Nuclear Magnetic Resonance Determination of Substituent Methyls in Fatty Acids[1]

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In spite of the plethora of applications of n.m.r. spectroscopy to elucidation of structural problems, there appears to be a paucity of data on application of this tool in the field of branched-chain fatty acids, perhaps on account of the limited availability of the necessary compounds. Since a wide variety of branched-chain acids has been synthesized in this laboratory,[3] appropriate compounds have been examined in order that the quantitative and qualitative applications of n.m.r. spectroscopy might be ascertained. Data on the more interesting compounds are presented here.

Quantitative determination of the number of methyl groups in branched-chain acids has been proposed, by comparison of the area of the band due to methyl hydrogens with that due to methylene and methinyl hydrogens.[4] We have found this method to be hopelessly inaccurate on account of overlap of the two bands, which is extensive for multibranched acids. Any error in extrapolation becomes multiplied by two since the overlapping bands are those whose ratio is being examined. This pyramiding of error is avoided, however, if the methyl ester is used for the determination, and the point of reference is established as the area of the unsplit, isolated band (about τ 6.35) attributed to the signal from the three protons in methoxyl (*cf.* Fig. 1).

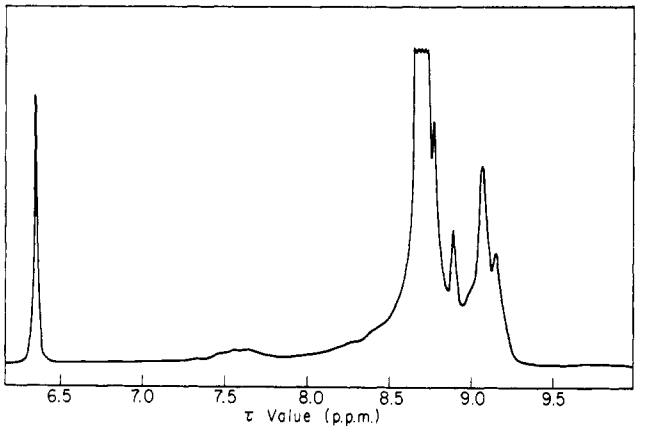

Fig. 1.—Tracing of n.m.r. spectrum of methyl 2,4,6-trimethylhexacosanoate (27 mg./0.4 ml. of carbon tetrachloride).

Data assembled in Table I illustrate that this method gives reliable results for substituent methyl groups until the number of such groups reaches four. For four or more methyl groups, the extrapolated area for the methyl band is consistently too large, an effect which has been noted in analysis of hydrocarbons in petroleum.[5]

TABLE I

QUANTITATIVE DETERMINATION OF METHYL GROUPS IN BRANCHED-CHAIN FATTY ACIDS

Methyl ester	No. of methyl groups	Area of methyl groups[a] / Area of methoxyl group
Stearate	1	1.13
Tetracosanoate	1	1.10
2-Methylheptadecanoate[b]	2	2.19 (1.00)
3-Methyloctadecanoate[b]	2	1.96
4-Methyloctadecanoate[b]	2	2.00
17-Methyloctadecanoate[b]	2	2.31
2-Ethyloctadecanoate	2	3.00
2,4-Dimethyldocosanoate	3	(1.83, 1.85)
2,5-Dimethylheptadecanoate[b]	3	3.00 (1.90)
4,8,12-Trimethyloctadecanoate	4	4.95
2,3,4-Trimethylhexadecanoate	4	(3.96)
2,4,6-Trimethyldocosanoate[c]	4	(3.80)
2,4,6-Trimethylhexacosanoate[d]	4	(4.12, 3.86)

[a] Values in parentheses were determined with exclusion of the area of the 2-methyl doublet, which is embedded in the edge of the methylene band (*e.g., cf.* Fig. 1). Areas were determined with a planimeter on the resultant bands after the overlapping bands had been extrapolated to their theoretical shape if alone. [b] *Cf.* Fig. 2. [c] *Cf.* J. Cason, P. Tavs, and A. Weiss, *Tetrahedron*, **18**, 437 (1962). [d] *Cf.* Fig. 1, also J. Cason, G. L. Lange, W. T. Miller, and A. Weiss, *Tetrahedron*, **20**, 91 (1964).

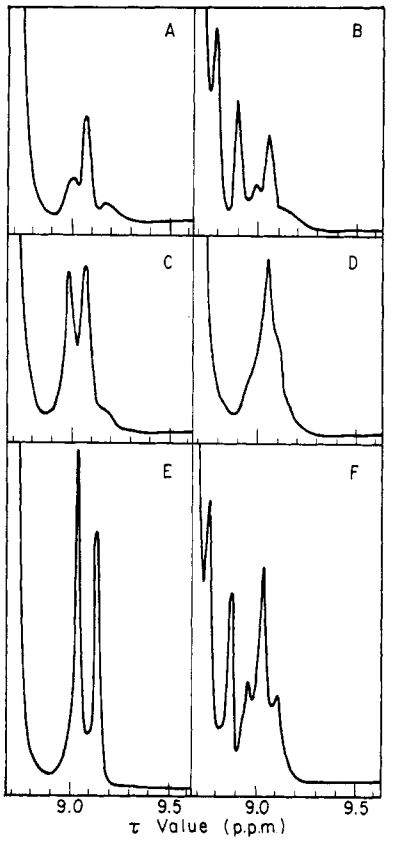

Fig. 2.—Methyl region of the n.m.r. spectra of the methyl esters of branched-chain acids: A, stearate; B, 2-methylheptadecanoate; C, 3-methyloctadecanoate; D, 4-methyloctadecanoate; E, 17-methyloctadecanoate; F, 2,5-dimethylheptadecanoate.

Even for the larger numbers of methyls, however, results are reproducible, and the number of substituent methyls in an unknown structure may be established by comparison with known compounds. In the case of

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(3) For paper XXXVI in the series "Branched-Chain Fatty Acids," see J. Cason and D. J. McLeod, *J. Org. Chem.*, **23**, 1497 (1958).

(4) M. Sonneveld, P. Haverkamp-Begemann, G. J. van Beers, R. Keunig, and J. C. M. Schogt, *J. Lipid Res.*, **3**, 351 (1962).

(5) B. J. Mair, N. C. Krouskop, and T. J. Mayer [*J. Chem. Eng. Data*, **7**, 420 (1962)] used electronic integration of the signal and also ascribed the error to band overlap.

a 2-ethyl substituent, the methyl band is similar in shape to that from a normal acid,[6] but there is more overlap, and the error is surprisingly large (*cf.* Table I). This appears to be a persistent difficulty with branches larger than methyl. In the case of methyl 4-butyl-4-ethylnonanoate, the overlap of the methyl and methylene bands was so extensive that extrapolation was not attempted.

The location of a methyl group at the 2- or 3-position appears reliable. The 2-methyl doublet (J = 6 c.p.s.) appears downfield from the other methyl protons, never quite buried in the huge methylene band (Fig. 1, 2B, 2F). In addition, the multiplet for the single proton in the 2-position is centered at about τ 7.62 (*cf.* Fig. 1), whereas the triplet for a 2-methylene group is centered in the region τ 7.70–7.75. In the case of 2,2-dimethyloctadecanoate, the unsplit band for the two α-methyls is shifted downfield to τ 8.83.

In the case of the 3-methyl substituent, the 2-methylene band is an unsymmetrical doublet, with the major peak (the upfield one, as expected) at τ 7.87. The doublet for the 3-methyl substituent (Fig. 2C) is shifted significantly downfield and lies on the band from the terminal methyl so as to give the appearance of one split band. It is readily distinguished from the split band from the terminal isopropyl group (Fig. 2E), for the latter has sharper peaks, is somewhat upfield, and shows the expected greater intensity for the lower-field segment.

A methyl substituent more remote from carboxyl than the 3-position results in a combined methyl band of rather ill-defined appearance (Fig. 2D), and nothing can be learned of the location. The tracing from 6-methyloctadecanoate is nearly identical with that from 4-methyloctadecanoate.

Determination of spectra was accomplished on a Varian A-60 instrument, operating at 60 Mc./sec., with 6–8% solutions of the esters in carbon tetrachloride. Tetramethylsilane was used as external standard.

(6) The unsymmetrical triplet for the terminal methyl, of the same form as in *n*-alkanes, has previously been noted; *e.g.*, *cf.* C. R. Smith, Jr., T. L. Wilson, R. B. Bates, and C. R. Scholfield, *J. Org. Chem.*, **27**, 3112 (1962).

Phenylation of Dinitroalkanes

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Publication by Kornblum and Taylor[1] of the method of phenylating nitroalkanes using Beringer's[2] diphenyliodonium salts prompts us to add a note on phenylation of dinitroalkanes. Using diphenyliodonium tosylate in *t*-butyl alcohol as solvent, phenyl derivatives of 1,1-dinitropropane and 1,1-dinitroethane were obtained from the potassium salts of the dinitroalkanes in 67 and 68% yields, respectively. Yields were less than 5% in N,N-dimethylformamide at room temperature in contrast to Kornblum's findings with mononitroalkanes.

We were unable to phenylate the potassium salts of phenylnitromethane and phenyldinitromethane in either solvent.

(1) N. Kornblum and H. J. Taylor, *J. Org. Chem.*, **28**, 1424 (1963).

(2) F. M. Beringer and P. S. Forgione, *Tetrahedron*, **19**, 739 (1963).

Experimental

Potassium 1-Nitropropylnitronate.[3,4]—In a 1-l. three-necked flask equipped with a mechanical stirrer, thermometer, and dropping funnel, and cooled with an ice bath, potassium nitrite (85 g., 1 mole) was dissolved in 140 ml. of water. To this was added a solution of 124 g. (1 mole) of 1-chloro-1-nitropropane in 280 ml. of 95% methanol. The temperature was maintained between 0 and 10° while a cold solution of 1 mole of potassium hydroxide in 150 ml. of 95% methanol was added over a 15 min. period. Stirring was continued for 15 min. after completion of the addition and the reaction mixture was allowed to stand overnight in the refrigerator.

The yellow salt was stirred in 300 ml. of warm water to remove large amounts of potassium chloride, cooled in ice, and collected on a Buchner funnel, yielding 150–160 g. (87–93%). The dry potassium 1-nitropropylnitronate can be detonated but can be safely stored at room temperature for at least 10 years!

The less stable potassium salt of 1,1-dinitroethane[4] was prepared in like manner.

1,1-Dinitro-1-phenylpropane.—Equimolar amounts of potassium 1-nitropropylnitronate (8.00 g., 0.0495 mole) and diphenyliodonium tosylate[1,5] (22.30 g., 0.0495 mole) in 800 ml. of dry *t*-butyl alcohol were refluxed for 6 hr. The precipitated potassium tosylate was removed by filtration and the solvent was removed at ambient temperatures on a rotating evaporator.

The crude oily mixture was run onto a chromatographic column of acid-free alumina. Elution with petroleum ether (b.p. 30–60°) first removed iodobenzene and then 1,1-dinitro-1-phenylpropane as a pale yellow oil. Distillation at reduced pressure gave 7.0 g. (67%) of colorless product, b.p. 136° (4 mm.), n^{25}D 1.5270; d^{25}_4 1.2340.

The infrared spectrum verified the presence of the *gem*-dinitro group with absorption at 7.45 and 7.55 μ.[6] The n.m.r. spectrum verified the presence of one ethyl and one phenyl group in the compound.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.40; H, 4.80; N, 13.34. Found: C, 51.46; H, 4.88; N, 13.69.

1,1-Dinitro-1-phenylethane was prepared in a similar manner in 68% yield, b.p. 82–83° (2 mm.), n^{25}D 1.5320, d^{25}_4 1.2875.

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.97; H, 4.11; N, 14.27. Found: C, 49.13; H, 4.29; N, 14.40.

In N,N-dimethylformamide, the reaction took a different course. Nine grams (0.020 mole) of diphenyliodonium tosylate and 3.24 g. (0.020 mole) of potassium 1-nitropropylnitronate was dissolved in 15 ml. of dry N,N-dimethylformamide[7] by mechanical stirring at room temperature. Within 5 min. an exothermic reaction started but the temperature was kept at 25° by efficient cooling and stirring. After standing overnight the reaction mixture was poured into 100 ml. of ice–water and extracted with 250 ml. of ether in five portions. The ether extract was dried over anhydrous sodium sulfate, reduced to small volume by evaporation, and put on a chromatographic column of alumina. Elution with petroleum ether first gave iodobenzene and then 1.77 g. (72%) of nitrobenzene (b.p. 210°). The infrared spectrum of the nitrobenzene showed only a small absorption at the expected position for a *gem*-dinitro group (*vide supra*), estimated to indicate less than 5% phenylation of the dinitroalkane. The ultimate fate of the alkyl carbons, not immediately apparent, is under investigation.

(3) Preparation worked out by J. S. Belew, R. J. Labrie, and D. E. Bisgrove and supported in part by the Office of Ordnance Research Grant DA-19-020-ORD-592.

(4) E. ter Meer, *Ann.*, **181**, 1 (1876); H. Shechter and L. Zeldin, *J. Am. Chem. Soc.*, **73**, 1276 (1951).

(5) F. M. Beringer, R. A. Falk, M. Karniol, I. Lillien, G. Masullo, M. Mausner, and E. Sommer, *ibid.*, **81**, 342 (1959).

(6) J. S. Belew, C. E. Grabiel, and L. B. Clapp, *ibid.*, **77**, 1110 (1955).

(7) E. Müller, "Methoden der Organische Chemie," Vol. 1, 4th Ed., Georg Thieme Verlag, Stuttgart, 1959, p. 831.