NMR Structure Determination of Some New 4-Hydroxyxanthone Derivatives

PIERO VALENTI, GIULIO CECCARELLI, and PAOLO DA RE
Department of Chemistry, University of Pisa, 56100 Pisa, Italy

Nuclear magnetic resonance spectra of a number of 4-hydroxyxanthone derivatives are reported. These spectra substantiate the proposed structure of substitution products. In the particular case of 4-methoxyxanthones, the presence of a long-range coupling between aromatic protons and the methoxy group has been observed.

AS A CONTINUATION of earlier studies of the xanthone group (*4, 5*) we report some substitution reactions on 4-hydroxyxanthone which, in comparison with the 1-, 2-, and 3-hydroxy isomers, has had less attention.

We have examined the following reactions: acylation (according to Friedel-Crafts and Fries), aminomethylation (Mannich), bromination, chloromethylation, Elbs oxidation, nitration, and sulfonation. Such reactions are summarized in Figure 1.

The structure of the resulting products was mainly demonstrated by nuclear magnetic resonance spectroscopy. The results, compared with those obtained with 8-hydroxy-2,3-dimethylchromone (*3*), are remarkably different. The unreactivity of 4-hydroxyxanthone in the Friedel-Crafts and Fries acylations (*12*) has been confirmed for a variety of conditions. 8-Hydroxy-2,3-dimethylchromone, on the contrary, gives a 7-acyl derivative (*3*).

The Mannich reaction, extensively studied on 1-, 2- (*13*), and 3-hydroxyxanthone (*1, 2, 5*), appears to be described only for 1-methyl-4-hydroxythioxanthone (*13*). With compound Ia, four Mannich bases were prepared, to which the structure of 1-substituted derivatives (IIc, d, e, f) has been assigned on the basis of NMR data. The aromatic protons of the substituted ring of compound IIf give an *AB* spectrum (*14*) due to the hydrogens in positions 2 and 3 with a typical ortho-coupling constant (J_{23} = 8.2 cps). The high field signal centered at 6.91 ppm, showing a long-range coupling (J = 0.7 cps), is to be assigned to H_2 hydrogen. The additional coupling between the methylene hydrogens of the morpholinomethyl group and

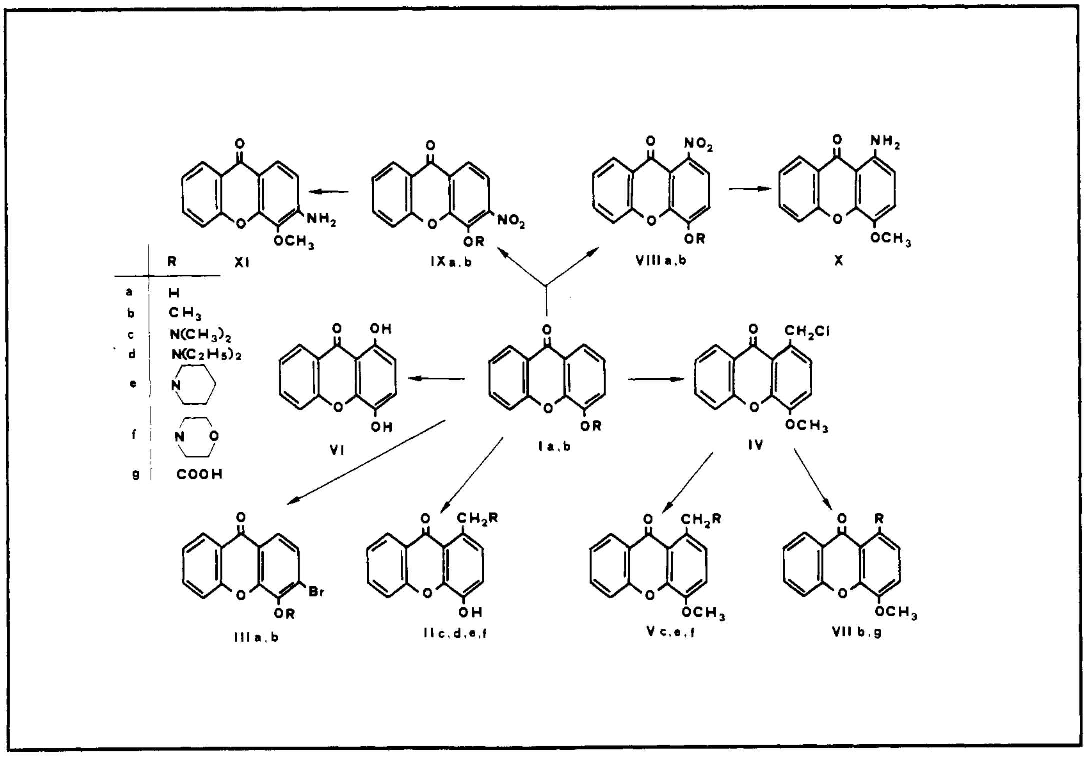


Figure 1. Substitution reactions of 4-hydroxyxanthone

H_2 has been confirmed by the double resonance technique. This *AB* pattern would also be valid for 3,4-disubstituted xanthones; however, the absence of a very strong deshielded proton excludes them. A hydrogen in the 1-position (as is evident for hydrogen in the 8-position) should actually be deshielded on account of the *peri* effect due to the cyclic carbonyl group (*10*).

The bromination of Ia in acetic acid yields a compound to which, according to the NMR spectrum of its methyl ether (IIIb), the structure of 3-bromo-4-hydroxyxanthone (IIIa) is to be assigned. Indeed, the presence of another hydrogen, beyond H_8, at a low field position ($\delta = 7.90$ ppm) suggests that the 1-position is free and therefore the H_1 hydrogen experiences the *peri* deshielding effect of the proximal carbonyl group. The actual chemical shift is not identical with that of H_8 for the simultaneous shielding by bromine atom in the meta position. In substituted aromatic systems the halogen atoms deshield the ortho as well as the para positions, but shield the meta one (*6*).

The chloromethylation of Ib yields only a chloromethyl derivative (IV) which, by reaction with secondary bases, gives the corresponding *N*-disubstituted aminomethyl derivatives (Vc, e, f). Because of the insolubility of IV, the NMR of this compound could not be determined. Its structure was then inferred from that of compounds Vf and VIIb, the latter obtained by catalytic hydrogenation of IV. The *AB* pattern for the NMR spectrum of protons of the substituted ring of Vf and VIIb is again recognizable. The NMR pattern of the H_2 doublet of Vf is perhaps more correctly described as having a triplet fine structure (the true pattern would therefore be ABX_2); likewise, for the corresponding H_2 doublet of VIIb a quartet fine structure (ABX_3 pattern) is noticeable. The magnitude of the above additional couplings ($J = 0.7$ cps for both) suggests that these are to be ascribed to an allylic coupling between H_2 and the $-CH_2-N<$ group (for Vf) or the methyl group for (VIIb). These couplings have been confirmed by the double resonance technique; by irradiating the methyl group of VIIb, it is possible to notice the disappearance of the H_2 quartet fine structure and also that the *a,b* lines of H_3 are lower than the corresponding *c,d* lines of H_2 (Figure 2, *B*). The line widths at half height are 0.76 and 0.40 cps, respectively. Since, in this manner the methyl couplings with H_2 ($J = 0.7$ cps) as well as with H_3 are eliminated, the broadening of H_3 lines ought to be assigned to a long-range coupling with the protons of the methoxy group. The presence of this coupling, pointed out by Farid (*7*) on some methoxy (ring A) flavone derivatives, has been confirmed in the present case. By irradiating the methoxy group of VIIb, according to the double resonance technique, the spectrum of Figure 2, *C*, was obtained, the line width of H_3, at half height, is now 0.35 cps. The use of the triple resonance, by simultaneously irradiating with two distinct oscillators the methyl and the methoxy groups of VIIb, has made it possible to obtain a clear *AB* type spectrum (Figure 2, *D*); the line widths

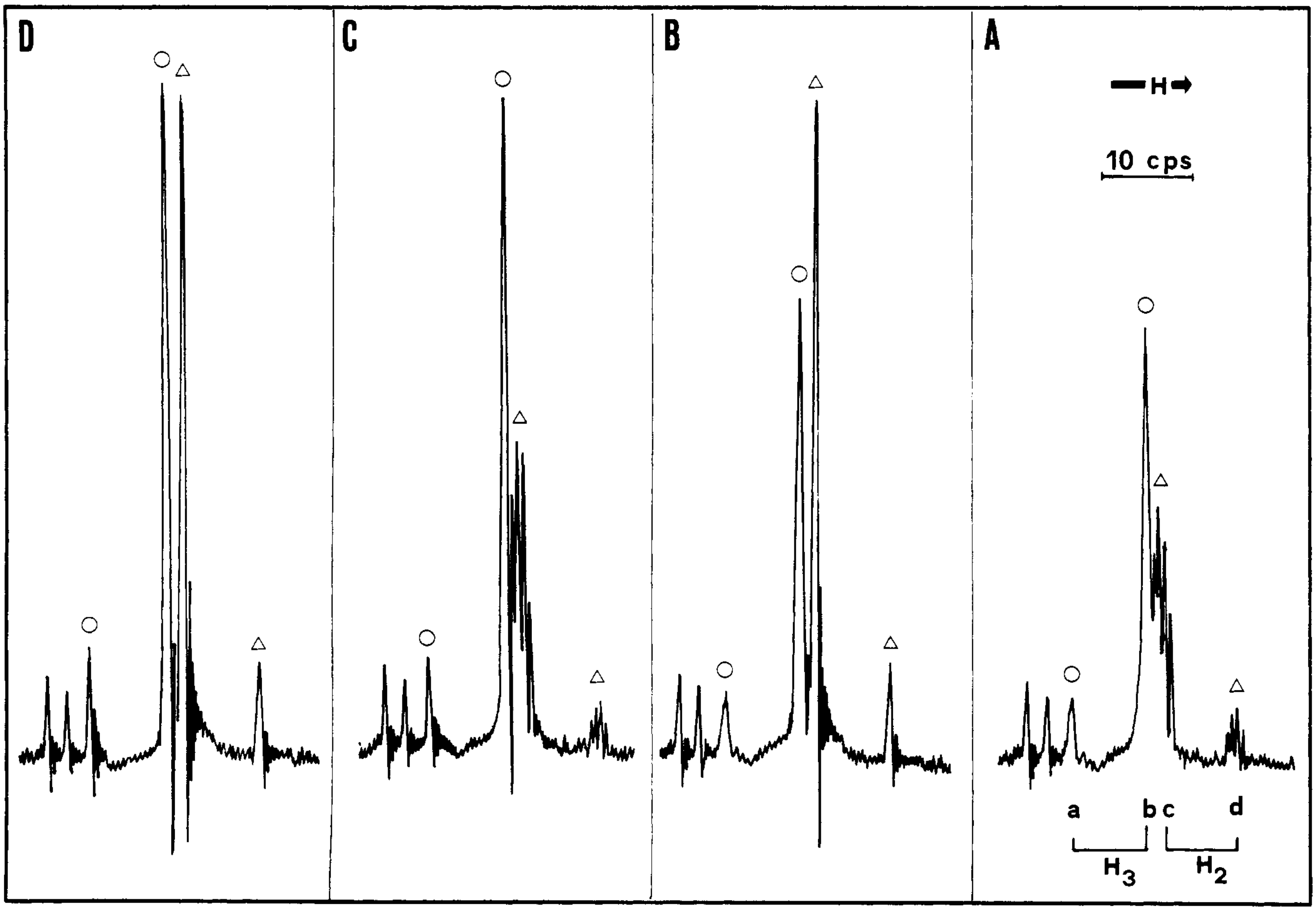


Figure 2. Proton resonance spectra of H_2 and H_3 regions of 1-methyl-4-methoxyxanthone (VIIb) at 60 Mc/s

△ Lines relative to H_2
○ Lines relative to H_3
A. Undecoupled
B. Decoupled from CH_3
C. Decoupled from OCH_3
D. Decoupled from CH_3 and OCH_3 (triple resonance)

at half height are 0.35 and 0.40 cps for H_2 and H_3, respectively. Similar results are obtained with compound Vf, which, after simultaneous decoupling of methoxy and methylene groups, shows line widths of 0.35 and 0.28 cps for H_2 and H_3 protons. From calculations on line widths we have found, in both cases, a value of $\sim$0.15 cps for $J_{OMe\text{-}H_3}$.

Elbs oxidation of Ia leads to 1,4-dihydroxyxanthone (VI), identical with a sample prepared according to Fujikawa and Nakamura (*8*). This compound presents, for the aromatic protons of the substituted ring, a simple *AB* spectrum with the H_2 doublet centered at 6.62 ppm and the H_3 doublet centered at 7.30 ppm, with the relative chemical shifts in the same order observed in the aromatic rings of xanthone (*11*). The presence of a symmetrical hydroxy disubstitution in VI shifts both the H_2 and H_3 protons to higher fields by 0.5 to 0.7 ppm in comparison with the parent compound.

The nitration of Ia in concentrated sulfuric acid gives rise to a mixture of 1-nitro- (VIIIa) and 3-nitro-4-hydroxyxanthone (IXa). By fractional extraction of the crude nitration mixture with ligroin, the two isomers could be separated. The nitration of Ib seems to lead to a single product (VIIIb).

The catalytic reduction of VIIIb yields X, whose NMR spectrum has been measured. This spectrum, relative to the aromatic hydrogens of the substituted ring, again shows an *AB* pattern, with an upfield shift (0.5 ppm) of H_3 due to the presence of a methoxy group and a greater shift of H_2 (1 ppm) in the same direction as a consequence of the substitution of an amino group in the 1-position.

The sulfonation of Ia with concentrated sulfuric acid as well as with fuming sulfuric acid and chlorosulfonic acid has given no positive results.

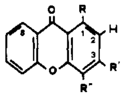
The chemical shifts and coupling constants values for the compounds examined are collected in Table I.

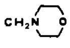
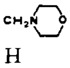
EXPERIMENTAL

The NMR spectra were obtained from samples dissolved in deuterated chloroform ($CDCl_3$) on a Varian DA-60-IL spectrometer operating at 60 Mcps. The shifts are in parts per million relative to tetramethylsilane (TMS) as internal reference and coupling constants are in cycles per second (cps). They were determined with the aid of a Marconi TF2414 frequency counter. The double and triple resonance experiments were performed using two identical Hewlett-Packard 204 C variable audio oscillators.

Mannich Reaction on 4-Hydroxyxanthone (General Procedure). An aqueous solution of 40% formaldehyde (0.01 mole) was added dropwise to a mixture of 4-hydroxyxanthone (Ia) (0.01 mole) and the secondary amine (0.01 mole) in 50 ml of ethanol. The reaction mixture was refluxed for 5 to 6 hours and after the volatile materials had been removed under vacuum, the residue was treated with water and the insoluble fraction extracted with chloroform and dried. Removing the solvent left the crude product, which was crystallized from ligroin.

Table I. δ and *J* Values of Some Substituted Xanthones



Compound	R	R′	R″	δ_{H_1}	δ_{H_2}	δ_{H_3}	$J_{H_1H_2}$	$J_{H_2H_3}$
[a]	H	H	H	8.36	7.38	7.73	7.96	7.14
X	NH_2	H	OCH_3	...	6.33	7.11	...	8.75
VIIb	CH_3	H	OCH_3	...	6.89	6.96	...	8.62
Vf		H	OCH_3	...	7.15	7.46	...	8.52
VI	OH	H	OH	...	6.62	7.30	...	8.80
IIf		H	OH	...	6.91	7.70	...	8.21
IIIb	H	Br	OCH_3	7.90	7.51	...	8.55	...

[a] Xanthone unsubstituted, from (*11*). Chemical shifts in ppm from TMS as internal reference. Coupling constants in cps.

1-DIMETHYLAMINOMETHYL-4-HYDROXYXANTHONE (IIc). White crystalline solid, m.p. 169–71° C. Analysis. Calculated for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C 71.30; H, 5.55; N, 5.00.

1-DIETHYLAMINOMETHYL - 4 - HYDROXYXANTHONE (IId). White crystalline product, m.p. 131–32° C. Analysis. Calculated for $C_{18}H_{19}NO_3$: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.50; H, 6.50; N, 4.57.

1-PIPERIDINOMETHYL-4-HYDROXYXANTHONE (IIe). White crystalline product, m.p. 127–28° C. Analysis. Calculated for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.75; H, 6.15; N, 4.65.

1-MORPHOLINOMETHYL-4-HYDROXYXANTHONE (IIf). White crystalline product, m.p. 148–50° C. Analysis. Calculated for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.35; H, 5.60; N, 4.30.

3-BROMO-4-HYDROXYXANTHONE (IIIa). To a solution of 2.12 grams of 4-hydroxyxanthone in 100 ml of acetic acid, a solution of 1.6 grams of bromine in 20 ml of acetic acid was added at 40° C and the reaction mixture was left to stand overnight. On pouring the acetic solution in water, a solid was separated and collected by filtration. On crystallizing the crude product from ethanol, 2.5 grams of white crystalline solid were obtained, m.p. 292–93° C. Analysis. Calculated for $C_{13}H_7BrO_3$: C, 53.64; H, 2.42; Br, 27.45. Found: C, 53.60; H, 2.40; Br, 27.35.

3-BROMO-4-METHOXYXANTHONE (IIIb). White crystalline product (from aqueous ethanol), m.p. 140–41° C. Analysis. Calculated for $C_{14}H_9BrO_3$: C, 55.11; H, 2.97; Br, 26.19. Found: C, 55.20; H, 2.85; Br, 26.10.

1-CHLOROMETHYL-4-METHOXYXANTHONE (IV). A mixture of 1.5 grams of compound Ib, 15 ml of concentrated hydrochloric acid, 15 ml of acetic acid, and 0.5 gram of paraformaldehyde was stirred at 80° C for 5 hours. During this time a stream of dry hydrochloride gas was passed into the reaction mixture. After cooling, the reaction mixture was poured into water and the separated solid collected by filtration, washed with water, and dried. Crystallization from ethyl acetate gave 1 gram of product, m.p. 225–26° C. Analysis. Calculated for $C_{15}H_{11}ClO_3$: C, 65.58; H, 4.03; Cl, 12.90. Found: C, 65.60; H, 4.01; Cl, 12.83.

Condensation of 1-Chloromethyl-4-methoxyxanthone (General Procedure). To a solution of IV (0.01 mole) in 30 ml of benzene, a secondary base (0.02 mole) was added and the reaction mixture refluxed for 4 to 5 hours. The benzene solution, transferred in a separatory funnel, was repeatedly washed with water and then dried. Removal of the solvent left a residue which was crystallized from ligroin.

1-DIMETHYLAMINOMETHYL-4-METHOXYXANTHONE (Vc). White crystalline product, m.p. 134–35° C. Analysis. Calculated for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.04; N, 4.94. Found: C, 71.96; H, 6.10; N, 5.00.

1-PIPERIDINOMETHYL-4-METHOXYXANTHONE (Ve). White crystalline product, m.p. 119–20° C. Analysis. Calculated for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.54; N, 4.33. Found: C, 74.30; H, 6.50; N, 4.10.

1-MORPHOLINOMETHYL-4-METHOXYXANTHONE (Vf). White crystalline product, m.p. 164–65° C. Analysis. Calculated for $C_{19}H_{19}NO_4$: C, 70.13; H, 5.88; N, 4.30. Found: C, 70.00; H, 6.02; N, 4.15.

1-CARBOHYDROXY-4-METHOXYXANTHONE (VIIg). A mixture of 1.2 grams of compound IV, 3 grams of potassium permanganate, and 1.5 grams of sodium carbonate in 100 ml of water was refluxed for 3 hours. At the beginning of the third hour 2 grams of potassium permanganate were added. The mixture was filtered hot and the filtrate acidified with 20% hydrochloric acid. The separated solid was collected by filtration, washed with water, and dried. Crystallization of the crude product from ethanol gave 0.5 gram of white crystalline solid, m.p. 263-65° C. Analysis. Calculated for $C_{15}H_{10}O_5$: C, 66.66; H, 3.73. Found: C, 66.67; H, 3.76.

1-METHYL-4-METHOXYXANTHONE (VIIb). A solution of 1 gram of compound IV in 50 ml of tetrahydrofuran was hydrogenated over 5% palladized charcoal, under the usual conditions, until the hydrogen uptake ceased. The solution was filtered from the catalyst and evaporated to dryness. The residue on crystallizing from ethanol gave 0.7 gram of white crystalline product, m.p. 168-69° C. Analysis. Calculated for $C_{15}H_{12}O_3$: C, 74.98; H, 5.03. C, 75.00; H, 4.96.

1,4-DIHYDROXYXANTHONE (VI). A solution of 2.1 grams of compound Ia in 100 ml of 0.1*N* sodium hydroxide was added dropwise in 2 to 3 hours under 20° C to 3 grams of potassium persulfate dissolved in a minimum of water. The reaction mixture was left to stand overnight and then treated with an excess of concentrated hydrochloric acid and boiled for 0.5 hour. After cooling, the solution was extracted with ether and the ethereal extract, after drying, evaporated. The residue on crystallizing from methanol gave 1.1 grams of light yellow product, m.p. 231-33° C [lit. (*8*) 236-37° C]. Analysis. Calculated for $C_{13}H_8O_4$: C, 68.42; H, 3.53. Found C, 68.65; H, 3.65.

3-NITRO-4-HYDROXYXANTHONE (IXa). Three grams of compound Ia dissolved in 50 ml of concentrated sulfuric acid were nitrated by adding at 0° C a solution of 0.8 ml of nitric acid (d = 1.42) in 2 ml of concentrated sulfuric acid. On pouring the reaction mixture in water a solid is separated, collected by filtration, washed with water, and dried. The crude product (a mixture of VIIIa and IXa) was extracted with boiling ligroin. The concentration of the ligroin extract gave 1.2 grams of IXa. Crystallization from ethanol gave an analytical sample, m.p. 215-17° C. Analysis. Calculated for $C_{13}H_7NO_5$: C, 60.70; H, 2.74; N, 5.44. Found: C, 60.56; H, 2.60; N, 5.59.

3-NITRO-4-METHOXYXANTHONE (IXb). White crystalline product, m.p. 144-45° C. Analysis. Calculated for $C_{14}H_9NO_5$: C, 61.99; H, 3.34; N, 5.16. Found: C, 61.95; H, 3.30; N, 5.26.

1-NITRO-4-HYDROXYXANTHONE (VIIIa). The residue of the preceding extraction, after crystallization from ethanol, gave 1.4 grams of light yellow solid, m.p. 251-53° C. dec. Analysis. Calculated for $C_{13}H_7NO_5$: C, 60.70; H, 2.74; N, 5.44. Found: C, 60.60; H, 2.84; N, 5.54.

1-NITRO-4-METHOXYXANTHONE (VIIIb). May be obtained by methylating VIIIa or by direct nitration of Ib. White crystalline product, m.p. 250-51° C. Analysis. Calculated for $C_{14}H_9NO_5$: C, 61.99; H, 3.34; N, 5.16. Found: C, 61.90; H, 3.32; N, 5.18.

1-AMINO-4-METHOXYXANTHONE (X). A solution of 0.6 gram of compound VIIIb in 200 ml of tetrahydrofuran was hydrogenated over 5% palladized charcoal, under the usual conditions, until hydrogen uptake ceased. The solution was filtered from the catalyst and evaporated to dryness. Crystallization of the residue from methanol gave 0.4 gram of an orange colored product, m.p. 169-70° C [lit. (*9*) 169-69.5° C]. Analysis. Calculated for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.60; H, 4.55; N, 6.10.

3-AMINO-4-METHOXYXANTHONE (XI). With the procedure described for X, 0.2 gram of compound IXb gave 0.1 gram of a yellow crystalline product, m.p. 200-03° C, from ligroin. Analysis. Calculated for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.55; H, 4.45; N, 6.05.

ACKNOWLEDGMENT

The authors are indebted to Giuseppe Cilia for his technical assistance.

LITERATURE CITED

(1) Agasimundin, Y.S., Rajagopal, S., *J. Indian Chem. Soc.* **41**, 471 (1964).
(2) Angadiyavar, C.S., Agasimundin, Y.S., Rajagopal, S., *J. Karnatak Univ.* **11**, 52 (1966).
(3) Da Re, P., Cimatoribus, L., *Ber.* **95**, 2912 (1962).
(4) Da Re, P., Mancini, V., Toth, E., Cima, L., *Arzneim. Forsch.* **18**, 718 (1968).
(5) Da Re, P., Sagramora, L., Mancini, V., Valenti P., Cima, L., *J. Med. Chem.* **13**, 527 (1970)
(6) Emsley, J.W., Feeney, J., Sutcliffe, L.H., "High-Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. **11**, pp. 704-61, Pergamon Press, Oxford, 1966.
(7) Farid, S., *Tetrahedron* **24**, 2121 (1968).
(8) Fujikawa, T., Nakamura, I., *J. Pharm. Soc. Japan* **64**, 2746 (1944).
(9) Koelsch, C.F., Lucht, F.J., *J. Amer. Chem. Soc.* **71**, 3557 (1949).
(10) Martin, R.H., Defay, N., Geerts-Evrard, F., Given, P.H., Jones, J.R., Wedel, R.W., *Tetrahedron* **21**, 1833 (1965).
(11) Mathis, C.T., Goldstein, J.H., *Spectrochim. Acta* **20**, 871 (1964).
(12) Mustafa, A., Hismat, O.H., *J. Amer. Chem. Soc.* **79**, 2225 (1957).
(13) Mustafa, A., Sidky, M.M., Soliman, F.M., *Can. J. Chem.* **41**, 1731 (1963).
(14) Pople, J.A., Schneider, W.C., Bernstein, J.H., "High-Resolution Nuclear Magnetic Resonance," pp. 103, 164, McGraw-Hill, New York, 1959.

RECEIVED for review October 14, 1969. Accepted April 13, 1970.