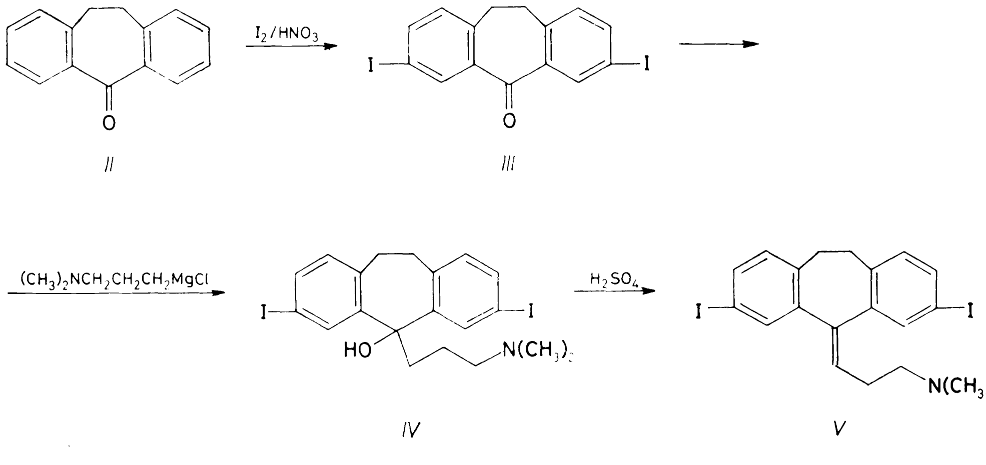
oxalic acid in ether 1·1 g white crystals were formed (88% theory), m.p. 198—201°C (recryst. from ethanol-ether). For $C_{22}H_{23}NO_4I_2$ (619·2) calculated 42·67% C, 3·74% H, 40·98% I, 2·26% N; found 42·42% C, 3·81% H, 40·51% I, 2·09% N. ^{1}H NMR (DMSO-$^2H_6$, 300 MHz, TMS): 0·98 dt, 1 H (H-13); 1·28 t, 2 H (H-14); 2·64 s, 6 H ($N-CH_3$); 3·17 m, 4 H (H-10, H-11); 5·86 t, 1 H (H-12); 6·3 bs, 1 H (NH); 6·8—7·1 d, 2 H (H-1, H-9, $J(1, 2) = J(8, 9) = 8·0$); 7·4 to 7·7 m, 4 H (H-2, H-4, H-6, H-8). ^{13}C NMR (DMSO-$^2H_6$, 300 MHz, TMS): 24·65 (C-23); 30·52 (C-14); 42·26 ($N-CH_3$); 55·78 (C-5); 91·56, 91·60 (C-10, C-11); 117·38 (C-12); 130·87, 132·57 (C-1, C-9); 135·78, 136·23, 136·57, 136·85 (C-2, C-4, C-6, C-8); 138·84, 141·05, 141·38, 142·04 (C-11a, C-4a, C-9a, C-5a).

The reagents used were commercially available and were purified by means of usual methods. The NMR spectra were recorded with Bruker 300 MHz spectrometer. Chemical shifts are in ppm with TMS as an internal standard. The samples for melting point measurement were dried for 4 hours at 40°C in vacuum of oil pump. The parameters of X-ray diffraction analysis are described above.

RESULTS AND DISCUSSION

Synthesis

Direct iodination of dibenzosuberone leads almost exclusively to a symmetrical de iododerivative. Small amount (less than 2%) of another unidentified diiododerivativi and some unreacted dibenzosuberone were present in the iodination mixture. On the basis of ^{1}H a ^{13}C NMR spectra of *III* as the main product it seems likely that the iodine atoms are in the positions 3 and 7. Since the interpretation of the NMR spectra was not unambiguous, the positions of the iodine atom were confirmed by means of X-ray diffraction analysis, which provided further information abou- molecular structure of the compound studied. From the X-ray data some conclu-



SCHEME 1

sions about the structure of another dibenzo[*a*,*d*]cycloheptene-based drugs could be made.

Conditions of the Grignard reaction (Scheme 1) had to be modified because, under the conditions published, some deiodination was observed. Replacement of ether by tetrahydrofuran solvent together with lower temperature eliminated the formation of deiodinated compound even though the conversion of starting diiodoketone *III* was lower.

Dehydration of *IV* by means of sufuric acid was smooth and proceeded without problems. The free base did not crystalize well but the isolation and purification as hydrogen oxalate salt was convenient.

X-*Ray Structure*

Coordinates of non-H atoms are presented in Table II and bond lengths and angles in Table III. Fig. 1 depicts a perspective view of the molecule together with atom numbering; crystal packing follows from Fig. 2.*

The structure of *III* consists of isolated molecules packed at van der Waals or longer distances with the exception of one short contact of 3·195(8) Å between I1 and O1′ ($1 - x, y - 1/2, 1/2 - z$) and of intermolecular C···C distances in the range of 3·5–3·6 Å between C1, C2 and C3 and the same atoms related through translation along the *a*-axis. None of these interactions affect the molecular geometry, however. All bond lengths and angles appear to be normal, lying within 2

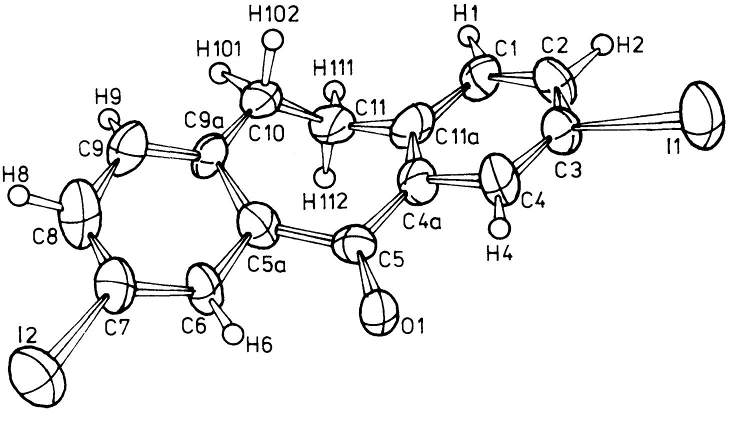


FIG. 1

Perspective view of the molecule with atom numbering

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* Tables of hydrogen atoms coordinates, anisotropic displacement parameters, observed and calculated structure factors and further experimental details have been deposited by the autors and are available on request.

esd's of the values tabulated[10] as the mean distances for a very large number of structures. The arrangement of the fused ring system is also typical for this class of compounds[11], being composed of two almost exactly planar aromatic ring and a central seven membered ring which adopts a boat conformation (Table IV). As

TABLE II

Atomic coordinates (. 10^4) with estimated standard deviations in parentheses. $U_{eq} = 1/3 \sum\sum a_i \, . \, a_j a_i^* a_j^* U_{i,j}$

Atom	x/a	y/b	z/c	$U_{eq}(.10^3)$, $Å^2$
I1	6034·8(4)	1292(1)	3496(1)	48·9(2)
I2	−1874(1)	3805(1)	1289(1)	56·0(2)
O1	2249(5)	4461(11)	2425(5)	51(2)
C1	4345(7)	3271(15)	5614(8)	47(3)
C2	5108(7)	2622(15)	5176(8)	50(3)
C3	4899(6)	2346(12)	4156(7)	39(3)
C4	3935(6)	2772(12)	3539(7)	37(3)
C4a	3173(6)	3435(11)	3985(7)	36(2)
C5	2184(6)	3929(11)	3241(6)	33(2)
C5a	1132(6)	3647(11)	3436(7)	36(2)
C6	323(6)	3836(12)	2576(7)	37(2)
C7	−671(7)	3503(11)	2586(8)	39(3)
C8	−921(8)	2964(15)	3476(9)	54(4)
C9	−131(9)	2859(16)	4325(10)	54(4)
C9a	910(7)	3225(12)	4353(7)	37(3)
C10	1656(8)	3103(16)	5358(7)	49(3)
C11	2558(8)	4316(15)	5519(7)	42(3)
C11a	3365(7)	3694(12)	5017(6)	37(2)

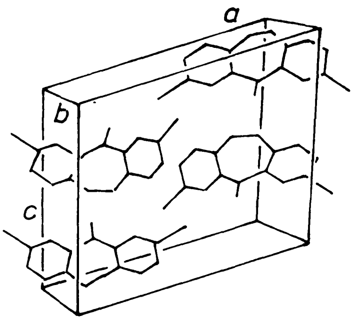

FIG. 2
Unit cell content

usual[11], the particular mode of distortion is not influenced by substituents at the aromatic rings but, instead, is largely determined by the keto group. Comparison of ten closely related structures as retrieved from a database[12] shows that two of them bearing a keto group at C5 are considerably more flattened and their central rings are more puckered in comparison with the remaining eight structures. This is best

TABLE III

Bond lengths (Å) and angles (°) with estimated standard deviations in parentheses

Atoms	Bond lengths	Atoms	Bond angles
I1—C3	2·102(9)		
I2—C7	2·10(1)		
O1—C5	1·21(1)		
C1—C2	1·39(1)	C2—C1—C11a	120·9(8)
C1—C11a	1·40(1)		
C2—C3	1·36(1)	C1—C2—C3	119·9(8)
C3—C4	1·40(1)	I1—C3—C2	120·1(6)
		I1—C3—C4	119·3(6)
		C2—C3—C4	120·6(8)
C4—C4a	1·40(1)	C3—C4—C4a	119·1(7)
C4a—C5	1·51(1)	C4—C4a—C5	114·4(7)
C4a—C11a	1·38(1)	C4—C4a—C11a	121·0(7)
		C5—C4a—C11a	124·4(7)
C5—C5a	1·50(1)	O1—C5—C4a	117·6(7)
		O1—C5—C5a	119·0(7)
		C4a—C5—C5a	123·1(6)
C5a—C6	1·40(1)	C5—C5a—C6	113·8(7)
C5a—C9a	1·39(1)	C5—C5a—C9a	126·8(7)
		C6—C5a—C9a	119·4(7)
C6—C7	1·35(1)	C5a—C6—C7	122·3(8)
C7—C8	1·39(2)	I2—C7—C6	121·7(6)
		I2—C7—C8	118·2(7)
		C6—C7—C8	120·2(9)
C8—C9	1·37(2)	C7—C8—C9	117·1(9)
C9—C9a	1·41(2)	C8—C9—C9a	125(1)
C9a—C10	1·49(1)	C5a—C9a—C9	116·2(8)
		C5a—C9a—C10	127·0(8)
		C9—C9a—C10	116·8(9)
C10—C11	1·51(2)	C9a—C10—C11	115·3(8)
C11—C11a	1·48(1)	C10—C11—C11a	111·3(8)
		C1—C11a—C4a	118·4(8)
		C1—C11a—C11	119·2(7)
		C4a—C11a—C11	122·3(7)

TABLE IV

Endocyclic torsion angless (in °) of the seven-membered ring (esd = 1°)

C11a—C4a—C5—C5a	−42	C9a—C10—C11—C11a	−79
C4a—C5—C5a—C9a	13	C10—C11—C11a—C4a	61
C5—C5a—C9a—C10	6	C11—C11a—C4a—C5	7
C5a—C9a—C10—C11	32		

demonstrated by the dihedral ange of the mean aromatic planes which is 140 − 145°C for the ketones (142·4(5)° for the title compound) and 122(4)° for the other molecules in question. The endocyclic torsion angles and all other geometric parameters behave similarly. Molecular models clearly show that sp^2 hybridization at C5, together with intramolecular contacts of O1 to H4 and H6, force the molecule to adopt this conformation. The important consequence is that the given arrangement leaves the keto group sterically little hindered by the iodine atoms and thus susceptible to chemical attack.

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