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NEIGHBORING GROUP PARTICIPATION BY THE PYRROLE NUCLEUS

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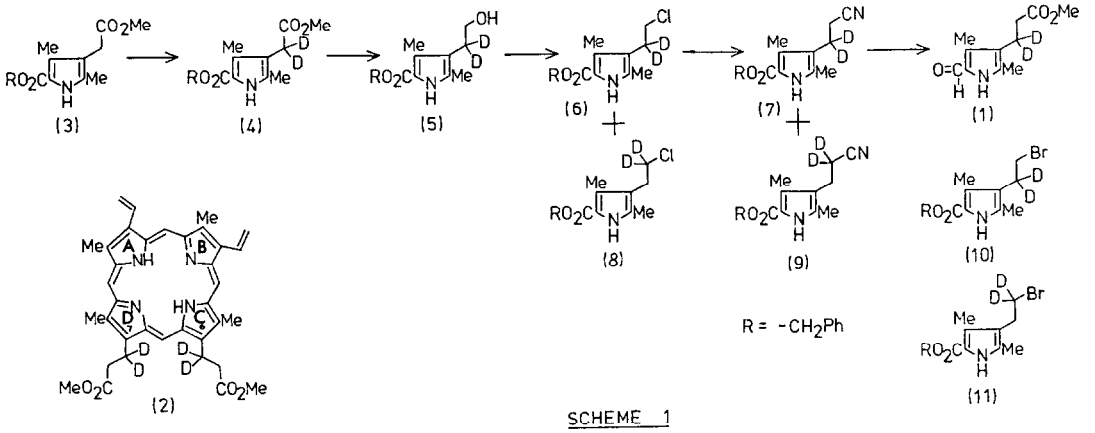
Using proton and carbon-13 NMR spectroscopy, the transformation of 2-hydroxyethylpyrroles (5,15) into 2-haloethylpyrroles by treatment with thionyl chloride or carbon tetrabromide/triphenylphosphine is shown to proceed by randomization of the two side-chain carbon atoms. A spirocyclopropylpyrrolium ion (19) is postulated as an intermediate in this unexpected process.

In connection with synthetic studies[1] undertaken to secure definitive assignments of resonances in the proton NMR spectra of heme proteins,[2] we chose a route whereby the methylene protons adjacent to the pyrrole nucleus in compound (1) would be exchanged for deuterons. The monopyrrole (1) would then be incorporated, using standard procedures,[1] into rings C and D of the protoporphyrin-IX (2) which it was planned to eventually reconstitute, as the heme, into various heme proteins. Using difference spectroscopy it would then be possible to identify the methylene protons in the 6 and 7 side-chains.

The proposed route is shown in Scheme 1, and involved standard synthetic chemistry such that the readily available[3] pyrrole (3) would be treated with MeOD/MeO^- to give (4) which would then be successively treated with diborane [to give (5)], thionyl chloride [to give (6)],[4] cyanide [to give (7)], and finally methanolyzed and formylated by the Vilsmeier procedure [to give (1)]. This sequence of transformations had already been carried out efficiently in the protio series, and in a carbon-13 enriched sequence using carbon-13 cyanide.

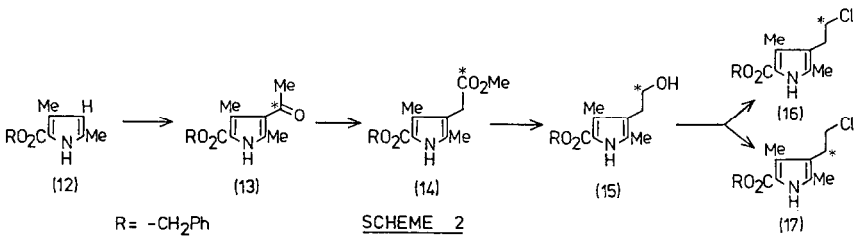
Exchange and diborane reduction proceeded in high yield[4] to give the 2-hydroxyethylpyrrole (5), the absence of α-methylene protons being established by NMR spectroscopy[5] (Figure 1). Upon treatment with thionyl chloride and pyridine[4] a quantitative yield of 2-chloroethylpyrrole was obtained, but the proton NMR spectrum (Figure 2) was not compatible with that expected for formation of (6).



SCHEME 1

Instead, the spectrum suggested that the material was a mixture of about equal amounts of (6) and (8), the lack of any coupling between the two methylene resonances suggesting a carbon rather than hydrogen/deuterium rearrangement. The 2-chloroethylpyrrole material was treated with sodium cyanide in DMSO and gave 2-cyanoethylpyrrole which, again, (Figure 3) appeared to be a mixture [of (7) and (9)]. Attempts to synthesize the corresponding 2-bromoethylpyrrole using (5) and carbon tetrabromide/triphenylphosphine similarly yielded a mixture (Figure 4) of (10) and (11), with the expected isomer (10) slightly predominating.

In order to establish that a rearrangement of the side-chain carbons was indeed taking place, the reaction sequence was repeated using carbon-13 enriched materials. Scheme 2 shows the synthetic sequence; the readily accessible pyrrole (12)[6] was acylated with 1-^{13}C-acetyl chloride and stannic chloride,[7] and gave a high yield of pyrrole (13). With thallium(III) nitrate in methanol this gave the rearranged[7] acetic ester (14) which was reduced with diborane to give



SCHEME 2

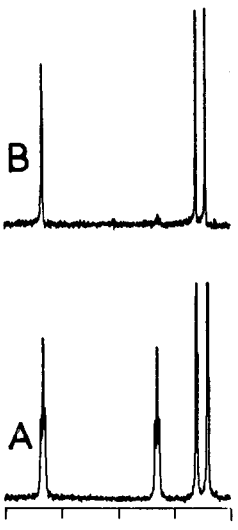


FIG. 1: Proton NMR spectra of, B, (5); A, same compound but undeuterated.

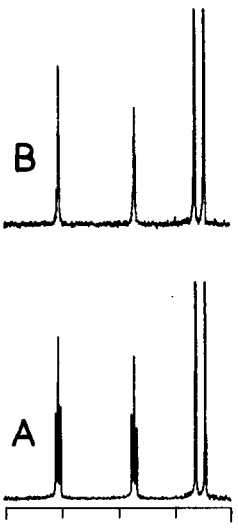


FIG. 2: Proton NMR spectra of, B, (6) and (8); A, same, but undeuterated.

FIG. 3: Proton NMR spectra of, B, (7) and (9); A, same, but undeuterated.

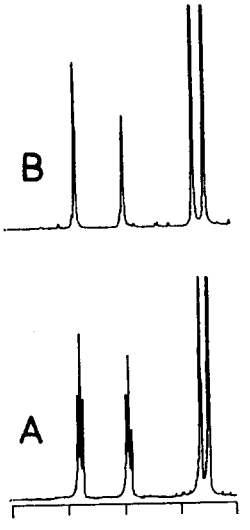


FIG. 4: Proton NMR spectra of, B,(10) and (11); A, same, but undeuterated

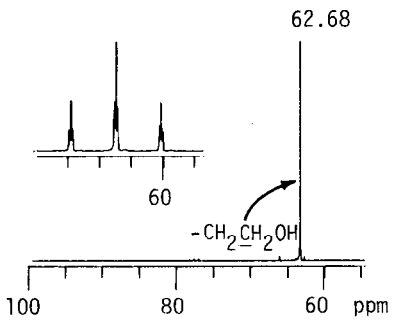


FIG. 5: Carbon-13 NMR spectrum of compound (15). The major spectrum is proton decoupled while the insert is proton undecoupled. Spectrum at 50.3 MHz.

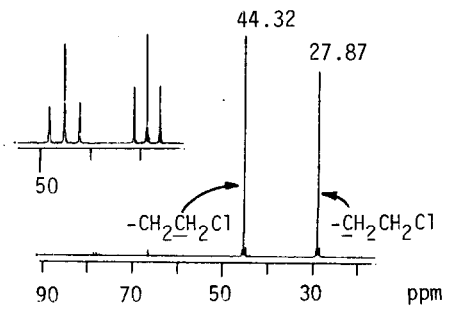
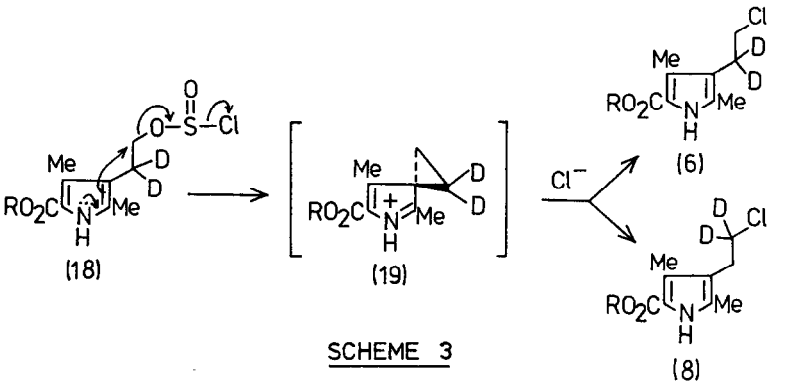


FIG. 6: Carbon-13 NMR spectrum of compounds (16) and (17) obtained from (15). The major spectrum is proton decoupled while the insert is proton undecoupled. Spectrum at 50.3 MHz.

pyrrole (15) which showed (Figure 5) only one enriched carbon. Treatment of (15) with thionyl chloride gave enriched 2-chloroethylpyrrole possessing carbon-13 enrichment in both side-chain carbons (Figure 6), thereby confirming the nature of the rearrangement.

Since neighboring group participation by aryl groups has been well-documented,[8] it seems reasonable to suggest that the key intermediate, produced from the thionyl chloride activated species (18), is the spirocyclopropylpyrrolium ion (19).

(Scheme 3). The slight predominance of (10) in the bromination reaction which is indicated by integration suggests that the mechanism involves substantially (19) in this case, but with some "direct" displacement occurring. A study of nucleophile dependence is in progress.



SCHEME 3

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