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MAGNETIC NONEQUIVALENCE IN THE NMR SIGNALS OF ISOPROPYL CH_3 PROTONS IN SOME CONDENSATION PRODUCTS FROM ISATIN AND METHYL KETONES

J. BERGMAN

Department of Organic Chemistry, Royal Institute of Technology, 100 44 Stockholm 70, Sweden

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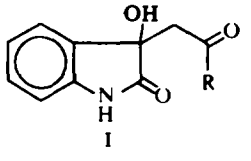
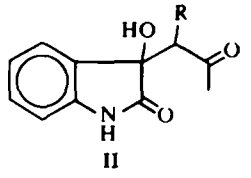
Abstract—Isatin was condensed with some methyl ketones [$CH_3\overset{O}{\overset{\|}{C}}(CH_2)_nCH(CH_3)_2$] to give 3-(2-oxo-alkyl)-3-hydroxyoxindoles (I). LAH-reduction of I gave the corresponding tryptophols. The related α-alkyltryptamines were prepared by known methods.

The NMR signals from the isopropyl methyl groups of the products showed extra splitting due to the presence of an asymmetric centre. For compounds of type I, the chemical shift differences decreased regularly with increasing values of *n*, whereas those for the tryptophols and the α-alkyltryptamines showed a maximum at $n = 1$.

The synthesis of some α-alkyltryptophols and α-alkyltryptamines required a series of compounds with the general structure I.



I



II

THESE compounds were easily prepared by a diethylamine catalysed condensation using isatin and the appropriate methyl ketone.[1–4] The structure and the purity of the isomers (I and II) were examined by NMR spectroscopy. The condensation products from isatin with methyl ethyl ketone and methyl n-propyl ketone showed the product ratio (I/II) 2/1 and 6/1, respectively. No crystalline products have so far been obtained from these mixtures (*cf* Ref 4 and 5). The product ratio was estimated by NMR spectroscopy. In all other condensations investigated isomer I was dominant. Pietra and Tacconi arrived at a similar conclusion.[2–4]

The condensation product (I) contains an asymmetric centre. Thus it is not unexpected that the NMR signals from the protons of the methylene bridge between this centre and the CO group appear as an AB-quartet ($J_{AB} = 17{\cdot}1 \pm 0{\cdot}3$ Hz). The spectrum of 3-(2-oxo-3-methylbutyl) 3-hydroxyoxindole (I R = $CH(CH_3)_2$) is shown in Fig 1, from which it is also evident that even the signal from the isopropyl Me groups shows additional splitting.

Magnetic nonequivalence of the signals from diastereotopical protons in methylene

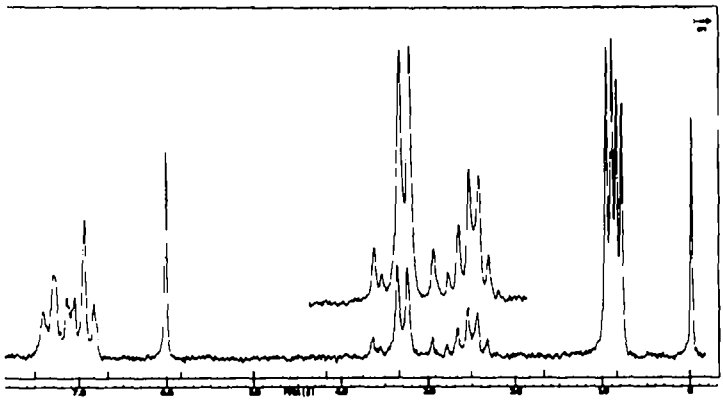


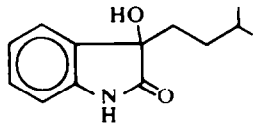
FIG 1. NMR spectrum of 3-(2-oxo-3-methylbutyl)-3-hydroxyoxindole in DMSO-d_6 at 42°.

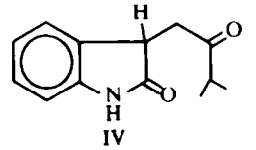
and isopropyl Me groups has recently received attention.[6–13] The effect of an increasing number of bonds between the asymmetric centre and the CX_2Y-group has however been studied comparatively little[6–8]. Whitesides *et al.*[8] have investigated this phenomenon in $C_6H_5(CH_3)CHO(CH_2)_nCH(CH_3)_2$, and some closely related compounds, and reported the following data: $n = 0$, $\nu^A - \nu^B = 5{\cdot}8$ Hz; $n = 1$, $\nu^A - \nu^B = 0{\cdot}0$ Hz; $n = 2$, $\nu^A - \nu^B = 2{\cdot}2$ Hz. The values were obtained from measurements in acetone. Carbon tetrachloride, but not benzene gave similar results. Whitesides *et al.* explained this irregular behaviour in terms of preferred conformations.

TABLE 1. THE VALUES ARE CALCULATED FROM MEASUREMENTS AT 42° ON A 60 MHz INSTRUMENT. THE VALUE ZERO IN THE TABLE ONLY INDICATES THAT NO SPLITTING COULD BE OBSERVED

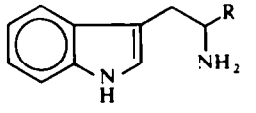
	$(\nu^A - \nu^B)$ Hz in $CH\begin{smallmatrix}CH_3(A)\\CH_3(B)\end{smallmatrix}$				$(\nu^A - \nu^B)$ Hz in $C\begin{smallmatrix}H(A)\\H(B)\end{smallmatrix}$	
	$DMSO_{d6}$	$Acetone_{d6}$	$Pyridine_{d5}$	$CDCl_3$	$DMSO_{d6}$	$CDCl_3$
I R = $CH(CH_3)_2$	3·8	2·5	0·6	0	18·5	14·7
I R = $CH_2CH(CH_3)_2$	1·9	0·9	0	0	15·5	11·7
I R = $CH_2CH_2CH(CH_3)_2$	0	0	0	0	14·6	12·6
I R = CH_3					14·0	

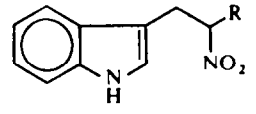
From Table 1 which summarizes the data obtained in the present study, it is apparent that the chemical shift differences decrease regularly with increasing distance from the asymmetric centre in this type of compound. The presence of the CO group, which is highly anisotropic, is fundamental for the display of magnetic nonequivalence. Thus compound III does not show this phenomenon. Compound IV also lacks this splitting which shows that the nature (bulkiness) of the substituents at the asymmetric centre also is of importance. Attempts to replace the OH group by still other groups, e.g. Me by methylation of I with diazomethane, gave a mixture which so far has not been separated.


III


IV

The regular solvent dependence shown in Table 1 may reflect variable power in H-bond formation between the solvent and the OH group. This effect is equivalent with an increase of the bulk of the substituents at the asymmetric centre, which should make the rotation of the isopropyl group more difficult and thus alter the population of the rotamers. As no splitting is observed in $CDCl_3$ even with I, R = $CH(CH_3)_2$, one must assume that in this solvent the possible rotamers are nearly equally populated. In addition the asymmetry term in the Gutowsky expression[14] must be small.


V


VI

The required α-alkyltryptamines and α-alkyltryptophols also gave interesting NMR spectra.

α-Isobutyltryptamine (V,R = $CH_2CH(CH_3)_2$ gave a spectrum (40°) which showed the signal from the isopropyl Me groups as two doublets ($\nu^A - \nu^B$ = 3·3 Hz in $DMSO_{d6}$ and $\nu^A - \nu^B$ = 2·3 Hz in $CDCl_3$). The signals from α-isopropyltryptamine (V,R = $CH(CH_3)_2$ and α-isopentyltryptamine (V.R = $CH_2CH_2CH(CH_3)_2$) did not show any extra splitting. The corresponding tryptophols, easily obtained by LAH reduction of compound I, gave analogous spectra in every respect.

This behaviour clearly shows that proximity to the asymmetric centre is not the only prerequisite for this splitting. One of the Me groups must apparently be in the shielding region of an anisotropic group (in this case the aromatic ring) and in α-isobutyltryptamine suitable coiled conformers may be significantly populated. In α-isopropyltryptamine such conformers should, in agreement with the Newman rule, be energetically disfavored (*cf* Ref 8).

Compound VI, which contains the highly anisotropic NO_2 group, differs markedly from the tryptophols and tryptamines. Thus VI (R = $CH(CH_3)_2$) does show extra splitting ($\nu^A - \nu^B$ = 4·5 Hz in $DMSO_{d6}$ and $\nu^A - \nu^B$ = 3·1 Hz in $CDCl_3$). Compound VI (R = $CH_2CH(CH_3)_2$) does not show (contrary to the OH- and NH_2-analogues) extra splitting, which may be due to steric hindrance of the NO_2 group.

EXPERIMENTAL

M. ps were determined on a micro hot stage and are uncorrected. The NMR spectra were determined with a Varian A-60 A spectrometer, using TMS as internal standard.

3-(4-*Methyl*-2-*oxopentyl*)-3-*hydroxyoxindole* (I, R = iso-Bu). A mixture of isatin (29·5 g, 0·2 mole), methyl isobutyl ketone (50 ml) and diethylamine (3 ml) was shaken for 12 hr. Ether (25 ml) was added and the mixture cooled to 0°. The separated solid was recrystallized from EtOH/water (1 : 2) and then from benzene,

yield: 24 g (62%), m.p. 85–87°. (Found: C, 68·1; H, 7·1; N, 5·6. Calc for $C_{14}H_{17}NO_3$: C, 68·0; H, 6·9; N, 5·7%).

The following compounds were similarly prepared:

3-(3-*Methyl-2-oxobutyl*)-3-*hydroxyoxindole* (I, R = iso-Pr), yield: 72%, m.p. 141–143° (Lit.[2,17] 138–139°, 128–129°).

3-(5-*Methyl-2-oxohexyl*)-3-*hydroxyoxindole* (I, R = iso-Am), yield: 60%, m.p. 119–120°. (Found: C, 69·0; H, 7·3; N, 5·4. Calc for $C_{15}H_{19}NO_3$: C, 68·9; H, 7·3; N, 5·4%).

α-*Isobutyltryptophol*. 3-(4-Methyl-2-oxopentyl)-3-hydroxyoxindole (12·35 g, 0·05 mole) was added in portions to a refluxing mixture of LAH (3·8 g, 0·1 mole) in ether (500 ml). After completed addition the reflux was continued for 5 hr. Excess of the hydride was destroyed by the careful addition of water with stirring. The ether phase was dried ($MgSO_4$), evaporated and the residue crystallized from cyclohexane/hexane (3:1), yield: 5·5 g (51%), m.p. 66–67°. (Found: C, 77·7; H, 8·9; N, 6·3. Calc for $C_{14}H_{19}NO$: C, 77·4; H, 8·8; N, 6·5%).

The following compounds were similarly prepared:

α-*Isopropyltryptophol*, yield: 45%, m.p. 56–57°. As Tacconi has described α-isopropyltryptophol as a liquid, my product was analysed. (Found: C, 76·9; H, 8·6; N, 6·8. Calc for $C_{13}H_{17}NO$: C, 76·8; H, 8·4; N, 6·9%).

α-*Isopentyltryptophol*, yield: 43%, m.p. 30–31°. (Found: C, 78·0; H, 9·3; N, 6·1. Calc for $C_{15}H_{21}NO$: C, 77·9; H, 9·2; N, 6·1%).

3-(4-*Methyl-2-nitropentyl*)*indole* (VI, R = iso-Bu). Na (2·5 g) was dissolved in EtOH (200 ml) and 3-methyl-1-nitrobutane[16] (12·9 g) followed by gramine (17·5 g) were added. To this soln Me_2SO_4 (19·2 ml) in EtOH (50 ml) was added during 0·5 hr at 30–35°. The mixture was stirred for 3 hr at 30–35°, and then poured into Na_2SO_4aq (800 ml, 5%). The solid formed was collected, washed with water, dried and crystallized from cyclohexane, yield: 16·8 g (68%), m.p. 99–100°. (Found: C, 68·2; H, 7·5; N, 11·4. Calc for $C_{14}H_{18}N_2O_2$: C, 68·3; H, 7·4; N, 11·4%).

3-(3-*Methyl-2-nitrobutyl*)*indole* (VI, R = iso Pr). The method described above was used, yield: 61%, m.p. 58–59°. (Found: C, 67·2; H, 7·1; N, 12·0. Calc for $C_{13}H_{16}N_2O_2$: C, 67·2; H, 6·9; N, 12·1%).

α-*Isobutyltryptamine*. 3-(4-Methyl-2-nitropentyl)indole (12·3 g) in ether (200 ml) was added, dropwise with stirring, to LAH (5·0 g) in refluxing ether (500 ml). Heating was continued for 6 hr. Excess LAH was destroyed by careful addition of water. The ether phase was separated, dried ($MgSO_4$) and the solvent evaporated. The residue was crystallized from cyclohexane. The crystals contained cyclohexane (NMR), which was removed by heating under reduced pressure (55°, 10 mm), yield: 8·1 g (75%), m.p. 112–113°. (Found: C, 77·8; H, 9·3; N, 13·0. Calc for $C_{14}H_{20}N_2$: C, 77·7; H, 9·3; N, 13·0%).

α-*Isopropyltryptamine*. The above method was used, yield: 70%, m.p. 111–112°. (Lit.[2,17] 113°, 108–110°).

3-(5-*Methyl-2-hydroxyiminohexyl*)-3-*hydroxyoxindole*. To 3-(5-methyl-2-oxopentyl)-3-hydroxyoxindole (7·0 g) in hot EtOH (50 ml) was added hydroxylamine hydrochloride (2·4 g) in water (15 ml) followed by NaOAc (4·2 g) in water (20 ml). The soln was kept at room temp for 1 hr and then evaporated on a water bath to a small volume, using reduced pressure. The solid formed was recrystallized from water/MeOH (1:1), yield: 5·2 g (71%), m.p. 150–152°. (Found: C, 64·9; H, 7·5; N, 10·0. Calc for $C_{15}H_{20}N_2O_3$: C, 65·2; H, 7·3; N, 10·1%).

α-*Isopentyltryptamine*. 3-(5-Methyl-2-hydroxyiminohexyl)-3-hydroxyoxindole (0·1 mole) was reduced using the procedure given by Franklin and White,[17] yield: 20%, m.p. 82–84°. (Found: C, 77·9; H, 9·7; N, 12·3. Calc for $C_{15}H_{22}N_2$: C, 78·2; H, 9·6; N, 12·2%)'

3-(3-*Methylbutyl*)-3-*hydroxyoxindole* (III). Isatin (14·7 g, 0·1 mole) was added in 10 portions to a refluxing soln of 3-methylbutylmagnesium bromide (0·25 mole) in ether (400 ml). The soln was refluxed for 4 hr, cooled and poured into ice–water containing AcOH (20 ml). The ether phase was separated, washed with 5% $NaHCO_3$aq followed by water. The dried ($MgSO_4$) extract was evaporated and the residue crystallized from chloroform. Recrystallization twice from toluene gave crystals of 3-(3-methylbutyl)-3-hydroxyoxindole, yield: 9·7 g (44%), m.p. 181–182°. (Found: C, 71·5; H, 8·0; N, 6·2. Calc for $C_{13}H_{17}NO_2$: C, 71·2; H, 7·8; N, 6·4%).

3-(2-*Oxo*-3-*methylbutyl*)*oxindole* (IV). 3-(2-Oxo-3-methylbutylidene)oxindole[2] (2·15 g, 0·01 mole) in ether was hydrogenated over 10% Pd/C (200 mg) until the theoretical amount had been taken up (50 min). The catalyst was filtered off and the solvent evaporated. The residue was crystallized twice from toluene with final cooling to −30°; yield: 1·1 g (52%), m.p. 83–85°. (Found: C, 72·1; H, 6·9; N, 6·6. Calc for $C_{13}H_{15}NO_2$: C, 71·9; H, 7·0; N, 6·5%).

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