DYNAMIC ^{13}C N.M.R. STUDIES OF ELECTROCHEMICALLY FORMED 4a-N' AND 4a-4a' DEHYDRODIMERS OF 1,2,3,4-TETRAHYDROCARBAZOLE

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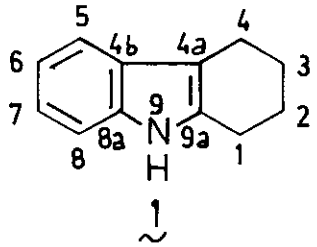
Abstract— The electrochemical oxidation of 1,2,3,4-tetrahydrocarbazole in strong base ($KOCH_3$ in CH_3OH) at a potential of + 0.15 V (vs S.C.E.) on a graphite felt anode produced a series of dehydrodimers having interesting stereochemical and ^{13}C dynamic N.M.R. properties. The 4a-N' dimer was isolated as a pair of atropisomers due to restricted rotation around a nitrogen-sp^3 carbon bond. Meso and dl forms of the 4a-4a' dimer were also isolated. Low temperature ^{13}C N.M.R. spectra of the 4a-4a' dimers showed that they represent a unique case of stereochemistry when rotation is restricted. The case corresponds to a situation where the anti conformation around an acyclic sp^3-sp^3 carbon-carbon bond is forbidden, and only the two gauche forms are present.

We have been studying the electrochemical oxidation of 1,2,3,4-tetrahydrocarbazole, 1 (1-H-2,3,4,-9-tetrahydrocarbazole), as a model for the biomimetic synthesis of dimeric and polymeric indole alkaloids. Under neutral conditions, the oxidation yields a 4a-7' dimer, 2, in good yield.[1] However, when the oxidation was carried out in CH_3OH and $KOCH_3$, only a trace of 2 was formed, and the products were the 4a-N' dimers 3a and 3b (9.2%), meso 4a-4a' dimer, 4 (9.4%) and dl 4a-4a' dimer, 5 (20%).

The high-resolution mass spectra and microanalyses of 3, 4, and 5 were in accord with a dehydrodimer, $C_{24}H_{24}N_2$. It is of interest that a major peak in the mass spectrum of 3 corresponds to a molecule of 1 at m/e 171. This is presumably due to the facile loss of a molecule of 1 and is supported by the parent ion peak at 143, characteristic of 1.[2] There are no peaks between 171 and 340. There is also a strong peak at 171 in the spectra of 4 and 5, but there are several between 171 and 340. Obviously the C-N' bond in 3 is easily broken.

Compound 3 is actually a mixture of atropisomers[3] (3a and 3b) similar to two published cases.[4,5] Its ^{13}C N.M.R. spectrum showed two sets of peaks, each set corresponding to one atropisomer. The isomers were not formed in equal amounts and were not separated. It was possible to assign most, but not all of the ^{13}C resonances (Experimental). Attempts to reach a temperature at which



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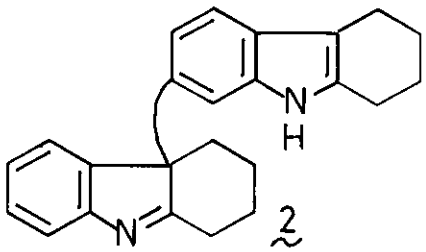

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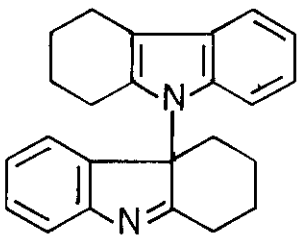
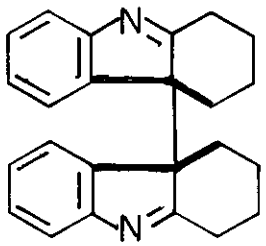


3a + 3b



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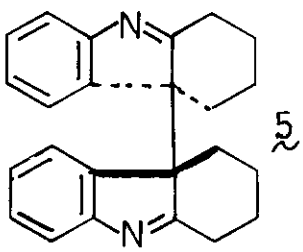

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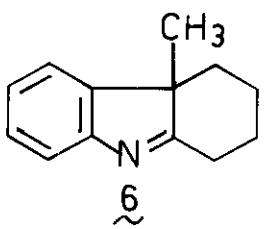


6

rotation became free led to decomposition. The structure of 3 is based upon its ^{13}C spectrum and its reduction with $LiAlH_4$.[6] The reduction yielded only compound 1, presumably produced by reduction of the imine bond in 3 and a deamination to two molecules of 1. Similar reductions of 4 and 5 yielded complex mixtures but no 1.

Proof for the carbon skeletons of 4 and 5 rests upon the similarity of the ^{13}C N.M.R. spectra with that of 4a-methyl-1,2,3,4-tetrahydrocarbazole, 6.[7] This comparison is shown in Table 1 (6 as compared with 4 and 5 at 28°C).

The assignment of meso and dl structures to 4 and 5 is based upon dynamic ^{13}C N.M.R. spectroscopy at low temperatures. In addition to providing structural assignments of 4 and 5, the spectra provide evidence for a steric effect around an acyclic sp^3-sp^3 bond in which only gauche conformations are present at low temperatures.

Table 1. ^{13}C N.M.R. Shift Values of 4 and 5 at Various Temperatures and Compared to 6[a]

Carbon	6	4			5		
		28°C	-113°C		28°C	-57°C	
1	38.6	39.9	37.5	42.4	40.3	41.9	34.6
2	29.7	33.3	31.5	34.8	33.9	33.8	34.5
3	29.0	30.1	29.2	30.7	29.5	29.3	29.6
4	21.4	23.4	[b]	[b]	21.4	20.5	22.2
4a	53.8	58.9	56.4	60.9	60.1	59.6	59.9
4b	146.8	143.7	143.2	144.0	143.2	142.0	142.8
5	121.2	123.3	121.6	124.7	123.4	121.5	123.9
6	124.7	124.8	125.3	125.3[c]	124.5	124.0	124.6
7	127.4	128.0	127.8	128.4	127.8	127.7	127.7[c]
8	120.1	120.0	120.1	120.5	120.5	119.0	120.8
8a	154.3	154.3	152.8	155.3	154.0	152.1	153.7
9a	189.9	186.6	186.6	187.4	188.3	187.2	189.0
4a-CH_3	19.8						

[a]The spectrum of 4 at -113°C was measured in CS_2-perdeuterotetrahydrofuran (1:1). The others were measured in $CDCl_3$. Shift values are in δ units from TMS.

[b]The peaks fall in the solvent region (THF).

[c]The peaks are very slightly split, if at all.

A conformational analysis of the 4a-4a' bond in 4 and 5 is difficult to visualize because of the complexity of the molecule. One conformation, the anti conformation of the meso compound is shown in Figure 1. The stereochemical argument is much easier to visualize using meso and dl 2,3-disubstituted butane, which is completely analogous to the more complex system. The conformers of the substituted butane are shown in Figure 2. We will make two assumptions about what might happen to 4 and 5 at low temperatures and predict the ^{13}C spectra using Figures 1 and 2 as guides. The first assumption is that rotation is completely restricted, and the second is that the anti conformation is of high energy and forbidden.

If these assumptions are correct, the remaining gauche forms of the meso isomer, 4, will have no degree of symmetry and are enantiomers. However, within a single gauche form (or enantiomer) all of the atoms will be in different environments. That is to say, the atoms in one half of the molecule are no longer identical with their corresponding atoms in the other half, since the gauche forms are completely unsymmetrical and cannot attain or go through any symmetrical conformations. Thus, the ^{13}C spectrum should show a set of equal peaks corresponding to any given atom (for

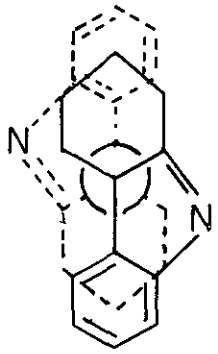
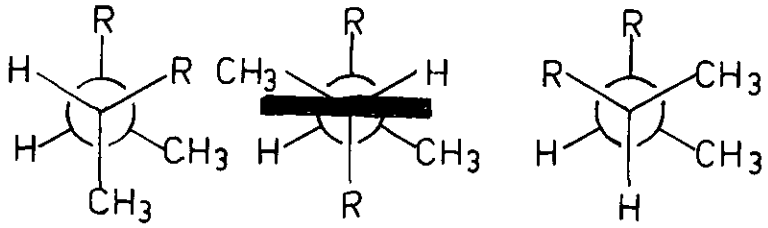
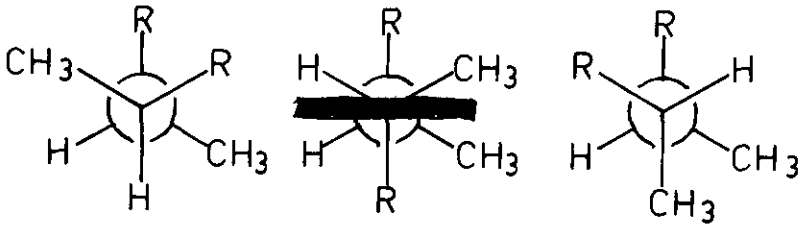


Figure 1. The anti conformation of 4.



meso – pair of enantiomers – all atoms different



dl – diastereomers – two pairs of enantiomers

Figure 2. Conformational analysis of a symmetrical 2,3-disubstituted butane with a forbidden anti form.

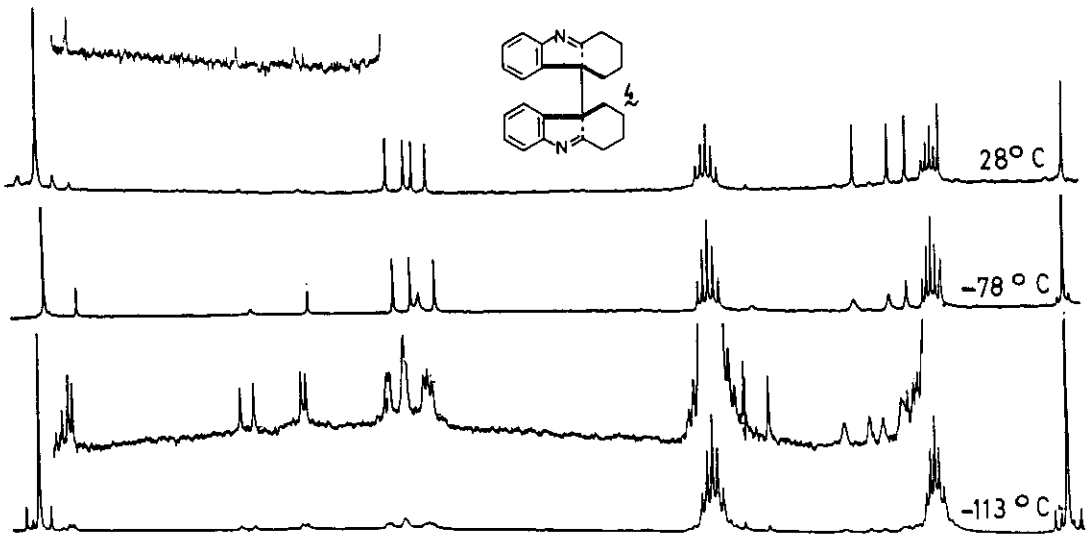


Figure 3. ^{13}C N. M. R. spectra of 4 at three temperatures, 28°C (two sensitivities), -78°C, and -113°C (two sensitivities).

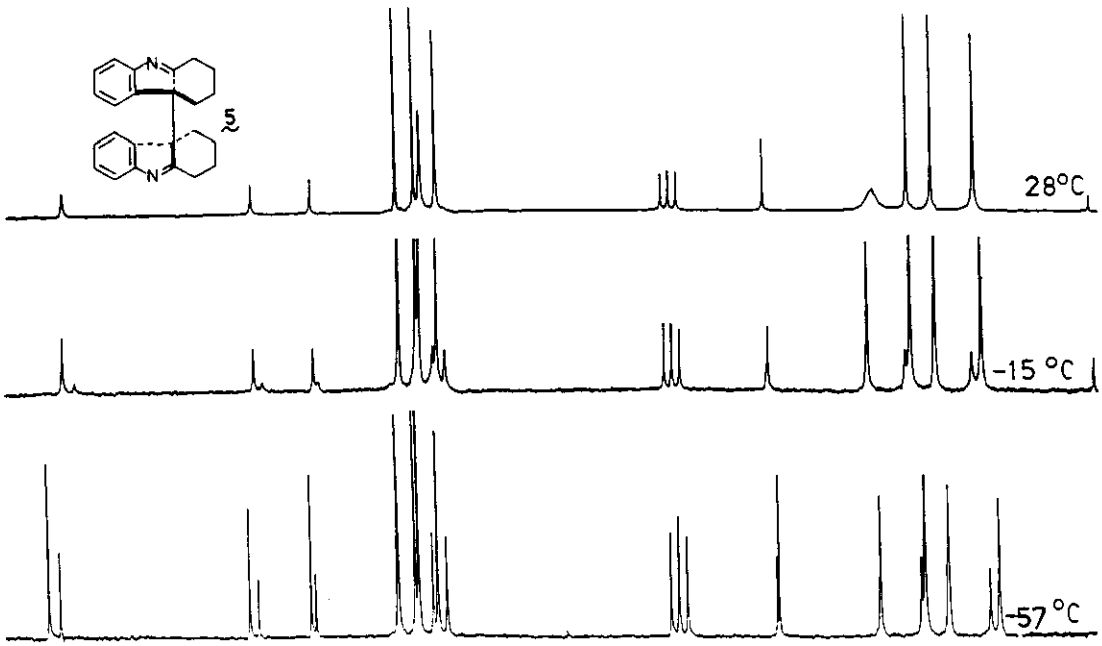


Figure 4. ^{13}C N. M. R. spectra of 5 at three temperatures, 28°C, -15°C, and -57°C.

example, C-1 and C-1'). The locations of these peaks are given at -113°C in Table 1, and the spectra at various temperatures in Figure 3 show that they are of equal size (within experimental error).[8]

The situation is quite different for the dl isomer, 5. The two gauche forms are diastereomers, each actually being a pair of enantiomers. Since they have different energies, the pair of peaks which result at low temperature should have unequal heights. This is clearly the case as shown in Table 1 and Figure 4.[8]

Our interpretation with respect to the meso isomer is unambiguous, but, in the case of the dl isomer, we cannot exclude the possibility that the two forms shown at low temperature represent one gauche form and the anti form. Since, however, the structure of the dl-anti conformer is quite similar to that shown for the meso isomer in Figure 1, we think this unlikely.

The probable reason for the high energy of the anti conformations of 4 and 5 is that, in such a conformation, the rings lie on top of one another. This is clearly shown in Figure 1.

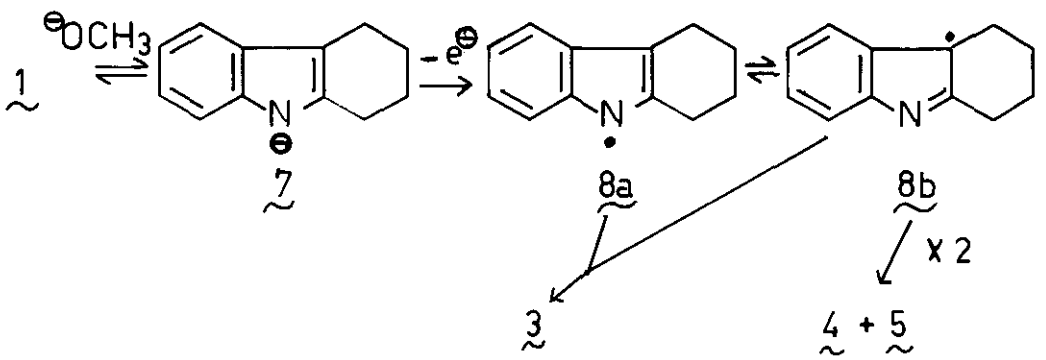
As kindly noted by a referee, a somewhat similar situation exists in very sterically hindered ethane derivatives, specifically sym-tetra-tert-butylethane and sym-tetra(trimethylsilyl)ethane.[9] Although the anti form is less stable than the gauche forms, the reasons are quite different, probably lying in a bond distortion around the heavily substituted ethane carbons. Since the molecules are symmetrical the spectral data are also quite different.

A similar situation does exist, however, in cyclic systems, in which an "anti" relationship is prevented by the presence of a ring. Thus, cis-1,2 -dimethylcyclohexane shows, at low temperature, a splitting phenomenon quite similar to 4 with all carbons different.[10] trans-1,2-Dimethylcyclohexane, like 5, exists as two diasteromers, axial-axial and equitorial-equitorial with, of course, very different energies.

A generalized statement which covers all cases of this type of isomerism would be as follows. In a symmetrical molecule containing two contiguous chiral centers, two isomers exist (with free rotation), meso and dl. If bond rotation is restricted and if an anti conformation is prohibited, the remaining gauche forms of the meso isomer will be enantiomers, but all of the atoms within a single enantiomer will be different. In the dl isomer, with the same restrictions, the remaining gauche forms will be diasteromers and will, presumably, consist of enantiomeric pairs.

The mechanism for this reaction is almost surely a simple pairing of radicals similar to that generally accepted for phenoxy radicals.[11] In the strong base medium, 1 is present in equilibrium with an anion such as 7.[12] This ion should be easily oxidized to a radical which can be written as 8a or 8b. Coupling of 8a and 8b will give 3 (a and b), and coupling of 8b with itself will give 4 and 5.

In 1972, O'Rell, Lee, and Boekelheide[13] reported that nickel peroxide oxidation of 1 yielded two



dehydrodimers melting at 158-160°C and at 141-147°C. Structures 4 and 5 were assigned to these two compounds, but it was not ascertained which was which. Unfortunately, samples of these compounds are not available for comparison, and only an IR spectrum of the isomer melting at 158-160°C was obtained.[14] This spectrum was quite different from those of 4 and 5, but was similar (identical from 2-10 μ and similar beyond 10 μ) with that of our mixture 3. In an attempt to resolve this problem, we repeated the nickel peroxide work and obtained two materials melting at 160-161°C and 151-153°C. The material melting at 160-161°C was identical in all respects with our electrooxidation products, 3. Since 3 does exist as a mixture of atropisomers, it is possible that the previous authors had a sample of 3 with different proportions of 3a and 3b (thus accounting for the similar, but not identical spectra). Our compound melting at 151-153°C from the nickel peroxide reaction contains extra oxygen and has not been characterized due to lack of material. We do not know what the low melting compound of O'Rell and coworkers is.

Several other materials seemed to be formed in the reactions, as seen by T.L.C., but none were crystalline or available in substantial amounts for further work.

EXPERIMENTAL

General. *Melting points were taken on a Kofler hot-stage apparatus and are corrected.* ^{13}C spectra were measured on a Bruker HA-90 spectrometer. All evaporations were carried out on a vacuum rotary evaporator.

The Electrochemical Cell. The cell itself was a 250 ml beaker closed with a large Neoprene stopper containing holes for the electrode contacts and nitrogen stream. The cathode was platinum (1 × 1.5 cm), and the anode was graphite felt (4.5 × 6.5 cm, obtained as WDF felt from Union Carbide Corp., Carbon Products Division, New York). The cathode was segregated by a sack made of duPont Nafion film (E. I. duPont, Wilmington, Delaware). A standard calomel electrode was placed

as close as possible to the anode. The anode potential was measured and controlled against the standard with a PAR Model 363 potentiostat (Princeton Applied Research, Princeton, NJ). The cell was further sealed with a soft rubber film, and especially purified nitrogen[15] was allowed to flow through the system. The contents were magnetically stirred.

Oxidation of 1. Potassium metal (0.3 g, 7.5 mmole) was added in small pieces to 125 ml of spectroscopic grade methanol, previously dried over molecular sieve 3a. The solution was preelectrolyzed at +0.5 V for 20 min. The potential was lowered to 0 V, and 0.859 g (5 mmole) of 1 was added. The potential was raised to +0.15 V, and an initial current of 47 mA was obtained. After the passage of 0.005 F of electricity, T.L.C. showed that there was no 1, and that several products had been formed. During reaction, the pH varied between 10.8 and 11.5. The reaction mixture was neutralized to pH 6-8 with Dry Ice (CO_2), and the solvent was evaporated under vacuum. The residue was partitioned between ether and water. After separation, the water was washed twice more with ether, and the combined ether extracts were dried ($MgSO_4$) and evaporated to give 0.803 g of gum. The gum was separated on a low-pressure liquid chromatography system (50-65 psi) on a column (3 × 48 cm) of silica gel (Lichrosorb Si 60, E. Merck, Darmstadt, Germany) using a mobile phase of hexane-ethyl acetate (5:3). Three major portions were obtained.

Compounds 3a and 3b. This was the first major peak to emerge. Evaporation to a small volumn gave 0.047 g of white crystals, mp 158-160°C.[16] An additional 0.031 g was obtained from the mother liquor and melted at the same point for a total yield of 9.2%: UV (EtOH) 230 nm (ε 17,680) and 272 nm (ε 8840); IR (KBr) 1452 and 1580 cm^{-1} (C=N–); m.s., 340.1937, calcd. for $C_{24}H_{24}N_2$, 340.1941; ^{13}C N.M.R. ($CDCl_3$), δ units, the two values correspond to the two isomers, 3a and 3b, not respectively: C-1, 40.5, 41.1; C-4a, 75.1 (other hidden in $CDCl_3$); C-4b, 140.3, 141.3; C-8a, 152.7, 153; C-9a, 186.9, 187.4; C-4, C-1', C-2', C-3', and C-4', 10 peaks 21.8-28.0; C-4, C-6, C-7, C-8, C-5', C-6', and C-7', 12-14 peaks 117.4-128.8; 8a' and 9a', 4 peaks 135.2-137.2

Anal. Calc. for $C_{24}H_{24}N_2$: C, 84.67; H, 7.10; N, 8.01. Found: C, 84.38; H, 7.18; N, 8.15.

Compound 4. This was the second major peak to emerge from the column. Evaporation yielded 0.08 g of 4, mp 144-147°C: UV (EtOH) 225 (ε 9775), 262 (ε 5418); IR (KBr) 1570 and 1450 cm^{-1} (C=N–); m.s. (m/e) 340.1945, Anal. Found: C, 84.44; H, 7.17; N, 8.45.

Compound 5. This was the third major peak from the column. Evaporation yielded 0.175 g (20%) of 5, mp 158-162°C: UV (EtOH) 227 nm (ε 10880) and 262 nm (ε 5048); IR (KBr) 1452 and 1580 cm^{-1} (C=N–); m.s. (m/e) 340.1942. Anal. Found: C, 84.23; H, 7.32; N, 8.08.

Reduction of 3 with $LiAlH_4$. Compound 3 (6 mg, 0.03 mmole) was dissolved in 5 ml of dry ether, and $LiAlH_4$ (0.12 g, 0.3 mmole) was added. The reaction was followed by T.L.C. (hexane-EtOAc, 5:1 on silica gel GF_{254}) for 3 h as 3 was clearly converted to 1. Hydrolysis of the reaction mixture,

extraction with ether and evaporation of the ether yielded only 1, (mp and IR spectrum). Nickel Peroxide Oxidation of 1.[13] A mixture of 0.5 g of 1 and 1.75 g of freshly prepared nickel peroxide[17] in 25 ml of ethylene glycol dimethyl ether was stirred at room temperature for 1.75 h. The solution was filtered and concentrated to a brown oil which was separated by flash chromatography[18] using hexane-ethyl acetate (5:3) on silica gel. The first zone out of the column was 1. The second zone gave, on evaporation to a small volume, 40 mg of compounds 3a and 3b as a mixture, mp 160-161°C, identical in all respects to the electrochemical product. The last zone gave a very small amount (5 mg) of material, mp 151-153°C which was not like any of our products and was not further characterized.

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