

Isotope exchange of active methyl hydrogens

III. Preparation of 2,4,6-tri-d₃-methylpyridine, 3,5-di-d₃-methylphenol, 3,5-di-d₃-methyl-2-acetylfuran, and 4,6,8-tri-d₃-methylazulene, from 2,4,6-tri-d₃-methylpyrylium perchlorate. ⁽¹⁾

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SUMMARY

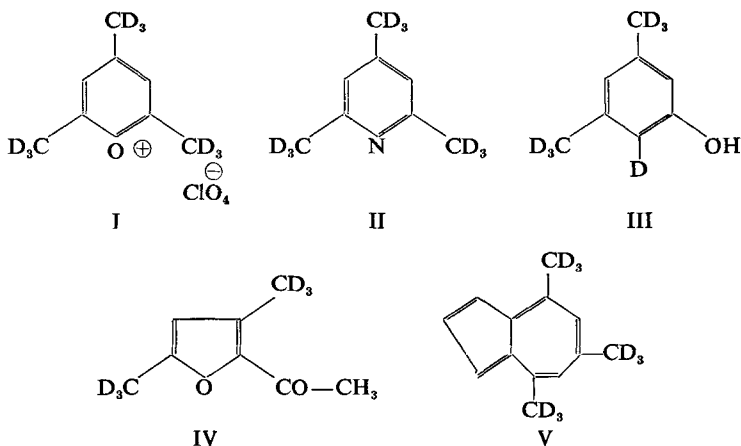
From 2,4,6-tri-d₃-methylpyrylium perchlorate the title compounds II-V were obtained by reaction with aqueous or gaseous ammonia, aqueous sodium hydroxide, aqueous hydrogen peroxide and sodium cyclopentadienide, respectively. The preparation of II-IV in aqueous solution proves that the nucleophilic additions to the pyrylium ring proceed faster than the dedeuteration. Infrared and nuclear magnetic resonance spectra of these compounds confirm that their methyl groups are deuterated.

INTRODUCTION.

In part I⁽²⁾, the preparation of 2,4,6-tri-d₃-methylpyrylium perchlorate [I] was reported by recrystallization of 2,4,6-trimethylpyrylium perchlorate ⁽³⁾ [Ia]¹ from deuterium oxide. This unusual activation of the methyl groups is due to the high electronegativity of the oxygen heteroatom. It is also encountered in methyltropylium salts ⁽¹⁾ and presumably also in other organic salts with low electron density on the carbon atom adjacent to the methyl group like heptamethylbenzenonium ⁽⁴⁾, dimethylcyclopentenyl carbonium ions ⁽⁵⁾, or some compounds with « active methyl groups » ². However 1-methyl-2,4,6-trimethylpyridinium perchlorate does not exchange in these conditions ⁽¹⁾.

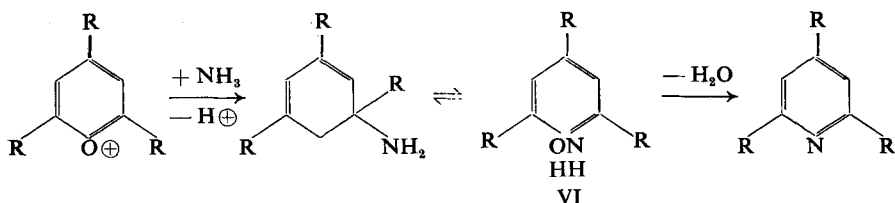
¹ The letter « a » after the roman numeral denotes the non-deuterated counterpart of the compound described by that numeral.

² Experimental testing of the scope of the deuteration through the intermediacy of anhydrobases is under way.

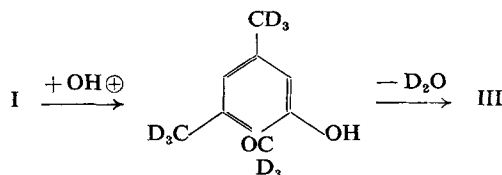


Starting from I, many new deuterated aromatic compounds may be prepared by reaction with nucleophilic reagents ⁽⁶⁾. The present paper reports the preparation of methyl-deuterated *s*-collidine [II], *s*-xylenol [III], dimethylacetyl-furan [IV] and 4,6,8-trimethylazulene [V], whose deuteration by direct hydrogen exchange would require very drastic conditions.

The conversion of pyrylium salts into pyridines by reaction with ammonia was described by BAEYER ^(7,8); the reaction proceeds through the formation of intermediate iminoenols which could be isolated for R = Ph ⁽⁹⁾.

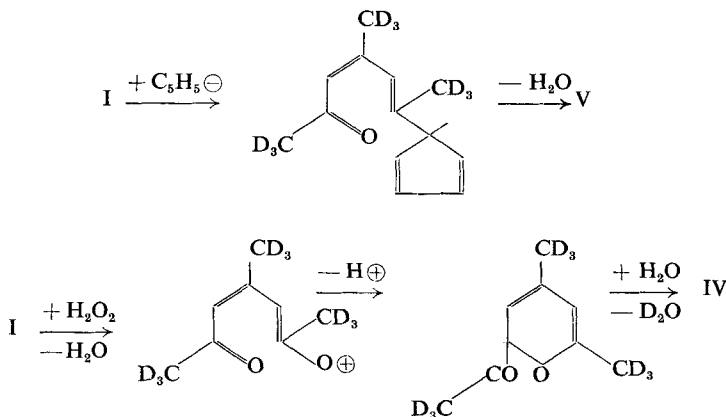


The formation of phenols, also first described by BAEYER and PICCARD ⁽⁸⁾ and applied for the characterization of pyrylium salts ⁽¹⁰⁾, can be explained by the following reactions :



By ring contraction under the influence of hydrogen peroxide in neutral or acid medium, 2,4,6-trimethylpyrylium perchlorate is converted into

3,5-dimethyl-2-acetylfuran ⁽¹¹⁾, and by reaction with sodium cyclopentadienide into 4,6,8-trimethylazulene ⁽¹²⁾.



EXPERIMENTAL PART.

Infrared spectra were recorded with a Jena UR-10 apparatus. Nuclear magnetic resonance spectra were registered with a 60 Mc Jeol apparatus JNM-3H-60.

2,4,6-Tri-*d*₃-methylpyridine [II] was prepared :

(i) from 2g I ⁽²⁾ and 20 ml conc. aqueous ammonia by shaking at room temperature in a separatory funnel with 10 ml ether until the crystals have disappeared; the separated ethereal layer is dried on powdered sodium hydroxide and distilled in vacuo. Yield 75 %. For analysis of the deuterium content it was converted into the picrate which was recrystallized from ethanol, dried, and analyzed as described previously ^(1,2) (Found : 54 vol % D₂O. Calcd. for C₆H₃N₃O₇·C₈H₂D₉N, 64.4 %).

(ii) from 2g I, suspended in 15 ml anhydrous *t*-butanol and treated with a stream of dry gaseous ammonia until the crystals dissolve; after addition of 40 ml water, the collidine was extracted with three successive portions of ether, and the combined ethereal extracts were worked up as above; b.p. 52° C/10 mm Hg.

3,5-Di-*d*₃-methyl-phenol [III] was prepared :

by introducing in portions 2g I into 20 ml 20 % aqueous sodium hydroxide heated at 90-95° C. After cooling, the non-acidic by-products were removed by extraction with ether, the aqueous layer was boiled for removing the ether, cooled and acidified with conc. hydrochloric acid. The xylenol crystallizes on cooling with ice and is filtered off. Yield 60 %; m.p. 60° C.

By refluxing *s*-xylenol with deuterium oxide for one hour, hydroxyl-deuterated xylenol is obtained.

3,5-Di-d₃-methyl-2-acetylfuran [IV].

I (5.5 g) was refluxed with 25 ml water, 1 drop of 70 % perchloric acid, and 4 ml 30 % hydrogen peroxide for 1 hr; it was then cooled and extracted twice with ether. The ethereal layer was dried over magnesium sulphate and distilled in vacuo. Yield 40 %; b.p. 124° C/75 mm Hg.

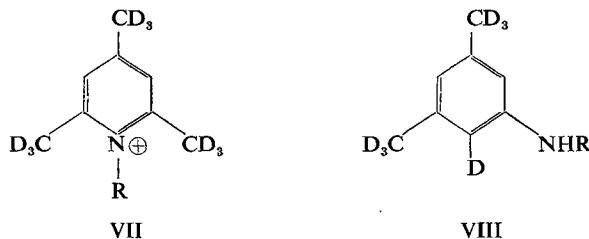
4,6,8-Tri-d₃-methylazulene [V] was prepared :

from 7g I, after the procedure of HAFNER and KAISER ⁽¹²⁾, modified in the purification stage by using chromatography on alumina from petroleum ether instead of the vacuum sublimation. Yield 40 %; m.p. 78° C.

RESULTS AND DISCUSSION.

The formation of deuterated compounds II-V is evidenced by isotopic analysis, infrared and nuclear magnetic resonance spectra.

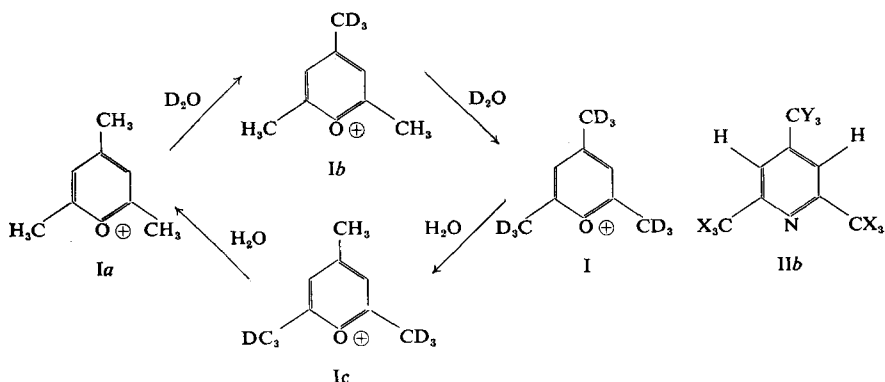
The infrared absorption bands of I-V and of their non-deuterated counterparts in the range of CH deformation and of CH and CD stretching vibrations are presented in Table I. The I.R. spectrum of I was reported previously ⁽¹³⁾. These data evidence clearly that the methyl groups are deuterated in all compounds I-V. A detailed discussion of the infrared spectra of compounds I-V and of compounds VII and VIII (R = Ph or Et) ⁽¹⁴⁾ will be published separately.



The proton magnetic resonance spectra of I and its non-deuterated analogue [Ia] in sulphur dioxide solution were described previously ⁽¹⁵⁾. The β -protons appear in both spectra at τ 2.39, but the α and γ methyl peaks appear only in the non-deuterated compound at τ 7.16 and 7.31 respectively (these data, with our apparatus are a little higher than the previous ones ⁽¹⁵⁾).

The nuclear magnetic resonance spectra of II and of its non-deuterated analogue [IIa] were examined with pure liquids (fig. 1) or with solutions in carbon tetrachloride. In non-deuterated collidine [IIa], the α and γ methyl groups give peaks at τ 7.64 and 7.94 respectively, and the β -protons give a peak at τ 3.45. The integrated intensities agree with the ratio 6:3:2. In the

NMR spectrum of II obtained by method (ii) only the β -protons appear at τ 3.50. The compound prepared by method (ii) shows, in addition, two weak methyl peaks at τ 7.70 and 7.94¹ whose integrated intensities correspond to 0.4 and 0.68 protons, respectively, corresponding to $X = .067$ H and $.933$ D, $Y = .227$ H and $.773$ D in formula IIb. These values lead to a calculated isotopic ratio (% vol D₂O) of the picrate of IIb equal to 56.5 %, in good agreement with the value experimentally found. This means that the dedeuteration of I in aqueous ammonia (which competes with the conversion of I into II) proceeds faster in the γ -methyl than in the α -methyl groups, i.e. that a cycle involving I, Ia, Ib and Ic could be written (in fact, the rates are not so different as to allow the preparation of pure Ib and Ic).



These conclusions are at variance with previous conclusions⁽²⁾ based on kinetic data, to the effect that the exchange proceeds faster with α -standing methyl groups, and agree with the data from part II on diphenylmethylpyrylium salts⁽¹⁾.

The NMR spectra of III and its non-deuterated analogue [IIIa] present in liquid sulphur dioxide two peaks due to the aromatic protons at τ 3.52 and 3.66; the former is half as intense as the latter and is therefore due to the proton *para* to the hydroxy group. The methyl groups in IIIa give a peak at τ 7.81; very weak absorption is apparent in the spectrum of III in this range.

The NMR spectra of IV and of its non-deuterated counterpart [IVa] were examined with neat liquids (fig. 2). The aromatic proton gives rise to a peak at τ 4.02, and the acetyl group to a peak at τ 7.79. In IVa, additional peaks are present at 7.75 (one methyl) and at τ 7.89 and 7.96 (amounting together to one methyl) which are absent in the spectrum of III and are therefore due to the 3- and 5-methyl groups. We suppose that the peak at τ 7.75

¹ The structure and the broadening of these peaks will be analyzed in a forthcoming paper including data for systems I-Ic.

is due to the 5-methyl and that the doublet at τ 7.89 and 7.96 is due to the 3-methyl peak in the two *s-cis* and *s-trans* isomers IVb and IVc. The higher intensity of the peak at τ 7.89 implies that the *s-cis* isomer IVb, with smaller

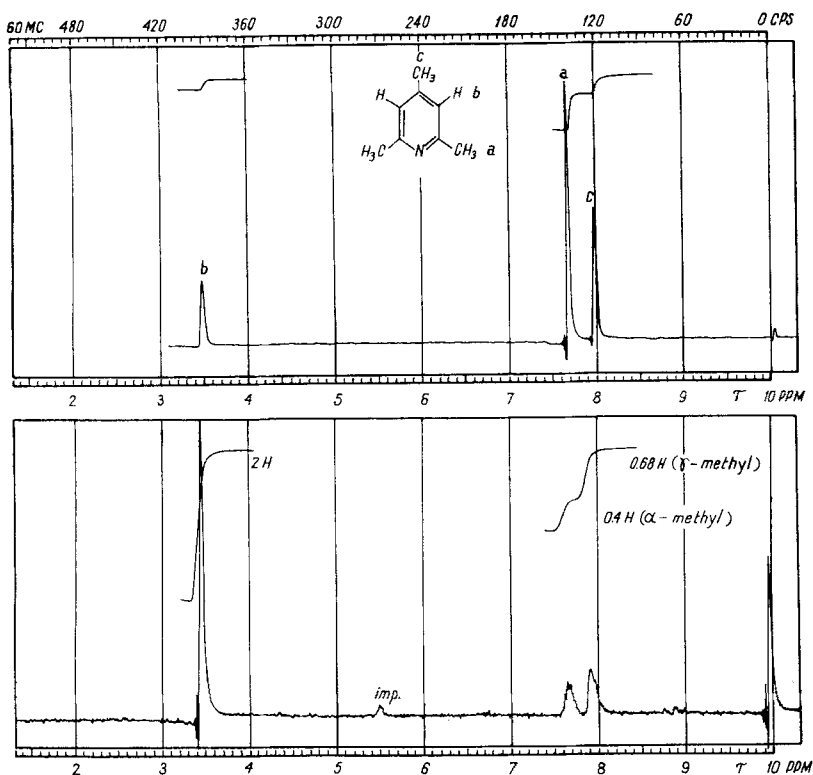
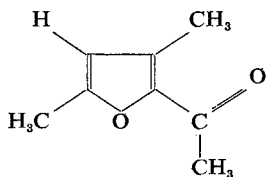
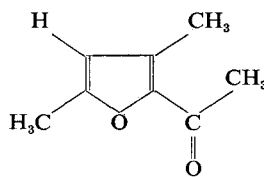


FIG. 1. — Nuclear magnetic resonance spectra : above, non-deuterated *sym*-collidine [IIa]; below, partially deuterated (by method (i)) *sym*-collidine [II].

steric hindrance⁽¹⁶⁾, prevails. The peak at τ ca 8.6, appearing in the NMR spectra of IV and IVa is probably due to an impurity. The presence of a non-deuterated methyl group in IV (the fine structure of the corresponding NMR



IVb (*s-cis*)



IVc (*s-trans*)

peak and its asymmetry are hard to interpret) is ascribed to dedeuteration of the acetyl group, subsequent to the reaction.

In the NMR spectra of V and its non-deuterated analogue [Va] in liquid sulphur dioxide, a complex pattern AB_2 of the three protons on the cyclopentadienic ring appears at τ 2.60-2.95. Trimethylazulene Va has the 4 and 8 methyl peaks at τ 7.24 and the 6 methyl peak at τ 7.44; there is no absorption in this range in the NMR spectrum of V.

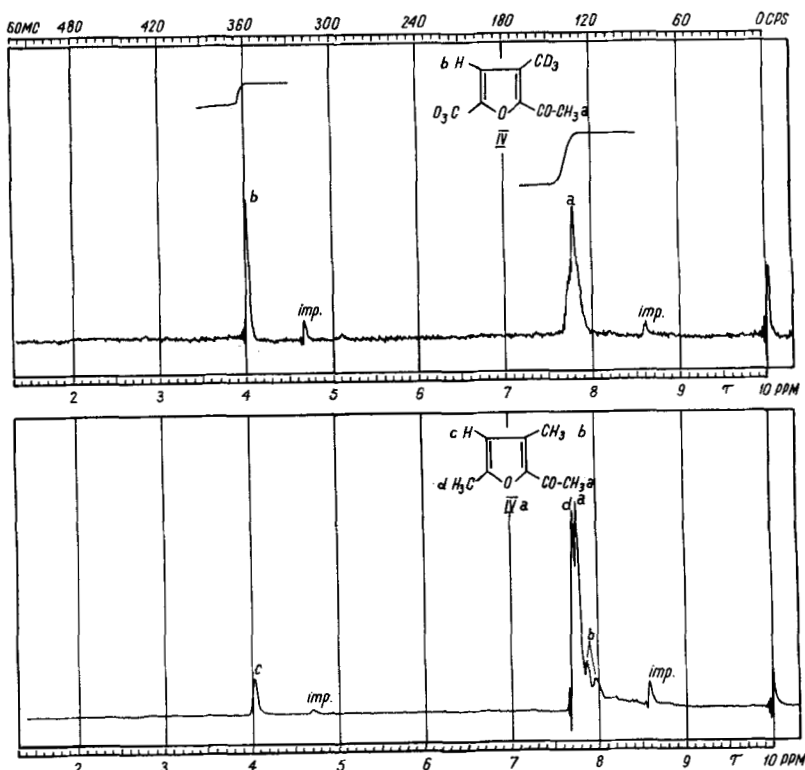


FIG. 2. — Nuclear magnetic resonance spectra of deuterated and non-deuterated 3,5-dimethyl-2-acetylfuran.

The formation of deuterated compounds II-V from I is based on the irreversibility of the labelling, compounds II-V being no longer capable of exchange. Since the reactions may be performed in aqueous medium at high pH values and at elevated temperature with little loss of deuterium (e.g. for II or III), i.e. in conditions favouring rapid dedeuteration of I, the rates of nucleophilic additions to the pyrylium ring followed by conversion into II-V,

must be higher than the rate of dedeuteration (whose rate-determining step involves the formation of the anhydrobase).

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REFERENCES

1. Part II. GARD, E., BALLY, I., VASILESCU, A., ARSENE, A. and BALABAN, A. T. — *This Journal*, **3** : 182 (1965).
2. BALABAN, A. T., GARD, E. and RENTEA, C. N. — *Abh. Dtsch. Akad. Wiss. Kl. Chem., Geol. Biol.*, 659 (1964), Part. I.
3. BALABAN, A. T. and NENITZESCU, C. D. — *Org. Synth.*, **44** : 98 (1964).
4. DOERING, W. v. E., SAUNDERS, E. F., BOYTON, H. G., EARHART, H. W., WADLEY, E. F. EDWARDS, W. R. and LABER, G. — *Tetrahedron*, **4** : 178 (1958).
5. DENO, N. C. and PITTMAN, C. V. Jr., — *J. Amer. Chem. Soc.*, **86** : 1744 (1964) and previous papers in the series.
6. DIMROTH, K. and WOLF, K. H. — *Newer Methods in Preparative Organic Chemistry*, Vol. 3, Academic Press, New York, 1964, p. 357.
7. BAEYER, A. — *Ber. dtsh. chem. Ges.*, **43** : 2337 (1910).
8. BAEYER, A. and PICCARD, J. — *Liebigs Ann. Chem.*, **384** : 208 (1911); **407** : 332 (1914).
9. BALABAN, A. T. and TOMA, C. — *Tetrahedron* (under press).
10. BALABAN, A. T. and NENITZESCU, C. D. — *Liebigs Ann. Chem.*, **625** : 74 (1959).
11. BALABAN, A. T. and NENITZESCU, C. D. — *Chem. Ber.*, **93** : 599 (1960).
12. HAFNER, K. and KAISER, H. — *Org. Synth.*, **44** : 94 (1964).
13. BALABAN, A. T., MATEESCU, G. D. and ELIAN, M. — *Tetrahedron*, **18** : 1083 (1962).
14. TOMA, C. and BALABAN, A. T. — *Tetrahedron* (under press).
15. BALABAN, A. T., BEDFORD, G. R. and KATRITZKY, A. R. — *J. Chem. Soc.*, 1646 (1964).
16. BALABAN, A. T., FRANGOPOL, P. T. and KEPLINGER, E. — *Spectrochim. Acta*, **19** : 367 (1963).