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ATROPISOMERIC INDOLE DERIVATIVES: A STRUCTURAL REVISION[1]

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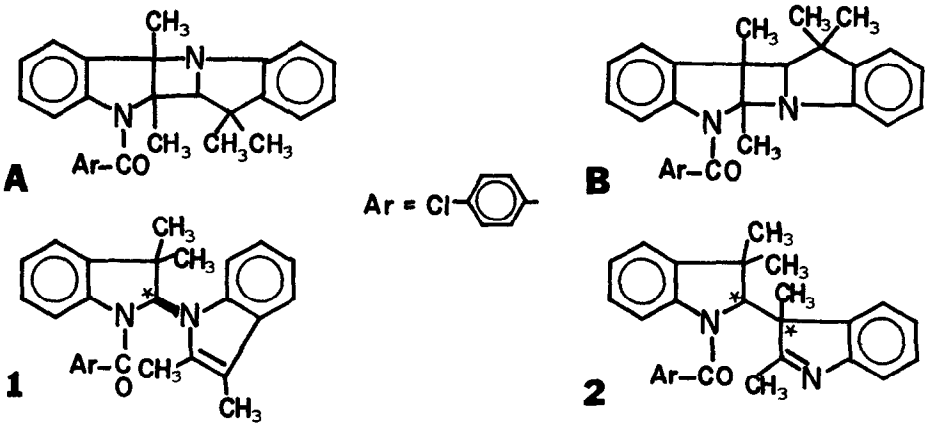
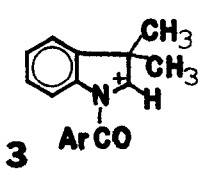
It was recently reported[2] that the reaction of equimolar amounts of trimeric 3,3-dimethyl-3H-indole and p-chlorobenzoyl chloride in refluxing pyridine gave rise to two compounds of the formula $C_{27}H_{25}ON_2Cl$, m.p. 204-206° and m.p. 133-135°. On the basis of the IR, UV, and ^{1}HMR spectra of both compounds, and the IR and ^{1}HMR spectra of the product of $LiAlH_4$ reduction of the carbonyl group of the higher melting isomer, the two compounds were proposed to be stereoisomers of the structure B or, more likely, A. However, on mechanistic grounds A was not plausible. Furthermore, the ^{1}HMR absorption of at least one methyl group in each isomer was at anomalously low field (δ 2.15 ppm). We would now like to report evidence which establishes that the two compounds are actually diastereomeric atropisomers of structure 1, to our knowledge the first such isolable atropisomers involving the heterocyclic ring of an indole.



Our repetition of the reaction gave two compounds with almost the same melting points (195-200° and 132-134°) and the same spectroscopic data reported by the Japanese workers.[2] On the assumption that both compounds do have the same structure, there are possible two other structures, 1 and 2, which could be formed from 3 and 4a or 2,3-dimethylindole (5) present in the reaction mixture. Formula 2 initially seemed more attractive to explain the existence of two isomers (2 chiral atoms marked with *) provided that hydride reduction of the imine was slow because of steric crowding.



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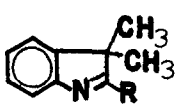
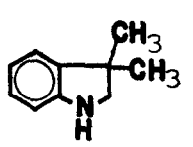


4a, R=H ; **b**, R=CH_3



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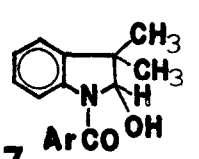

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However, other reducing conditions ($NaBH_4$ + i-PrOH, Zn + HOAc, H_2 + Pt + MeOH + H^+, and $LiAlH_4$ + refluxing THF) with the compound of m.p. 200° also gave either no reaction or else reductive cleavage into 3,3-dimethylindoline (6) and 2,3-dimethylindole (5). Subtraction of the ultraviolet spectrum of 7 from the spectrum of each of the two compounds left a chromophore that matched that of (5) but not that of 2,3,3-trimethylindolenine (4b) or 6 (Fig. 1). The higher melting compound contained no group titratable in the 80% MCS system, a fact in better agreement with structure 1.[3]

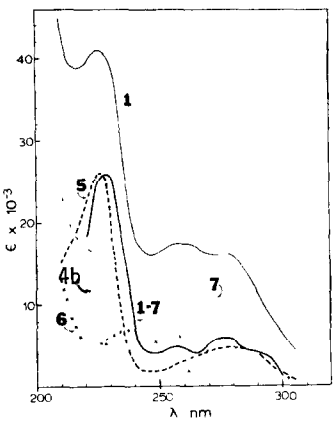
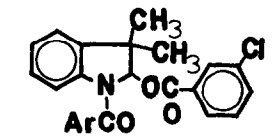


Fig. 1. Ultraviolet spectra of methanol solutions of compounds 1, 5, 6, 7, 4b and the difference spectrum of 1 and 7.

The ^{13}CMR spectra of the two isomers (Table I) were virtually the same except for two carbon atoms whose absorption positions were interchanged. Each contained only six signals for sp^3-hybridized carbon. Moreover, the absorption of the sp^2-hybridized C-2 in the model imine 4b at 187.5 ppm was more than 45 ppm downfield from the lowest field aryl signal in the spectrum of either isomer. On the other hand in each of the latter spectra was a peak (107.6 and 110.2 ppm) which corresponded well with the absorption of C-3 (106.8 ppm) in 5.[4]

Oxidation of the higher melting isomer with m-chloroperbenzoic acid in $CHCl_3$ at room temperature gave 8 (ν^{CHCl_3} 1715 and 1650 cm^{-1}) and 2-acetamidoacetophenone (9), the latter type of product being characteristic of the peracid cleavage of an indole.



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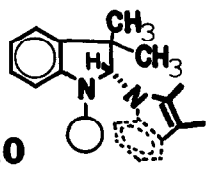

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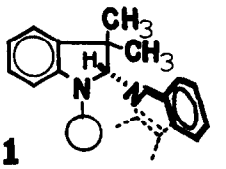

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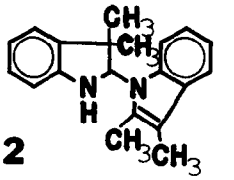

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From these spectra and experiments the two isomeric compounds cannot have structure A, B or 2, and they must contain an indole moiety. Structure 1 remains as the only one which agrees with the data, but the single chiral atom (*) by itself cannot account for the existence of two diastereomers. However, if rotation about a single bond in 1 were restricted, then the combination of one chiral atom with atropisomerism would allow the existence of two diastereomers. Proof of this supposition was provided by heating each pure isomer separately above its melting point, whereupon each isomer was converted into an equilibrium mixture of both containing ~70% of the higher-melting and ~30% of the lower-melting compound. The products were separated by t.l.c. (the higher melting isomer has the lower R_f on silica gel) and identified by m.p., m.m.p., IR and ^{1}HMR comparison. The barrier to rotation is high (ΔG^* >30 kcal./mol.) because in boiling toluene solution the interconversion has not reached equilibrium after 1 hr. (from lower m.p. isomer).

Although, a priori, restricted rotation about either the amide N-CO bond or the bond (heavy line) from the indole nitrogen to C* in 1 would explain the observed interconversion, the former is excluded because it would require an energy barrier >5 kcal./mol. higher than known amide rotation barriers which do not exceed ΔG^* ~25 kcal./mol.[5]

To confirm that the atropisomerism involved the heavy bond in 1, each amide was reduced to the p-chlorobenzyl derivative. From the high melting amide was obtained ($LiAlH_4$-ether) the previously reported[2] compound, m.p. 102°, $\delta(CDCl_3)$ 0.86 (s, CH_3), 1.35 (s, CH_3), 2.05 (s, CH_3), 2.18 (s, CH_3), 3.67 and 4.40 (AB, J=15 Hz), 5.44 (s, NCHN). From the lower melting amide was obtained (B_2H_6-THF) a different oily derivative, $\delta(CDCl_3)$ 0.85 (s, CH_3), 1.36 (s, CH_3), 1.87 (s, CH_3), 2.15 (s, CH_3), 3.90 and 4.40 (AB, J=16 Hz), 5.77 (s, NCHN). Although both products were sensitive to thermal decomposition, the latter was partially (~40%) converted into the former by heating at 145°. The differences in the ^{1}HMR absorption of one indole methyl group (δ2.05 vs. 1.87) and the methine hydrogen (δ5.44 vs. 5.77) of the two p-chlorobenzyl isomers allow the confident assignment of the stereochemistry 10 to the higher melting amide and its reduction product, and the stereochemistry 11 to the lower melting amide and its reduction product, because in 11 the indole 2-methyl is shielded by the indoline benzene ring, while the methine hydrogen is deshielded by the indole benzene ring.

A bulky group on the indoline nitrogen atom is essential, in addition to the other hindering groups, for the high rotational barrier in 1. Removal of this bulky group by debenzoylation of the diastereomeric amides with $LiAlH_4$ at 0° in ether, gave the same product 12, m.p. 142-144°,[6] λ_{max}^{MeOH} 230 (29,000) and 295 nm (6100) from each isomer: the IR spectra (ν^{CHCl_3} 3440 $cm.^{-1}$, NH) and ^{1}HMR spectra [$\delta(CDCl_3)$ 0.90 (s, CH_3), 1.43 (s, CH_3), 2.21 (s, CH_3), 2.39 (s, CH_3), 4.26 (s, NH), 5.75 (s, N-CH-N) and 6.5-7.5 ppm (m, ArH)] of 12 from both isomers were identical. Nevertheless, the ^{1}HMR spectrum of 12 did give evidence of a low barrier to rotation on the ^{1}HMR time scale. In the ^{1}HMR spectra of pure 12 from each isomer, two of the methyl peaks had a small high field shoulder at δ0.84 and 2.15, while a separate small singlet appeared at δ2.02. When the temperature was raised in stages to 60°, these smaller peaks coalesced with the larger methyl signals. We attribute these minor peaks to three of the methyl groups of the minor atropisomer of 12 with the interconversion being slow at room temperature.[7]

TABLE 1: ^{13}C Shieldings[a] of 4b and Isomers of 1

Carbon type	m.p. 200° **1b**	m.p. 134°	**4b**
CH_3	8.6, 10.1, 20.8, 31.9	8.7, 12.0, 20.5, 32.4	15.3, 23.0 (2C)
$-\dot{C}H(sp^3)$	81.0	81.0	
$-\dot{C}-(sp^3)$	45.4	45.7	53.5
C=O	169.1	169.8	
$=CH(sp^2)$	(111.4) 116.6, 117.9, 119.1, 121.4, 121.9, 125.1, 127.3 (2C), 128.2 (3C)	(107.2) 116.9, 117.8, 119.3, 121.1, 121.9, 125.0, 126.7 (2C), 128.2 (3C)	119.7, 121.0, 124.9, 127.4
$C=(sp^2)$	(107.6) 129.4, 131.5, 133.6, 134.6, 135.6, 139.1, 141.0	(110.2) 128.0, 130.4, 133.9, 135.5, 136.6, 139.0, 141.7	145.4 153.6 187.5 (N=C-2)

[a] Obtained in the Fourier transform mode at 25.2 MHz with a Varian XL-100-15 system using 5-10% solutions in $CDCl_3$; the peak positions are given relative to internal TMS.

[b] Interchanged peaks in the spectra of the two isomers are encircled.

Acknowledgement. This work was supported by the National Research Council of Canada.

REFERENCES and FOOTNOTES

1. Part 39 of ^{13}C NMR studies (J.B.S.).

2. K. Takayama, M. Isobe, K. Harano, and T. Taguchi, Tetrahedron Lett., 365 (1973).

3. We would like to thank Dr. W. Simon, ETH, for the titration.

4. R.G. Parker and J.D. Roberts, J. Org. Chem., 35, 996 (1970). TMS scale factor 192.8 ppm.

5. I.O. Sutherland in Annual Reports on NMR Spectroscopy, ed. by E.F. Mooney, Vol. 4, Academic Press, New York, N.Y., 1971, pp. 201-207.

6. Anal. Calcd. for $C_{20}H_{22}N_2$ (290.4): C, 82.72; H, 7.64. Found: C, 82.87; H, 7.44.

7. At room temperature the lowest field methyl absorption (δ2.39 ppm) of 12 is less than 3H by the amount of absorption of the weak peak at δ2.02 ppm.