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Spectral studies on 1-substituted-3-(1-oxo-3-hydroxy-2-cyclohex-ene-2-yl)-4-oxo-4,5,6,7-tetrahydroindoles – an unexpected mass spectral fragmentation†

K NAGARAJAN[a]*, S J SHENOY[b], D R MÜLLER, W J RICHTER[c]*, L KOZERSKI[d]* and V PATTABHI[e]*

[a]Hindustan CIBA-GEIGY Research Centre, Bombay 400063, India. Present address: 'b'
[b]Searle R & D Centre, 25, MIDC Land, Thane-Belapur Road, Thane 400601, India
[c]Research Services Physics, CIBA-GEIGY AG, CH 4002, Basel, Switzerland
[d]Institute of Organic Chemistry, Polish Academy of Sciences, 00–961, Warszawa, Poland
[e]Department of Crystallography and Biophysics, University of Madras, Guindy, Madras 600025, India

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Abstract. IR, UV, NMR and mass spectral data for the title compounds are discussed. The EI mass spectra of 4 and the analogues 5–9 and 11–15 display major $(M-C_2H_3O_2)^+$ fragment ions that correspond to the loss of a structural element not present in the parent molecules. These $(M-59)^+$ ions have no equivalent in the model compound 1-phenyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole (27). The unusual fragmentation is thought to be initiated by α-cleavage within the alicyclic 1,3-diketone moiety (ring C) under concomitant formation of a benzylic radical site. Reclosure of this 'open' intermediate to a lactone-type molecular ion provides two O-atoms in the proximity required for an ejection of a CH_2COOH radical as the neutral species in question. The ^1H NMR spectra of 4 and its methyl ether 16 reveal restricted rotation of substituents at positions 1 and 3 of the pyrrole ring, the eight methylene protons becoming fully anisochronous at 500 MHz. X-ray studies on single crystals of 8 confirmed its structure.

Keywords. CGI 14600; hypoglycemic; ^{13}C and ^1H NMR spectra; X-ray crystal structure.

1. Introduction

In earlier papers (Nagarajan *et al* 1988, 1989), we noted the potent oral hypoglycemic properties of some of the title compounds, especially the 1-phenyl-2,6,6-trimethyl derivative 4 (CGI 14600) which were obtained by the condensation of polyketones 1–3 and primary amines. We observed that the condensation products arose by elimination of two moles of water per one mole of each of the two reactants and most spectral data, barring a single fragment ion signal in the mass spectra, were in consonance with general structures depicted for 4–15. We discuss these in detail in this paper.

The product of condensation of 1 with aniline is probably 4 formed by a Knorr

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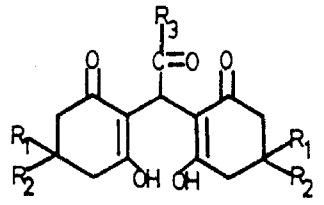
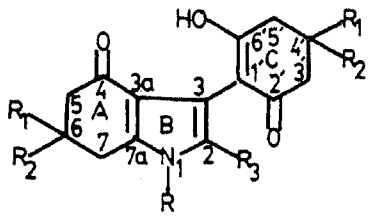
*For correspondence



1–3



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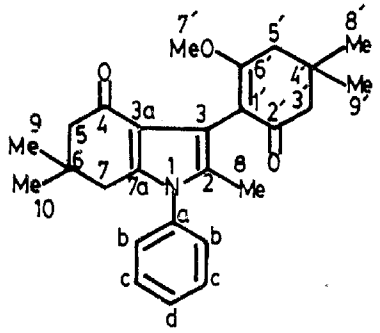

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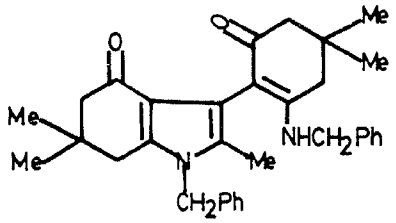

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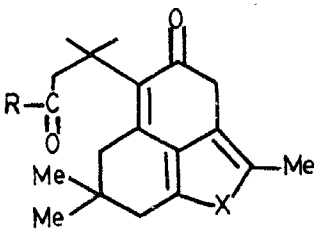
1 $R_1 = R_2 = R_3 = Me$
2 $R_1 = R_2 = Me$; $R_3 = H$
3 $R_3 = R_2 = H$; $R_3 = Me$
4 $R = Ph$; $R_1 = R_2 = R_3 = Me$
5 $R = 3\text{-}ClC_6H_4$; $R_1 = R_2 = R_3 = Me$
6 $R = 4\text{-}FC_6H_4$; $R_1 = R_2 = R_3 = Me$
7 $R = 4\text{-}MeC_6H_4$; $R_1 = R_2 = R_3 = Me$
8 $R = C_6H_5CH_2$; $R_1 = R_2 = R_3 = Me$
9 $R = 3,4\text{-}diOMe\text{-}C_6H_3CH_2$; $R_1 = R_3 = R_3 = Me$
10 $R = PhCH_2CH_2$; $R_1 = R_2 = R_3 = Me$
11 $R = Ph(CH_2)_4$; $R_1 = R_2 = R_3 = Me$
12 $R = Ph$; $R_1 = R_2 = Me$; $R_3 = H$
13 $R = Ph$; $R_1 = R_2 = H$; $R_3 = Me$
14 $R = Me_2CH$; $R_1 = R_2 = R_3 = Me$
15 $R = H$; $R_1 = R_2 = R_3 = Me$

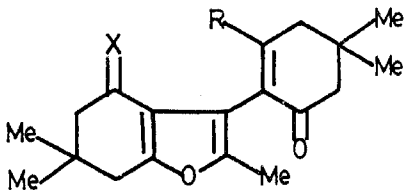
reaction or the isomeric tricyclic compound 18 arising by hydrolytic cleavage of the 1,3-dicarbonyl system in 4 followed by cyclization at the C=O group at C–4 ring A. Alternatively, the 1,4-dicarbonyl system in 1 can dehydrate to the furan 20 and the latter be transformed to the imine 19 or the enamine 21, both being isomeric with 4. A further possibility for CGI 14600 is 23, the anilide of 22, the formation of which from 20 would be analogous to that of 18 from 4. Some of the other structural possibilities isomeric with 4 are : the perhydroacridine 24 from the condensation of the 1,5-dicarbonyl system in 1 with aniline; and the imine 26 arising from the perhydroxanthene 25, the product of cyclodehydration of 1. We postulate that structure 4 explains the following available data best. The same applies to analogues 5–15 made from polyketones 1–3 and primary amines as well as to others reported earlier (Nagarajan *et al* 1989). X-ray structure study of single crystals of 8 confirmed its structure (Pattabhi 1989).

2. Chemical properties

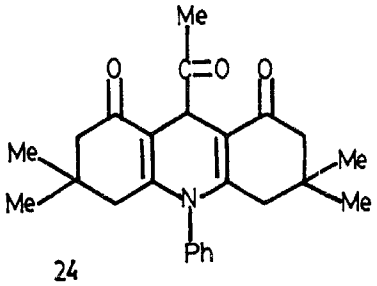
These products gave a positive ferric reaction; they were soluble in alkali and were recovered unchanged on acidification. Treatment of 4 with diazomethane gave the



18 X= NPh; R= OH
22 X= O; R= OH
23 X= O; R= NHPh



19 X= PhN; R= OH
20 X= O; R= OH
21 X= O; R= NHPh



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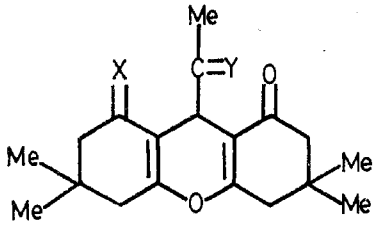
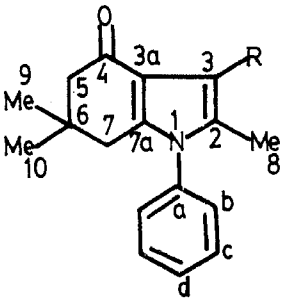
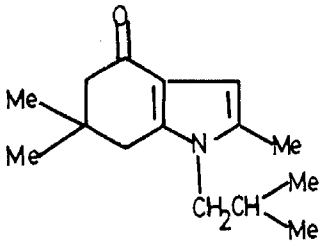


25 X= Y= O
26 X= PhN; Y= O or vice versa



27 R= H
28 R= CHO



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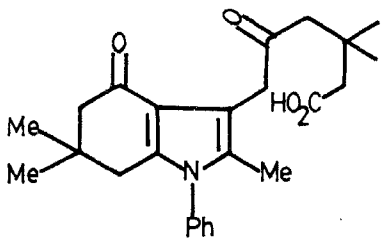

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O-methyl derivative 16. The sodium salt of 4 was alkylated with piperidino and dimethylaminoethyl chlorides to give the O-alkyl derivatives (Nagarajan *et al* 1989). Treatment of 8 with benzylamine yielded the enamine 17. These data eliminated from consideration all structures except 4 and 19 with 18 left on the border line.

Treatment of 4 with hot aqueous sodium hydroxide in dioxane solution for several hours left it unchanged with no detectable 1,3-diketone cleavage. Action of 3N HCL on 4 in dioxane under reflux conditions for 24 h gave rise in very low yield to the aldehyde 28, $C_{18}H_{19}NO_2$, m.p. 207–210°C, forming a *bis*-2,4-dinitrophenylhydrazone derivative, m.p. 300°; $C_{30}H_{27}N_9O_8$ (M^+-1 at 640); but the keto acid 30, $C_{25}H_{31}NO_4$ (M^+-1 at 408) was also formed in trace amounts, providing some support to structure 4.

3. Spectral properties

3.1 *UV spectra*

The UV spectra (table 1) of 4, 8 and 11–14 had a strong resemblance to that of 27 (Nagarajan *et al* 1985), although except in the case of 12, the longer wave-length maximum around 285–290 nm was seen only as a shoulder.

Table 1. UV, IR and NMR data for compounds 4–15 and related derivatives.

Compound No.	UV(MeOH)[a] λmax(log ε)	IR(Nujol)[b] $r(cm^{-1})$	^1H NMR [c](δ in ppm)
1		2550–2700(*br*), 1710, 1600, 1570	1·07(6Me), 2·02(COMe), 2·27(4CH_2), 4·47(CH), 10·73(OH)
4	257(4·34), 290(*sh*)(4·15)	3440, 1645, 1620, 1590, (CH_2Cl_2) 2550–2700(*br*), 1650, 1585, 1570	1·08(2Me), 1·15(Me), 1·18(Me), 1·80(=CMe), 2·33(CH_2), 2·38(CH_2), 2·43(2CH_2), 5·63(OH), 7·03–7·27(2ArH), 7·27–7·63(3ArH).
			^{13}CNMR[d]: 11·7(8); 27·8(two C), 28·9, 29·3, (9, 10, 8′9′); 31·3(4′); 35·5(6); 36·9(7); 43·1, 51·1(3′, 5′), 52·2(5); 107·1, 110·7, 117·8(3, 3a, 1′); 127·6(b), 128·7(d); 129·5(c); 131·4(2), 136·9(7a), 143·7(a); 171·7(6′); 195·0(2′); 196·4(4)
5		3320, 2550–2700(*br*), 1630, 1600, 1580	
6		2550–2700(*br*), 1650, 1590, 1580	
8	259(4·24), 290(*sh*)(4·10)	3140, 2580–2700(*br*), 1630, 1600, 1560	1·07(2Me), 1·13(Me), 1·18(Me), 1·93(=CMe), 2·30(CH_2), 2·40(2CH_2), 2·50(CH_2), 4·97(PhCH_2), 6·60(OH), 6·8–7·0(2ArH), 7·1–7·4(3ArH)
9		3120(*sh*), 2600–2700(*br*), 1625, 1600, 1565	1·08(2Me), 1·15(Me), 1·20(Me), 1·92(=CMe), 2·33(CH_2), 2·43(2CH_2), 2·55(CH_2), 3·80(OMe), 3·89(OMe), 4·95(ArCH_2), 6·33(*dd*, ArH), 6·37(*d*, ArH), 6·65(OH), 6·72(*d*, ArH)
10			1·03(2Me), 1·15(Me), 1·23(Me), 1·92(=C–Me), 2·27(CH_2), 2·37(2CH_2), 2·43(CH_2), 2·45(*t*, PhCH_2), 4·05(*t*, NCH_2), 6·9–7·5(*m*, ArH + OH)
11	258(4·23), 290(*sh*)(3·91)	3120(*sh*), 2700, 2620, 1628, 1600, 1570	1·08(2Me), 1·12(Me), 1·17(Me), 1·67(*qui*, CH_2–CH_2–CH_2–CH_2), 1·93(=CMe), 2·30(CH_2), 2·40(2CH_2), 2·50(CH_2), 2·63(*t*, PhCH_2), 3·70(*t*, N–CH_2), 4·90(OH), 7·12(5ArH)
12	256(4·29), 284(4·23)	3100, 2550–2700(*br*), 1650, 1610, 1590	0·8(2Me), 1·10(2Me), 2·17(CH_2), 2·02(2-CH_2), 2·33(2-CH_2), 6·33(OH), 7·13(2C–H), 7·20(5ArH)

(*Continued*)

Table 1. (*Continued*)

Compound No.	UV(MeOH)[a] λmax(log ε)	IR(Nujol)[b] r(cm^{-1})	^{1}H NMR [c](δ in ppm)
13	255(4·35), 288(*sh*), (3·98)	3200(*sh*), 2580–2700(*br*), 1625, 1610, 1585	1·75(= CMe), 1·97(*q*, $2CH_2$), 2·30–2·80(*m*, $4CH_2$), 3·42(OH), 7·20–7·70 (*m*, 5ArH)
14	258(4·22), 285(*sh*) (4·05)	3100, 2550–2700(*br*), 1630, 1600, 1565	1·15(3Me), 1·20(1Me), 1·50($CH\underline{Me}_2$), 2·02(= CMe), 2·30(CH_2), 2·73(CH_2), 4·43($C\underline{H}$ Me_2), 7·5(*br*), = − OH).
15			1·17(3Me), 1·22(1Me), 1·97(= CMe), 2·17(CH_2), 2·37($2CH_2$), 2·67(CH_2), 9·5(*br*, = − OH, NH).
16		1660, 1640, 1590	1·02(2Me), 1·13(Me), 1·23(Me), 1·77(= CMe), 2·27(CH_2), 2·33($2CH_2$), 2·45(CH_2), 3·6(OMe), 7·0–7·2(*m*, 2ArH), 7·25–7·50(*m*, 3ArH). $^{13}\underline{C}$ NMR[c]: 11·2(8); 28·0, 28·4(two C), 28·99(9, 10, 8′, 9′); 31·6(4′),35·1(6); 36·8, 52·5(5, 7); 40·2, 50·6(3′5′); 55·9(7′); 109·8, 112·4, 117·7(3, 3a, 1′) 127·6(b); 128·1(d); 129·1(c); 129·5, 137·2(2, 7a); 142·0(a); 171·1(6′); 192·8(2′); 196·9(4)
20		2580–2720(*br*), 1670, 1590	1·17(4Me), 2·10(= CMe), 2·33(CH_2), 2·40(CH_2), 2·70($2CH_2$), 5·10(OH)
25		1710, 1650, 1610	1·10(2Me), 1·13(2Me), 2·30($2CH_2$), 2·48($2CH_2$), 2·57(COMe), 4·55(*br s*, CH)
27	248(4·17), 286(3·89)	1645, 1590(*w*)	1·08(2Me), 2·03(= CMe), 2·32(CH_2), 2·35(CH_2), 6·30 (unresolved *q*, = CH), 7·0–7·30(*m*, 2ArH), 7·35–7·55(*m*, 3ArH). $^{13}\underline{C}$ NMR[c]:12·5(8); 28·5(9, 10); 35·5(6); 36·7(7); 52·0(5); 103·2(3); 118·9(3a); 127·5(b), 128·5(d), 129·4(c), 131·4(2), 137·0(7a), 143·1(a), 193·5(4)
28		1680, 1665, 1610	1·07(2Me), 2·30($2CH_2$), 2·33(= CMe), 7·0–7·3(*m*, 2ArH), 7·40–7·70(*m*, 3ArH), 10·57(CHO).
29			0·93(*d*, $CH\underline{Me}_2$), 1·17(2Me), 2·00, (*m*, $C\underline{H}Me_2$), 2·23(= C–Me), 2·30(CH_2), 2·57($\underline{C}H_2$), 3·53(*d*, CH_2, $CHMe_2$), 6·13(C–3H)

[a] Spectra run on UVIKON 810 spectrophotometer, *sh* = shoulder

[b] Spectra run on Perkin Elmer 681 Infrared spectrophotometer, *br* = broad; *w* = weak

[c] Spectra run in $CDCl_3$ on Varian EM 360 using TMS as internal reference; signals are singlets unless otherwise stated; *d* = doublet; *t* = triplet; *q* = quartet; *qui* = quintet; *m* = multiplet; *br* = broad

[d] Measurement on Bruker FT 500 at 125 MHz of a $CDCl_3$ solution using TMS as internal reference; the numbering of 4 is arbitary and the assignments are tentative; figures in parentheses refer to the carbon atoms as numbered on the structural formula. Degree of protonation of C atoms was ascertained by DEPT experiments

[e] Measurement on Varian XL 200 at 50 MHz of a $CDCl_3$ solution; other details are the same as in 'd' above

3.2 *IR spectra*

IR spectra (table 1) exhibited generally weak absorptions at 2500–2700 cm^{-1} characteristic of enolised 1,3-diketone system; occasionally weak absorptions were also seen around 3300–3400 cm^{-1} (intermolecularly bounded OH), and 3100–3200 cm^{-1}

(intramolecularly bonded OH); C=C and C=O stretching bands were present for compounds 4–14 between 1590 and 1650 cm^{-1}. For the O-methyl derivative 16, OH absorption was lacking and C=O and C=C stretching bands were seen at 1660, 1640 and 1590 cm^{-1}. The frequencies for these bands in the dimethylaminoethyl ether of 4 were 1660, 1640 and 1610 cm^{-1} while for the piperidinoethyl derivative of 4, these were 1645 and 1620 cm^{-1}. In structure 19, C=O absorptions could arise from the dimedone moiety; however, these should be at frequencies lower than 1600 cm^{-1} due to extensive enolisation (cf 1); perhydroacridine 24 or perhydroxanthene 26 (X = PhN; Y = O) having a free acetyl group should show a C=O stretching band at 1710 cm^{-1} (cf 25). Structure 18 with a pendant acetic acid unit should have the carboxyl band at around 1730 cm^{-1}; even assuming that this had moved to lower frequencies due to heavy hydrogen bonding, the O-methyl derivative should exhibit a normal ester C=O band which was missing. These observations left in the field only 4 as a structural possibility for the product from aniline and 1.

3.3 *Mass spectra*

Electron impact (EI) mass spectral data for compounds 4–9 and 11–15 are reported in table 2 and for the remaining compounds, in table 3. In the EI spectra of the former series, molecular ions M^+ are quite pronounced (> 65% relative intensity except for 5; base peak for 9, 12, and 13). Major fragmentation paths are suggested in scheme 1 on the basis of MS/MS experiments in which mass selected ions of 4 and 4–d_8 (obtained by H/D exchange of the 4 activated $-CH_2$ groups)

Table 2. Mass spectral data[a] for compounds 4–15.

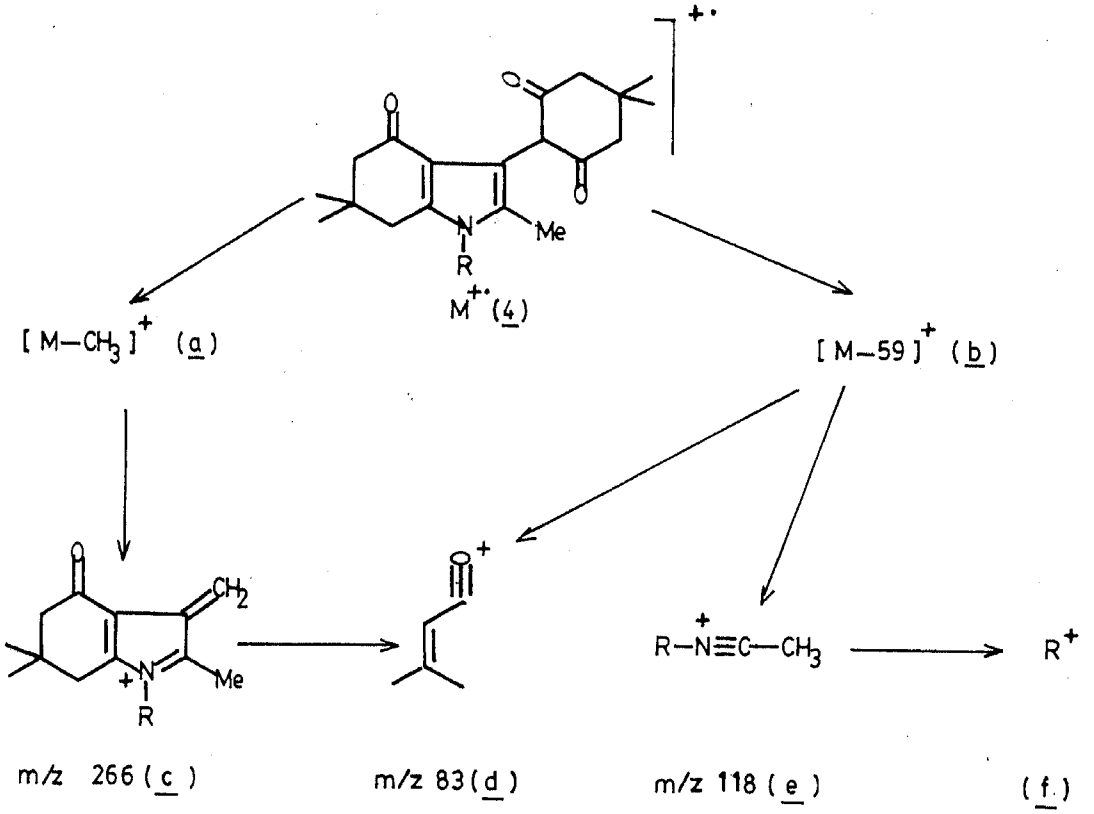
Compound	M^+	a	b	c	d	e	f	Others
4	391(67)	376(100)	332(53)	266(25)	83(11)	118(11)	77(23)	320(10) , 169(14)
5	425(38)	410(59)	366(53)	300(20)	83(27)	152(11)	111(14)	78(100)
6	409(65)	390(100)	350(85)	284(34)	83(35)	136(24)	95(28)	
7	405(75)	390(100)	346(84)	280(28)	83(15)	132(12)	91(25)	77(5)
8	405(90)	390(100)	346(90)	280(20)	83(5)	132(2)	91(95)	314(4), 160(15)
9	465(100)	450(72)	406(65)	340(2)	83(12)	(0)	151(95)	160(1), 137((12), 107(21)
11	447(80)	432(100)	388(60)	322(15)	83(11)	174(7)	—	356(10), 328(10), 318(11), 317(12), 91(55)
12	377(100)	362(74)	318(51)	252(15)	83(10)	104(4)	77(10)	321(30), 180(19), 167(18).
13	335(100)	—	276(100)	—	—	118(27)	77(21)	318(27), 292(22), 264(23), 238(75), 223(20), 222(21), 194(38), 180(28).
14	357(57)	342(95)	298(85)	232(28)	83(12)	—	—	356(58), 341(100), 297(89), 231(29).
15	315(100)	300(98)	256(57)	190(15)	83(4)	—	—	314(77), 299(87), 298(83), 255(57)

[a] EI spectral data obtained using Shimadzu QP 1000 GC-MS instrument at an ion source temperature of 200° and ionising energy of 70 eV; figures in parentheses represent relative intensities (%).

Table 3. Mass spectral data for miscellaneous compounds[a].

1	334(5), 316(52), 301(38), 291(92), 83(100)
16	405(37), 390(100), 374(67), 334(11), 118(21), 83(21), 77(30)
20	316(82), 301(100), 274(18), 260(14), 257(14), 233(10), 232(16), 218(52), 217(26), 83(50)
25	316(10), 301(11), 274(49), 273(100), 217(42), 161(29), 133(18), 105(10), 43(32)
27	253(63), 238(4), 197(91), 169(100), 168(77), 154(14), 118(42), 77(61)
28	281(50), 279(20), 266(5), 253(15), 250(10), 225(2), 198(19), 197(91), 169(100), 154(14), 118(41), 72(82)
29	233(100), 232(99), 218(9), 177(53), 176(49), 162(21), 161(22), 149(34), 148(34), 121(60), 120(51)
30	409(10), 266(100), 210(22), 118(15), 117(14), 83(4), 77(24)

[a] Conditions same as those reported in footnote to table 2



Scheme 1.

were analysed using a Finnigan TSQ 70 triple stage quadrupole mass spectrometer. The following ions appear to be characteristic for the entire series:

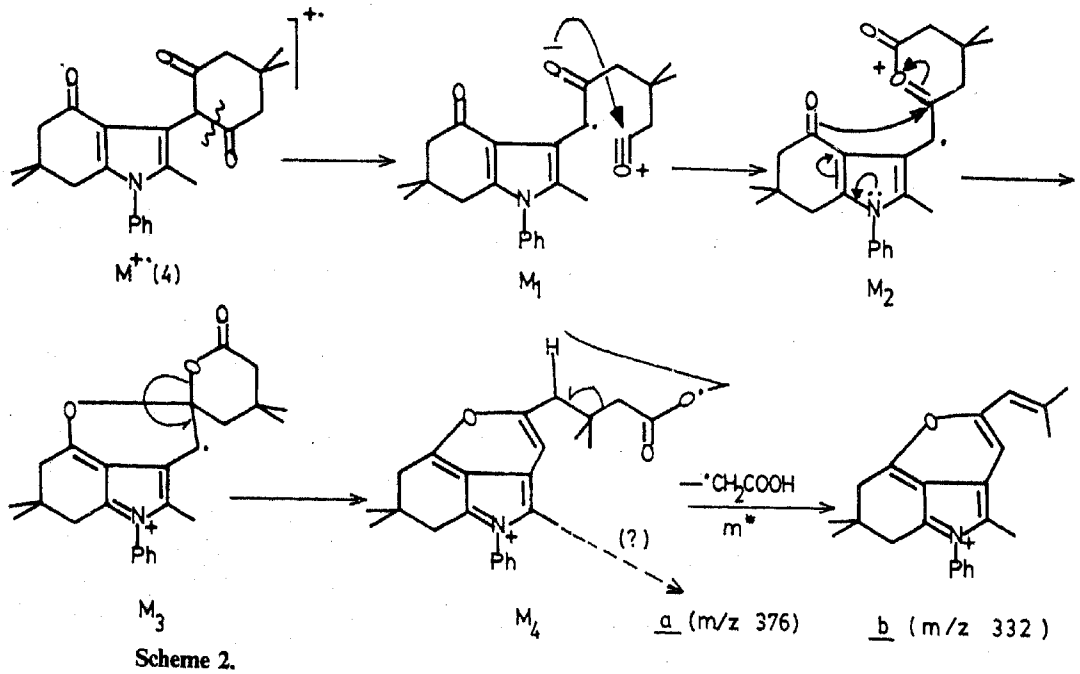
(i) $(M-15)^+$ ions a due to loss of methyl radical, most likely from ring C (base peak for 4, 6–8 and 11, about relative intensity 95% for 14 and 15, 70% for 9 and 12 and 59% for 5).

(ii) $(M-59)^+$ ions b, which are especially prominent within the series (50–100% relative intensity) and in the furan analogue 20, requiring a more detailed discussion (see below).

(iii) $(M-125)^+$ ions c corresponding to (overall) loss of $C_7H_9O_2$ from ring C (relative intensity 15–35% for 4–8, 11–12 and 14–15, only 2% for 9). In 13, a corresponding $(M-97)^+$ species is seen instead.

(iv) Ions d at *m/z* 83, corresponding to $(CH_3)_2C{=}CH{-}C{\equiv}O^+$ (relative intensity 5–50%) and probably arising from the dimedone moiety of ring A (missing in 13, 25, 27 and 28, yet present in 20 and 30).
(v) Ions e of low to moderate intensity, corresponding to $R_3C{\equiv}N^+R$ for R = aryl; these ions are characteristic of 1-aryl-4-oxotetrahydroindoles (Ramadas *et al* 1978; Dogher *et al* 1982) such as 27, 28 and 30.
(vi) Ions of f representing the residue R at position 1, with the expected moderate intensity (10–28%) for aryl substituents and high intensity (91–100%) for benzyl homologues; for 11 bearing a $Ph(CH_2)_4$ substituent, a $C_7H_7^+$ ion is observed instead of R^+.

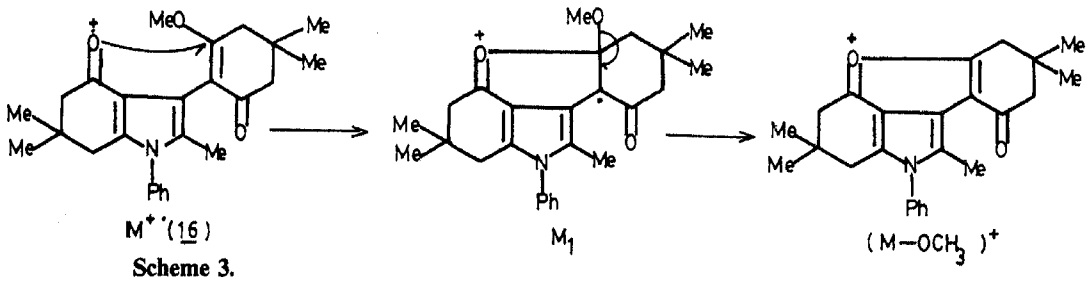
$(M-56)^+$ ions due to retro Diels-Alder fragmentation (loss of $(CH_3)_2C{=}CH_2$– from ring A) were reported previously to prevail in simple 6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindoles. Their notable absence in most compounds of this study may result from the ease of fragmentation of ring C (see below). Appreciable losses of 56 daltons from M^+ are observed only in 12 (*m/z* 321) and the ketobenzofuran 20 (*m/z* 204). As a secondary mode of fragmentation following the facile loss of the acetyl group (even-electron xanthylium ion *m/z* 273), such loss is observed for the perhydroxanthene 25 (*m/z* 217), and also in the enol ether 16 following primary loss of CH_3. Except for the $(M-59)^+$ ion b, the above fragment ions correspond to structural elements already present in the parent molecules. $(M-59)^+$ ions have not been encountered in the earlier studies of simple analogues and the model compound 1-phenyl-2,6,6-trimethyl-4-oxo-4,5,6,7-tetrahydroindole (27). Accurate mass measurements on 4 indicated a $C_{23}H_{26}NO$ composition of b (332·2016 measured mass, 332·2015 calculated mass). Together with a metastable-peak signal for the transition $M^+ \rightarrow b$, this suggests the loss of a $C_2H_3O_2$ moiety (e.g. a CH_2COOH radical) from M^+ as a *single* neutral species. In view of the molecular structure of 4 lacking a pertinent structural element, such a loss is entirely unexpected and would rather suggest a structure such as 18 resulting from 1 on condensation with aniline. This latter structure, however, is ruled out on the basis of the IR spectra of 4 and its O-methyl derivative 16.



Scheme 2.

One of the conceivable pathways for the formation of $(M-CH_2COOH)^+$ ions from 4 is shown in scheme 2. In an initial step, α- (and simultaneously benzylic) cleavage of ring C in a non-enolic M^+ ion is assumed to produce an 'open' intermediate (M_1), which should lend itself to recyclization to a lactone-like isomer M_2. Nucleophilic attack by the carbonyl function of ring A at the lactonic δ-carbon atom could subsequently initiate further rearrangment via spirocyclic intermediate (M_3) and a ring-opened species (M_4), from which eventual loss of CH_2COOH appears plausible after favourable 6-centre H-transfer. The resulting structure of b is highly stabilized by extensive conjugation. As an alternative to the loss of CH_2COOH, a CH_3 radical from ring C may be lost in the formation of ion a via the same intermediate.

In analogy to the series 4–9 and 11–15, compound 16 (enolic methyl ether of 4) shows a pronounced loss of a methyl group (*m/z* 390, base peak), from $M^{+\cdot}$ upon EI. Further decomposition of *m/z* 390 proceeds via secondary retro Diels-Alder elimination of $(CH_3)_2C{=}CH_2$ (*m/z* 334). In addition to fragment d (*m/z* 83), ion e (*m/z*118) typical of the 1-phenyl-2-methyl-4-oxotetrahydroindoles is also present in the spectrum. As expected, a $(M-59)^+$ fragment (or an equivalent thereof) is not produced. However, a characteristic fragment is formed by the loss of the enolic CH_3O group (*m/z* 374, relative intensity 67%) from $M^{+\cdot}$, possibly via M_1 (scheme 3).



Scheme 3.

3.4 *NMR spectra*

3.4a *Proton NMR spectra*: The 60 MHz ^1H NMR spectrum (see table 1)' of compound 4 was characterized by the following resonances: a singlet at δ 1·08 ppm attributed to the *gem*-dimethyl group in ring A, by comparison with the spectra of 27 and 28 and 2 singlets at δ 1·15 and 1·18 ppm for the two methyl groups in ring C. The other assignments are as follows: δ 1·80 (*s*, C–2 Me); 2·33 (*s*, C–5 H_2), 2·38 (*s*, C–7 H_2) and 2·43 ppm (*s*, C–3'H_2, C–5'H_2). The protons of the phenyl groups were seen in two clusters, a multiplet of 2 protons at 7·03–7·27 ppm (ortho) and another for 3 protons at 7·27–7·63 ppm (meta and para). The enolic proton had variable chemical shift and in this experiment was seen at 5·63 ppm and identified by D_2O exchange.

Comparison of the chemical shifts of C–2 methyl (1·80) and C–7 methylene (2·38) protons in 4 with those of similar protons in 14 (2·02, 2·73 respectively) shows the former to be shielded. This would require the phenyl ring in 4 to be twisted out of the plane of the pyrrole ring (B). The shielding is experienced even by the geminal Me protons at C–6 (Δδ 0·07 ppm). A similar shielding influence is apparent in the NMR spectrum of 27 compared to that of 29.

A consequence of the orthogonality of the phenyl and pyrrole rings is the shielding effect on the ortho protons of the former with respect to the meta and para protons. Otherwise the former would have been expected to be more deshielded than the latter.

Comparison of the chemical shift of C–2 Me protons in 4 (1·80 ppm) with that of

the same protons in 27 (2·03 ppm) again shows a shielding of the former. This would mean that ring C is also twisted out of the plane of pyrrole (ring B) and that the methyl group is in the shielding zone of the anisotropic effect of the enol double bond. The same upfield shifts are seen for the C–2 Me protons in 14 (2·02 ppm) and 15 (1·97 ppm) compared to that in 29 (2·23 ppm).

The spectra of 8–13 were very similar to that of 4 but for the following observations: the Me group C–2 in 8–11 and 13 was slightly less shielded compared to 4; the spectrum of 12 lacked this Me singlet while that of 13 did not show the signals for Me groups in rings A and C.

The 60 MHz ^{1}H NMR spectra of the methyl ether 16 resembled closely that of 4 except that the signal due to the OH in 4 was replaced by a 3-proton singlet at 3·60 ppm. The chemical shift in particular of C–2 Me protons (1·77) requires postulation of shielding influence from both the phenyl ring and the enol ether double bond of ring C. It is likely that hydrogen bonding between C–2′ OH and C–4 ketone in 4 may be accommodated by a partial twisting of ring C out of the plane of the pyrrole ring. In 16, this bonding is not possible and yet the shielding phenomenon persists. Hence this is to be attributed to steric repulsion of the oxygen function in ring C by C–4 carbonyl and C–2 Me groups.

The nonequivalence of the two Me groups at C–4′ in 4–12, 14 and 15 may be a consequence of the conformation of ring C, but this was not reflected in the resonance of protons at C–3′ and C–5′ at 60 MHz.

In the 200 MHz ^{1}H NMR spectrum of 4 in $CDCl_3$, the signals due to the Me groups in ring A and C were seen as 4 separate singlets at 1·05, 1·08, 1·16 and 1·22 ppm. The four sets of CH_2 protons gave rise to 13 signals between 2·25 and 2·60 ppm. Allowing for some accidental overlaps, these can be visualised as sixteen signals (4 AB quartets) implying that the eight protons were anisochronous. The ortho protons of the phenyl ring became a hump (width at half height 17 Hz) while the other protons were a resolved multiplet. The OH signal was a sharp singlet at δ 7·87 ppm.

The 500 MHz ^{1}H NMR spectrum of 4 in $CDCl_3$ exhibited, apart from five methyl singlets, fourteen lines for the eight alicyclic protons. Correct assignments could be made using knowledge gained from a study of the spectrum in hexadeutero benzene (see below). Data for the $CDCl_3$ spectrum are presented in table 4.

It was particularly interesting to note that the ortho phenyl protons gave a very broad signal (width at half height 28 Hz). Thus compared to 60 MHz, rotation of the phenyl ring was slower at 200 and 500 Hz.

Considerable sharpening occurred of this signal in the 500 MHz ^{1}H NMR spectrum of 4 in dioxane-d_8 at about + 80°C. The ortho protons were seen as a sharp doublet at 7·32 (J = 7·2 Hz); the para proton as a triplet (J = 7·4 Hz) with further meta coupling and the meta protons as a triplet at 7·49 (J = 7·5 Hz) with again some fine structure. The two methyl signals of ring C at 1·17 and 1·10 appeared to be slightly broader than the one at C–6 and even more so than the one at C–2 indicating that free rotation of ring C was not occurring. The signals due to the eight CH_2 protons could not be analysed, but indicated that some more coalescence had taken place compared to the $CDCl_3$ spectrum at ambient temperature.

The 500 MHz ^{1}H NMR spectrum of 4 in C_6D_6 was instructive. The high field methyl signals suffered some shielding, while the one due to C–2 was slightly deshielded. The signals due to the protons at C–7 were pushed upfield more significantly

Table 4. Selected 500 MHz ^{1}H NMR data for 4, 14 and 16.

Compound No.	C–5 H		C–7 H		C–3′ H*		C–5′ H*		$C(2)H_3$	$C(6)H_3$		$C(4')H_3$		Others
	δ	J	δ	J	δ	J	δ	J	δ	δ	δ	δ	δ	
14	2·41	15·58	2·78	15·68	2·55	17·65	2·40	15·88		1·08	1·11	1·20	1·15	enol OH 7·60
($CDCl_3$)	2·22	15·58	2·71	15·35	2·45	17·66	2·32	15·78	2·018					$CHMe_2$, 4·47
														$CHMe_2$, 1·52, 1·50
14	2·27	15·76	2·21	15·73	2·44	17·80	2·32	15·87 (1·40)						$CHMe_2$ 3·85
(C_6D_6)	2·20	15·36	2·11	15·66	2·36	17·85 (1·42)	2·26	15·81	2·00	0·81	0·80	1·02	0·89	$CHMe_2$, 0·96, 0·95
4	2·47	15·68	2·43	16·44	2·59	17·86	2·48	15·54						
($CDCl_3$)	2·27	15·86	2·36	16·36	2·48	17·82	2·34	15·92	1·82	1·08	1·05	1·22	1·16	
4	2·28	15·25	2·09	16·36	2·46	17·86	2·34	15·90 (1·50)						
(C_6D_6)	2·17	15·88	2·05	16·40	2·39	17·82 (1·50)	2·28	15·90	1·96	0·74	0·69	0·99	0·80	
16	2·34	15·62	2·47	16·30	2·63	17·39	2·45	15·52						
($CDCl_3$)	2·22	15·86	2·36	16·30	2·46	17·85	2·32	15·49	1·82	1·06	1·03	1·27	1·16	

* These assignments may be interchangeable

and seen as a quarter centred at 2·07 ppm. Irradiation of these protons produced NOE effects of 4·2 and 2·7% respectively on the ortho protons in the phenyl ring. In the control experiment the signal at δ 1·96 ppm due to C–2 Me was irradiated to produce an NOE effect of 5% on the ortho aromatic proton. Protons at C–3′ and C–5′ were identified using the fact that one from each set was coupled to one from the other (1·50 Hz; W coupling), which further suggested an equatorial conformation for these. Protons at C–5′ adjacent to the double bond were assigned to the more shielded signals compared to those at C–3′ adjacent to the C=O group. The remaining four signals would then be attributed to the two protons at C–5.

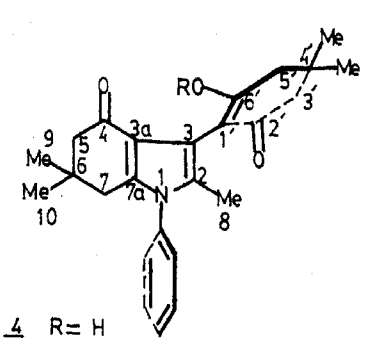
The 500 MHz ^{1}H NMR spectrum of 16 in $CDCl_3$ was similar to that of 4. Fourteen signals were seen for the ring methylene protons and could be assigned as shown in table 4. The five protons on the phenyl ring were segregated clearly into three groups, meta, para and ortho as in the case of the high temperature dioxane spectrum of 4.

The 500 MHz ^{1}H NMR spectrum of 14 in $CDCl_3$ showed fifteen lines for the CH_2 protons with overlap of only two lines. The AB quartet at 2.74 ppm was readily assigned to the two protons on C–7. The other assignments were made by analogy with 4. Compared with the spectrum at 60 MHz, the Me protons of the isopropyl group were seen as a pair of doublets at 1·50 and 1·52 ppm indicating hindrance to free rotation around the C–N bond. In dioxane-d_8 at the same field strength and at around 80°, these methyl protons gave rise to three signals as two overlapping doublets.

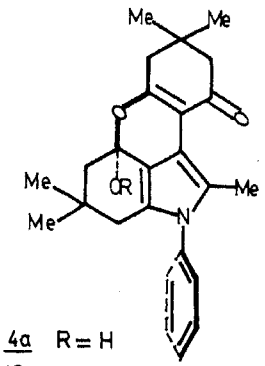
In the 500 MHz ^{1}H NMR spectrum of 14 in C_6D_6, the eight methylene protons gave rise to sixteen lines (four of them with fine structure) which were readily analysed (table 4). Protons at C–7 and of the isopropyl group underwent significant upfield shift of about 0·6 ppm indicating complex formation around the pyrrole N atom.

3.4b ^{13}C *NMR spectra*: Data from the broad band decoupled ^{13}C NMR spectrum in $CDCl_3$ of 4 at 125 MHz and 16 and 27 at 50 MHz are given in table 1 and indicate an overlapping of two methyl carbon signals in 4 and 16. Assignments for 4 and 16 were made using 27 as a model compound.

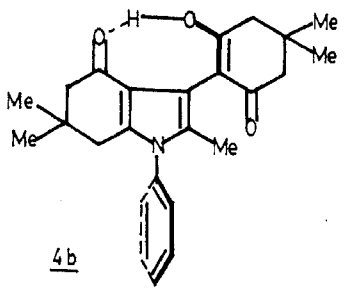
The following points may be further noted: the enolic carbon (6′) appears at 171·7 ppm, consistent with its being a vinylogous carboxylic carbon atom. Two carbonyl signals were seen at 195·0 and 196·4 ppm. Signals due to quaternary carbon centres at 107·1, 110·7 and 117·8 ppm are attributed to the three nonprotonated olefinic carbon atoms nonadjacent to the nitrogen atom. In the structure 4a, instead of a signal for a carbonyl carbon atom, one due to the quaternary hemiketal carbon atom would be expected around 110 ppm. Thus the hemiketal structure 4a can be ruled



4 R= H
16 R= Me



4a R= H
16a R= Me



4b

out for 4. Signals at 131·4, 136·9 and 143·7 ppm arising from other nonprotonated olefinic carbon atoms are assigned as shown in the table. The data do not preclude the possibility of contribution from the hydrogen-bonded structure 4b.

The 50 MHz ^{13}C NMR spectral data for the methyl ether 16 of 4 are very similar to that of 4.

4. X-ray single crystal structure studies

The potent biological activity of the series and the intriguing features presented by their mass and NMR spectra prompted us to seek firm evidence of the structures by X-ray studies. Among several compounds looked at, 8 was found to be suitable.

Table 5. Positional parameters and their estimated standard deviations for 8.

Atom	*X*	*Y*	*Z*	$B(A^2)$
01	0·5325(2)	0·7886(1)	−0·0272(1)	3·42(3)
02	0·2031(3)	0·7903(2)	0·2350(2)	7·57(6)
03	0·3284(2)	0·4645(1)	0·0281(1)	3·36(3)
N1	0·0247(2)	0·8449(1)	−0·0756(1)	2·62(3)
C2	0·1535(2)	0·9003(2)	−0·1067(2)	2·55(4)
C3	0·2644(2)	0·8279(2)	−0·0435(2)	2.48(4)
C4	0·1971(2)	0·7245(2)	0·0307(2)	2·54(4)
C5	0·0510(2)	0·7368(2)	0·0093(2)	2·61(4)
C6	0·1703(3)	1·0185(2)	−0·1943(2)	3·14(4)
C7	0·3471(3)	1·0226(2)	−0·2411(2)	3·11(4)
C8	0·4336(2)	0·9873(2)	−0·1408(2)	3·27(4)
C9	0·4181(2)	0·8593(2)	−0·0649(2)	2·67(4)
C10	0·4188(3)	0·9278(2)	−0·3216(2)	4·06(5)
C11	0·3645(4)	1·1559(2)	−0·3078(2)	4·93(6)
C12	−0·0708(3)	0·6566(2)	0·0644(2)	3·82(5)
C13	−0·1109(2)	0·8862(2)	−0·1317(2)	3·12(4)
C14	−0·0771(2)	0·8434(2)	−0·2446(2)	3·56(5)
C15	−0·1353(3)	0·9256(3)	−0·3354(2)	4·99(7)
C16	−0·1086(4)	0·8860(4)	−0·4398(2)	7·05(9)
C17	−0·0232(4)	0·7662(4)	−0·4525(3)	8·1(1)
C18	0·0370(5)	0·6858(3)	−0·3626(3)	8·1(1)
C19	0·0097(4)	0·7241(3)	−0·2583(2)	5·84(7)
C20	0·2629(2)	0·6323(2)	0·1247(2)	2·71(4)
C21	0·3273(2)	0·5092(2)	0·1208(2)	2·49(4)
C22	0·3978(3)	−0·5846(2)	1·2137(2)	3·14(4)
C23	0·4241(3)	−0·5261(2)	1·3057(2)	3·77(5)
C24	0·2867(4)	−0·4197(3)	1·3342(2)	5·47(7)
C25	0·2520(4)	−0·3209(2)	1·2282(2)	4·81(6)
C26	0·5770(4)	−0·4685(3)	1·2547(3)	5·55(7)
C27	0·4566(4)	−0·6247(2)	1·4097(2)	6·06(7)

Anisotropically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as:

$$(4/3) \times [a^2 \times {}^*B(1,1) + b^2 \times {}^*B(2,2) + c^2 \times {}^*B(3,3) + ab(\cos\gamma) \times {}^*B(1,2) + ac(\cos\beta) \times {}^*B(1,3) + bc(\cos\alpha) \times {}^*B(2,3)]$$

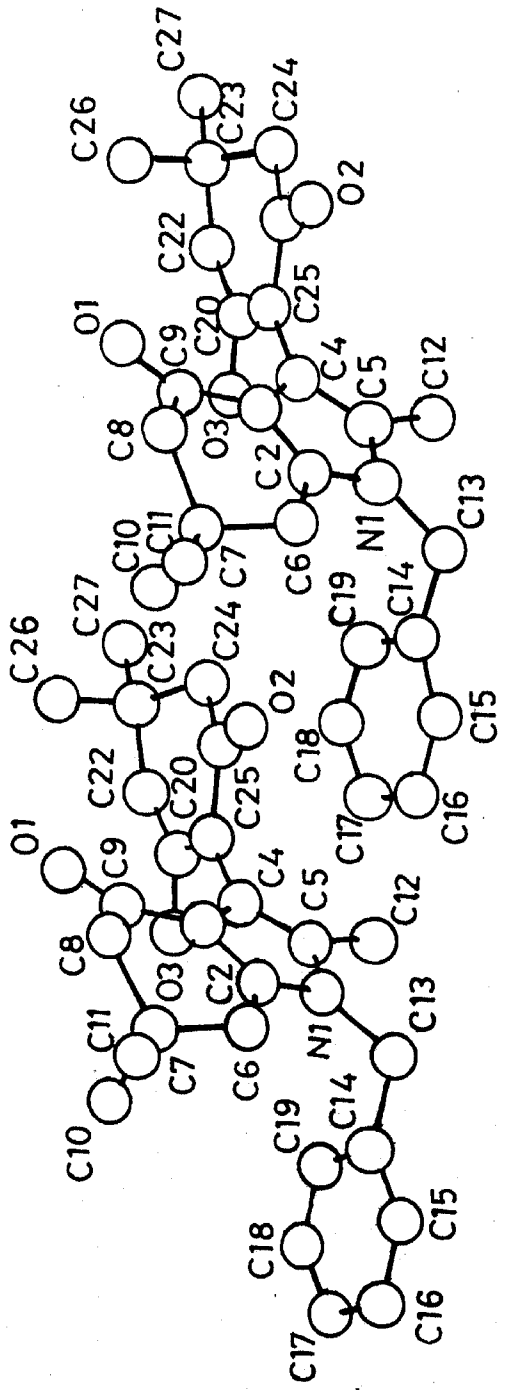


Figure 1. Stereoview of 8.

4.1 *Crystal data of 8*

Transparent rectangular crystals of 8, size $0{\cdot}15 \times 0{\cdot}25 \times 0{\cdot}25\,mm^3$ were crystallized from methanol.

$C_{26}NO_3H_{31}$, cell data: Triclinic $P\bar{1}$, $a = 8{\cdot}906(5)$, $b = 11{\cdot}088(2)$, $c = 12{\cdot}307(3)$ Å, $\alpha = 75{\cdot}92$, $\beta = 75{\cdot}29(2)$, $\gamma = 75{\cdot}55(2)$, $Z = 2$, $M_\gamma = 405{\cdot}5$, $R(F) = 0{\cdot}059$, $V = 1117{\cdot}1$ Å^3, $F(000) = 436$, $D_c = 1{\cdot}206\,g/cm^3$, $CuK_\alpha(\lambda = 1{\cdot}5418)$, $\mu = 6{\cdot}28\,cm^{-1}$, $T = 295$ K.

Three-dimensional intensity data were collected on Enraf-Nonius CAD4-automated diffractometer, with graphite monochromated CuK_α radiation, in $\theta/2\theta$ scan mode; data were corrected for polarization and Lorentz effects. Cell constants were refined using 21 reflections in the range $11 \leqslant 2\theta \leqslant 34$. Empirical absorption corrections with minimum and maximum correction factors 0·985 and 0·999 respectively were applied. Three standard reflections monitored every hour did not show any significant variation in intensity. Scan width using the relation $(A + B\tan\theta)$ where A and B are 0·7 and 0·14 respectively was used. 4545 reflections with $2\theta_{max} = 140$ were measured, out of these 4195 unique and 3886 were observed with $I \geqslant 2{\cdot}5\sigma(I)$, $-10 \leqslant h \leqslant 10, 0 \leqslant k \leqslant 13$, $-14 \leqslant l \leqslant 14$. No extinction correction was applied. Aperture width used was $(3 + 2\tan\theta)$ and maximum time spent on any reflection was 30 s and the background count was half the scan time. Structure solution was by direct methods. Hydrogens were from $\Delta\rho$ map. Full matrix least square refinement on F_o with nonhydrogens anisotropic and hydrogens isotropic gave a final $R(F) = 0{\cdot}059$ with individual weighing scheme based on counting statistics where $W = 4(F_o)^2/(\sigma^2(F_o)^2)$, $\sigma(F_o)^2 = [\sigma^2(I) + p^2I^2]^{1/2}/L_p$ and p is the ignorance factor ($p = 0{\cdot}05$). Atomic scattering factors were from *International Tables for X-ray Crystallography* (1974), All calculations were done on a VAX 11/730 computing system using an SDP package (Frenz 1978).

The study confirmed the structure of 8 and by extrapolation, the structures of other members of the series. Positional parameters (table 5) and a stereoview (figure 1)* of the molecule are presented. The phenyl and pyrrole rings are planar in the compound and make an angle of 85·4°. Ring C is also twisted with respect to the pyrrole ring, the angle between the two being 85·6°. The packing of 8 is stabilised by O(3)-H...O(1) (2·77 Å) intermolecular hydrogen bond.

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*The numbering of the various atoms is arbitrary

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