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Isotopic Exchange of Active Methyl Hydrogens. V.(1) Reactivity of α- and γ-Methyl Groups and β-Hydrogens in Pyrylium Salts

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SUMMARY

The deuteration and dedeuteration of 2,4,6-trimethylpyrylium perchlorate in water (D_2O *and* H_2O*, respectively) was studied by nuclear magnetic resonance using as a quantitative standard for protons tetramethylammonium bromide. γ-Methyl groups exchange faster than α-methyl groups; β-standing hydrogens exchange very slowly. A mechanism involving anhydrobase and pseudobase formation is discussed and theoretical calculations are mentioned. Geminal hydrogen-deuterium spin-spin coupling in incompletely deuterated methyl groups is observed.*

INTRODUCTION.

Starting from the observation (2) that the infrared spectra of alkyl-substituted pyrylium salts undergo deep changes on recrystallization of these salts from deuterium oxide, it was established (3) that α- and γ-standing side-chains of pyrylium salts exchange their benzylic hydrogens in mild conditions (neutral or even acid medium, at 40-100° C, in D_2O or AcOD). The rate of exchange increases with increasing pH in the range pH = 1-7; at higher pH values the formation of pseudobase and its polymerization are lowering the yield of recovered pyrylium salt. By nuclear magnetic resonance spectroscopy it was found (4) that on exhaustive deuteration, β-standing hydrogens or alkyl groups undergo little, if any, deuterium exchange. The deuterated 2,4,6-trimethylpyrylium cation (I) is thus a readily available starting material for the preparation of various alkyl-deuterated aromatic (benzene and naphthalene derivatives, azulenes) or heterocyclic compounds (pyridine and furan derivatives) (1,5).

By plotting the residual deuterium content of initially completely deuterated 2,4,6-trimethylpyrylium perchlorate (II) against the time it was heated at a certain temperature in a buffer containing normal water, the dedeuteration was found to yield a composite kinetic curve. The attempt to resolve this curve into two separate contributions for the α- and γ-methyl groups, neglecting the exchange of β-hydrogens seemed to indicate a faster rate for the exchange of α-methyl than for γ-methyl groups (3). This result was, however, affected by a relatively large experimental error and by the imprecision of the graphical decomposition of the kinetic curve. The nuclear magnetic resonance spectra of deuterated 2,4,6-collidine obtained from I and ammonia indicated, on the contrary, that the γ-methyl exchanges faster than the α-methyls(5).

A study of the hydrogen exchange of 2,6-diphenyl-4-methyl-pyrylium and 2,4-diphenyl-6-methyl-pyrylium, where the presence of one exchangeable methyl avoids kinetic complications, also showed a higher rate of exchange for γ-than for α-methyl groups (6).

In order to resolve this contradiction we have undertaken the present study, using as analytical tool NMR spectra. The deuteration of 2,4,6-trimethylpyrylium perchlorate (I) in D_2O and the dedeuteration of 2,4,6-tri-d_3-methylpyrylium perchlorate (II) in H_2O were investigated at 100° C for various times.

An internal standard for the number of protons was used, namely tetramethylammonium bromide. Weighed amounts of pyrylium salt and of $Me_4N^+Br^-$ were dissolved in liquid sulphur dioxide in sealed tubes for NMR spectra determination.

EXPERIMENTAL PART.

The deuterations were performed by dissolving rapidly the finely divided and dry trimethylpyrylium perchlorate (I) (7) in the preheated 50-molar amount of deuterium oxide. After complete dissolution under stirring, the heating was continued in a boiling water bath for a prescribed time (up to 150 hr for the deuteration of β-protons). Then the solution was chilled in ice-water, filtered off and the crystalline perchlorate was dried *in vacuo* over phosphorus pentoxide. In some cases, in order to avoid dilution of deuterium oxide by exchange, the deuteration was repeated with a fresh 50-molar excess of deuterium oxide and the heating times for both deuterations were summed up.

The dedeuteration was performed analogously, except that a larger excess of distilled water (100-150 moles for one mole of II) was employed and that only the dedeuteration of methyl groups was followed for shorter heating times (owing to the kinetic isotopic effect, deuterium atoms in β positions would require weeks for exchange).

Approximately 0.1 g of deuterated or dedeuterated product together with ca. 15 mg of tetramethylammonium bromide (both compounds weighed exactly in NMR vials) were dissolved in liquid sulphur dioxide and the vial was sealed. Nuclear magnetic resonance spectra were run on Varian A-60 or A-60A apparatus. Integrals were also recorded. The signals of the β-protons (τ 2.23), α-methyl protons (τ 7.10) and γ-methyl protons (τ 7.26) are well separated from one another and from tetramethylammonium (τ 6.76) allowing the easy measurement of the integrals relatively to the Me_4N^+ peak taken as 12 protons; however, the α- and γ-methyl protons are measured with a lower degree of accuracy because of some overlapping, especially at high deuterium contents.

RESULTS AND DISCUSSION.

Results of deuteration experiments are presented in Table 1, and of dedeuterations in Table 2. There is a certain scatter of the experimental results, evidenced for instance by the experimental data for the non-deuterated salt I

TABLE 1. Kinetics of the deuteration of 2,4,6-trimethylpyrylium perchlorate (1 mole I) in 50 moles D_2O at 100° C : numbers of protons remaining in various positions as a function of time.

Position	Time, hours									
	0	0.01	0.033	0.083	0.25	7	17	37	69	148
α-Methyl	6.12	6.10	5.88	4.80	4.0	0	0	0	0	0
γ-Methyl	3.43	3.06	1.31	0.83	0.18	0	0	0	0	0
β-	2.05	2.06	1.83	1.71	1.7	1.67	1.29	0.91	0.70	0.46

TABLE 2. Kinetics of the dedeuteration of 2,4,6-tri-d_3-methylpyrylium perchlorate (1 mole II) in 100 moles H_2O at 100° C : numbers of protons introduced into various positions as a function of time.

Position	Time, minutes						
	0	1	2	5	15	60	180
α-Methyl	0	0.24	0.32	0.55	0.81	3.52	6.02
γ-Methyl	0	0.43	0.58	1.32	2.58	2.98	3.47
β-	1.67	1.42	1.45	1.61	1.54	1.75	1.80

(initial value from Table 1) where the γ-methyl signal is ca. 10% more intense than expected, probably owing to some contribution from the α-methyl peak. Despite this scatter which is more evident in the values for the β-protons from Tables 1 and 2, the results from these two tables clearly evidence that the γ-methyl exchanges appreciably faster than the α-methyl groups. The exchange of the β-standing hydrogens proceeds much more slowly. The rate constants found graphically for these processes agree with those found by calculating individual rate constants after formula (1) and averaging the resulting values (taking for n and n_0 the corresponding numbers of protons in the deuteration, and the numbers of deuterium atoms in the case of the dedeuteration).

$$k = -(2.303/t) \log (n/n_0) \qquad (1)$$

The rate constants are presented in Table 3. They show quantitatively that α-methyl groups exchange ten times more slowly than the γ-methyl group and about a hundred times faster than the β-hydrogens. However, the rate constant for β-hydrogen exchange is a rough value because the values from Table 1 do not afford a straight logarithmic plot. The slowing down of the β-exchange is perhaps due to the competition between pseudobase and anhydrobase formation. Anhydrobases (III) are formed by expulsion of a proton from I, pseudobases (IV) by addition of a hydroxyl anion; at higher pH values both kinds of bases can be formed. No quantitative data for them are as yet available. Whereas anhydrobases (methylene-pyrans III*a* or III*b*) are the intermediates in the isotopic exchange of benzylic α- and γ-methyl protons, pseudobases (1,5-enediones, IV*b*) are involved in the exchange of benzylic and of β-standing protons. Such an equilibrium between I, III and IV can afford a kinetic equation in which the concentration of the pseudobase goes through a maximum, rationalizing the irregular course of β-hydrogen exchange.

TABLE 3. Unimolecular rate constants for isotopic exchange at 100° C (min^{-1}).

	$k_{\alpha\text{-Me}}$	$k_{\gamma\text{-Me}}$	k_β
Deuteration	0.027	0.27	0.0003
Dedeuteration	0.013	0.13	—

The kinetic isotope effect is illustrated by Tables 3 and 4. The dedeuteration is twice as slow as the deuteration, evidencing that the rate-determining step involves bond breaking.

An explanation of the faster hydrogen exchange in γ- than in α-positions is provided by theoretical calculations (8) which indicate that the loss in π-electron energy in passing from trimethylpyrylium I to the anhydrobases is

TABLE 4. Data for the kinetic isotopic effect.

Time, minutes		0	2	5	15
No. of H atoms in deuteration	α-Me	6.12	5.88	4.80	4.0
	γ-Me	3.43	1.31	0.83	0.18
No. of D atoms in dedeuteration	α-Me	6.02	5.70	5.47	5.21
	γ-Me	3.47	2.89	2.15	0.89

smaller for the symmetrical anhydrobase III*a* than for the non-symmetrical III*b*, therefore the activation energy is lower in process I → III*a* than in process I → III*b* (Chart 1).

On the basis of these differences in rate, a deuteration-dedeuteration cycle can be imagined (Chart 2), leading to over 90% 2,6-dimethyl-4-d_3-methylpyrylium (V) on short deuteration of I, or to ca. 90% 2,6-di-d_3-methyl-4-méthylpyrylium (VI) on partial dedeuteration of II. Taking into account the easy

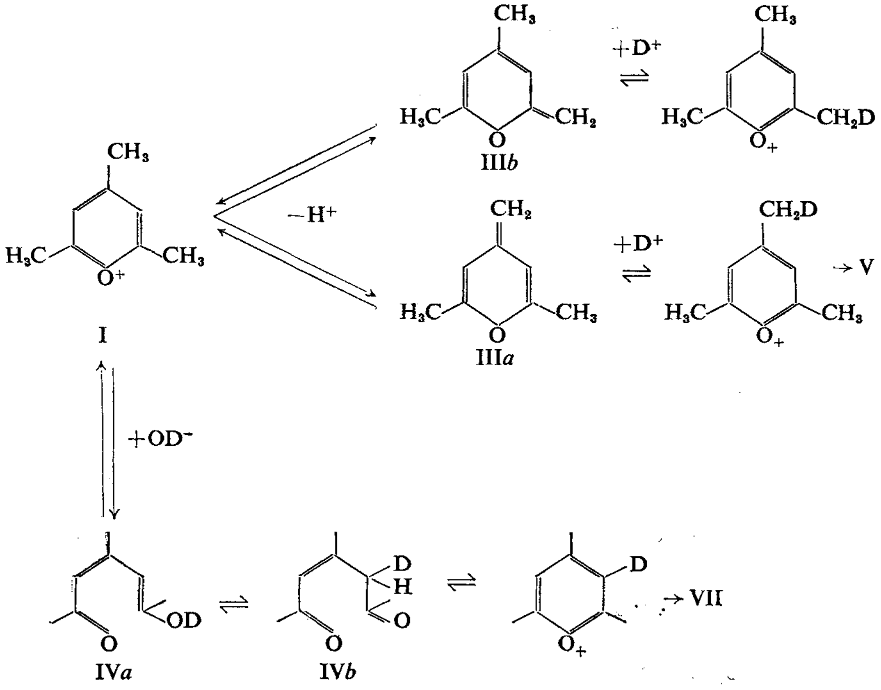

CHART 1. Mechanism of the deuteration.

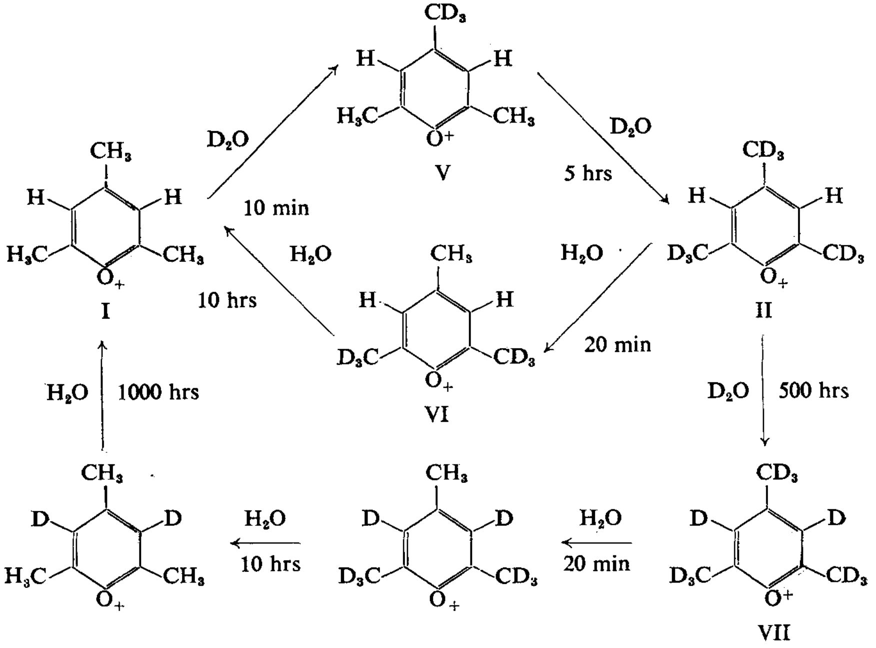

CHART 2. Deuteration and dedeuteration cycle at 100° C.

conversion of 2,4,6-trimethylpyrylium into other aromatic or heterocyclic compounds (1, 5), this cycle considerably extends the range of deuterated compounds which can be prepared starting from pyrylium salts.

The intermediate formation of partially deuterated side-chains (i.e. CH_2D and CHD_2) is evidenced by the complex spectra obtained in some cases (Figs. 1-3). In agreement with literature data,(9) the proton resonance signal of the CH_2D groups (in incipient deuterations, Figs. 1*a* and 1*b*, or in almost complete dedeuterations, Figs. 3*a*, 3*b*) appears as a triplet of equal intensities owing to the nuclear spin 1 of the deuterium atom. The proton resonance signal of the CHD_2 groups (in incipient dedeuterations, Figs. 2*a*, 2*b*, or in almost complete deuterations) appears as a quintuplet (poorly resolved). The geminal hydrogen-deuterium spin-spin coupling constant is ca. 2 cps at 60 Mc/sec, consistent with literature values.(10) An estimation of the deuterium isotope effect on the proton signal (9, 10) is difficult owing to superposition with the CH_3 signal.

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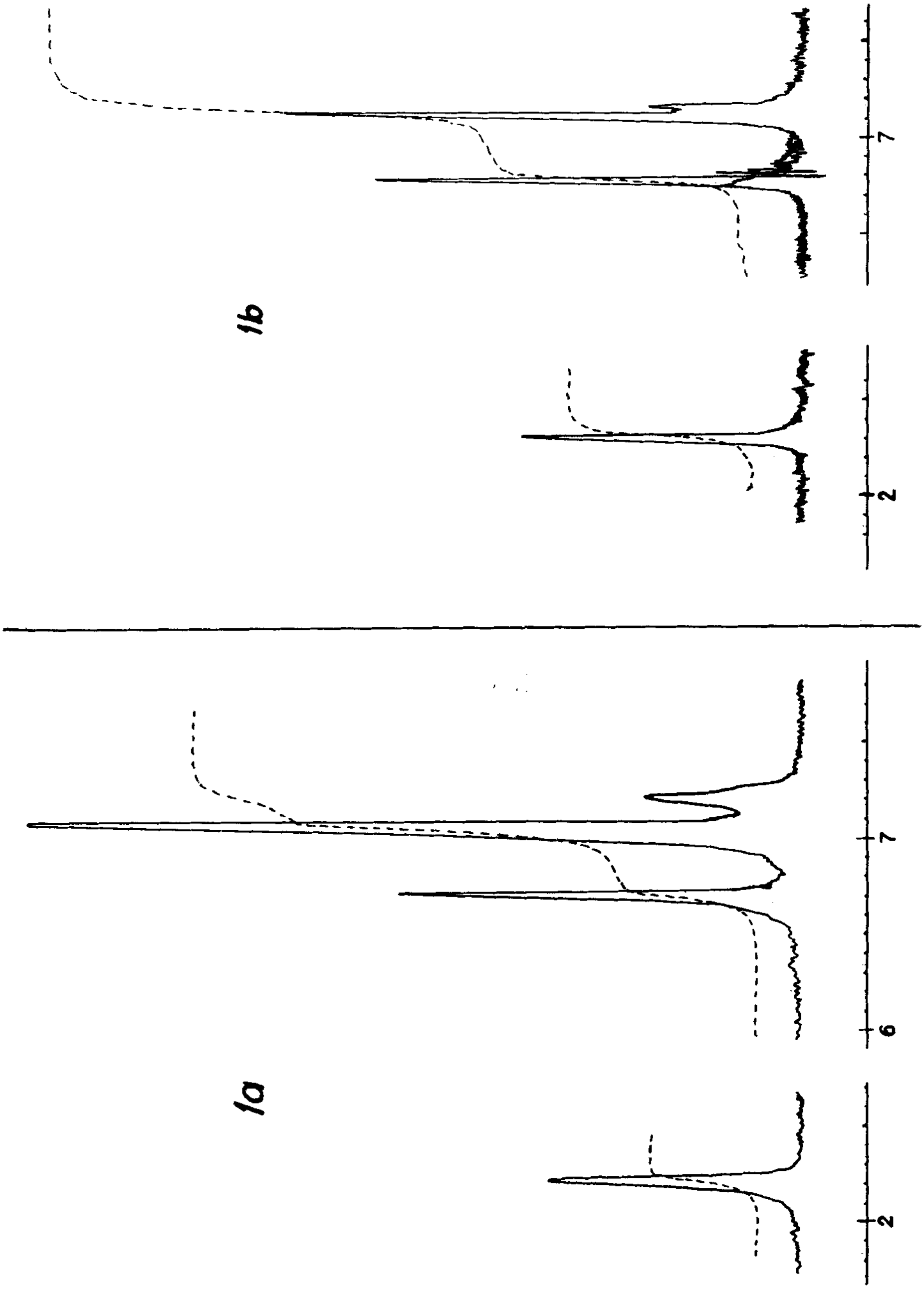

FIG. 1. Proton magnetic resonance spectra of I (99.8 mg), deuterated in D_2O at 100° C for (*a*) 2 min; (*b*) 15 min (solution in SO_2 with 13.7 mg $Me_4N^+Br^-$).

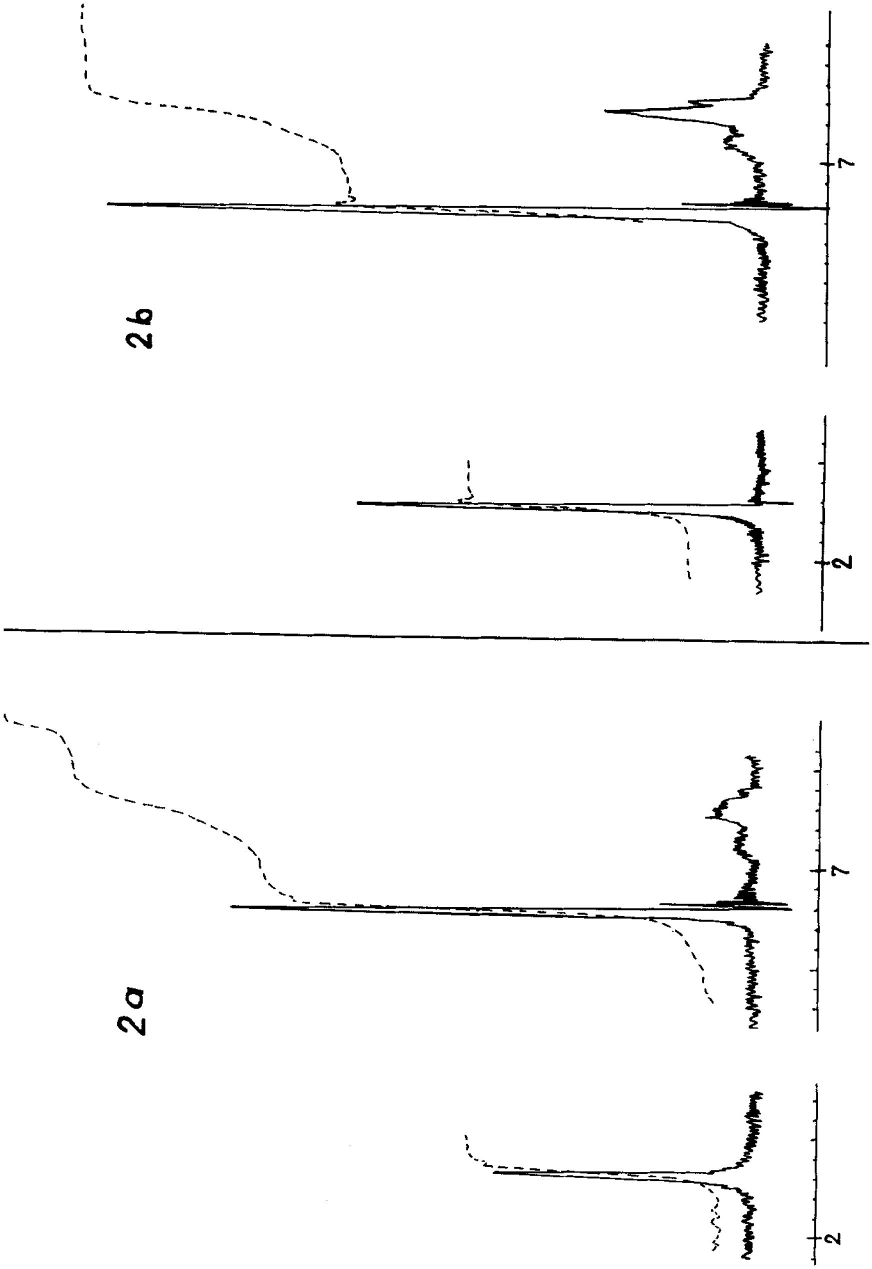

FIG. 2. Proton magnetic resonance spectra of II (100.2 mg), dedeuterated in H_2O at 100° C for (*a*) 2 min; (*b*) 5 min (solution in SO_2 with 13.3 mg $Me_4N^+Br^-$).

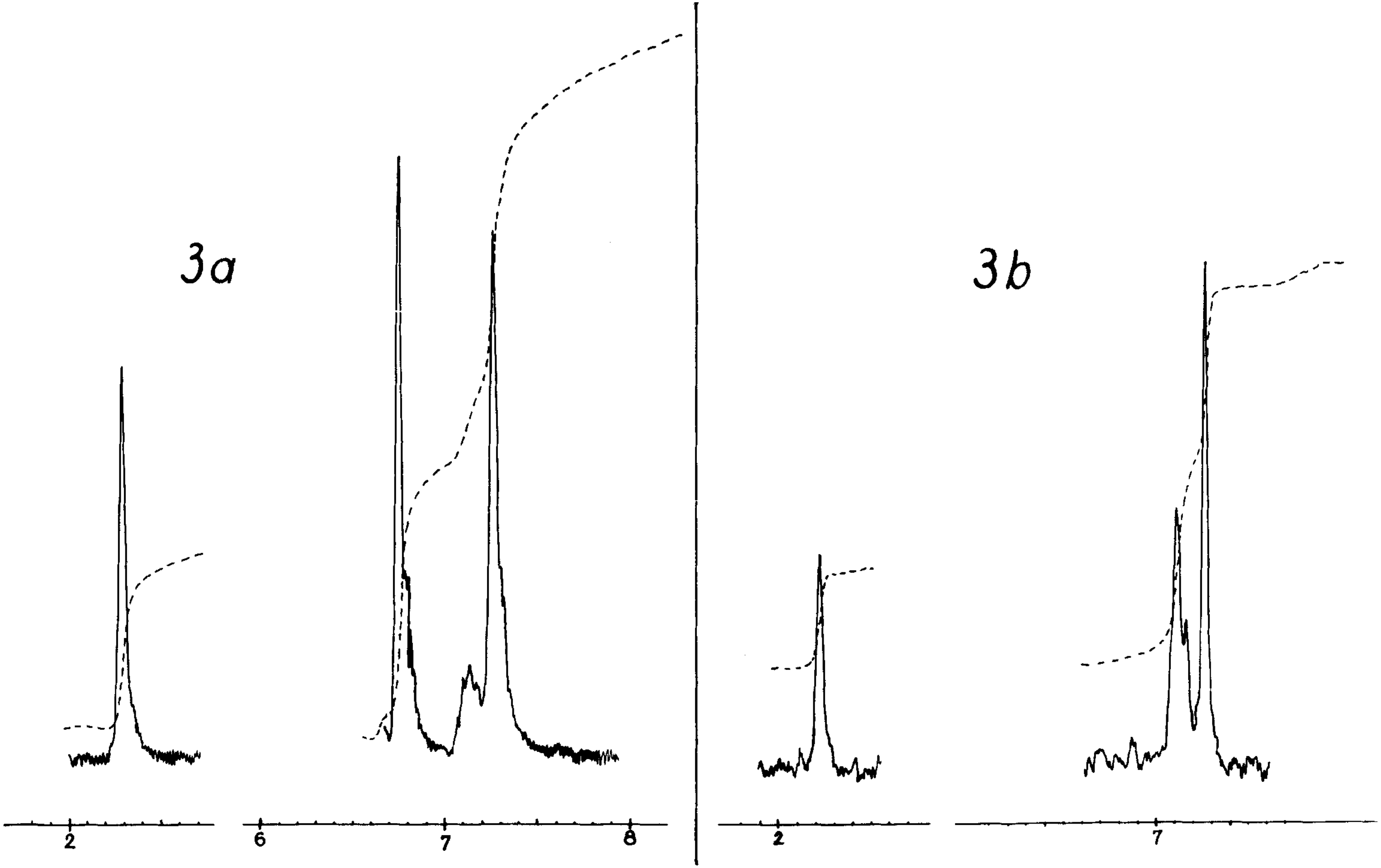

FIG. 3. Proton magnetic resonance spectra of II (100.6 mg), dedeuterated in H_2O at 100° C for (*a*) 15 min (solution in SO_2 with 13.4 mg $Me_4N^+Br^-$); (*b*) 1 h.

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