Conversion of xanthyrones into glutaconic anhydride–pyrone (GP) compounds in strong acid media: selective deuteriation as between chelated and unchelated acetyls

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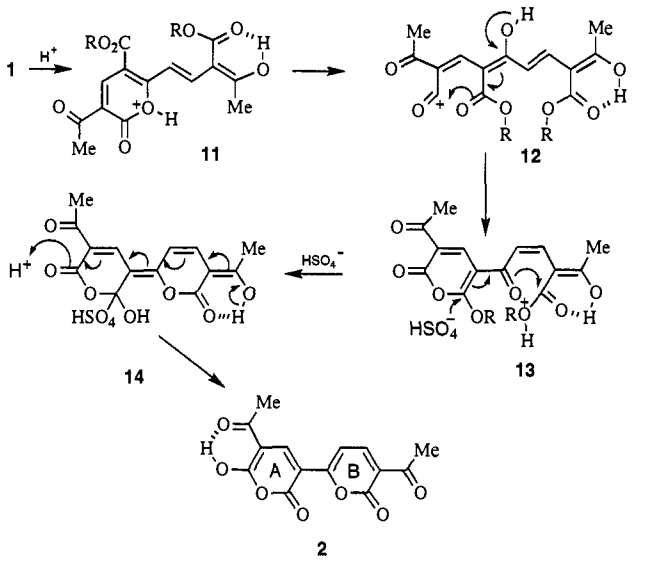
The structure, and mechanism of formation, of the pyrone–glutaconic anhydride (GP1) obtained by treatment of dialkylxanthophanic enols with concentrated H_2SO_4 or F_3CCO_2H, is further supported, and a new example GP2 is prepared. Experiments with deuteriated acids show that deuterium is introduced at C-5′ and the unchelated acetyl of GP1, the second acetyl being apparently protected by chelation. This is supported by benzenoid test examples, though in the naphthalene series acetyl migration also occurs through deacylation/reacylation. An explanation of the protective effect of chelation against acid catalysed enolisation of the acetyl methyl is suggested.

In earlier studies of xanthyrones,[1,2] diethyl and dimethylxanthophanic enols **1** (R = Et or Me) were treated with strong acids—concentrated sulfuric or trifluoroacetic acid—and the green fluorescent solution so formed, following dilution with water, yielded golden laminar crystals known colloquially in our laboratory as 'gold plates' but having a glutaconic anhydride–pyrone structure (GP1).[3] The latter was sparingly soluble in many solvents, decomposed rather easily on attempted recrystallisation, gave a blood red colour with Fe^{III}, and with one exception was not responsive to the many chemical reactions tried. The tentative pyrone–enolised[4] glutaconic anhydride structure **2** proposed by us[3] was based mainly on the ^1H NMR spectrum of GP1 in trifluoroacetic acid. In this paper[5] we present further information supporting structure **2** and the possible mechanism by which it is formed. The deuteriation methods used have also led to interesting conclusions about the ability of chelated and unchelated acetyls to deuteriate in strong acid media.

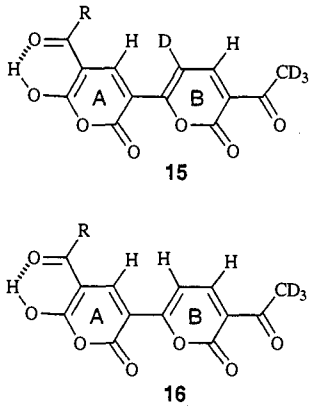
The ^{13}C NMR spectrum of GP1 has been obtained in trifluoroacetic acid and is, like the ^1H spectrum, quite consistent with structure **2**, as shown in the Experimental section. It had been hoped to confirm this structure for GP1 by X-ray single crystal methods but a number of attempts by the late Dr M. Begley of this laboratory failed, because of the insufficiency of reflections from the thin plate-like crystals.

A number of xanthyrone types have now been made[6,7] and five examples **3–7** were tested to see if they would give a GP type of product under strong acid conditions. Of the five, **3** and **4** were recovered unchanged, whilst **5** and **6** merely charred. However, **7** gave a brownish crystalline product designated GP2 **8**, spectroscopically (^1H NMR, UV, IR) analogous to **2** with the anhydride in enolic form. The one successful reaction of GP1 (magnesium methoxide in methanol–chloroform) leading to 4-hydroxyisophthalate **9**, was also given by GP2. Both GP compounds contain the fragment **10**, attainable from each by retro-aldol reactions and formally necessary to give **9**. A suggested mechanism of formation of **2** from **1** or **8** is given in Scheme 1 and it will be observed that **3** and **4** do not have the necessary structural elements to form the enolic glutaconic anhydride or the pyran segments. Xanthyrones **5** and **6** do not meet the requirements for formation of the pyrone ring-B of **2**.

Experiments using concentrated deuteriosulfuric acid were then set in train. Dissolution of **1** (R = Me) in the acid for 24 h at room temperature, followed by work-up, gave GP1 with the labelling pattern **15** (R = Me), as determined by absences from the ^1H NMR spectrum. The xanthyrone **1** (R = Et) behaved similarly giving the same tetradeuterio GP1 **15**. Xanthyrone **7** gave **15** (R = OMe). However, dissolution of unlabelled preformed GP1 or GP2 in D_2SO_4 for a similar period brought about only trideuteriation of the acetyl methyl attached to ring-B. Deuteriation at 5′ in ring-B must occur before formation of the GP compounds and the mechanism of Scheme 1 would allow for this. Monitoring in H_2SO_4 or D_2SO_4 by ^1H NMR spectroscopy over 24 h showed that the starting material, dimethylxanthophanic enol **1** (R = Me) was rapidly removed along with immediate formation of methanol. Methanol



Scheme 1 The formation of GP1 from dialkyl xanthophanic enols in concentrated sulfuric acid medium



approximately equivalent to hydrolysis of one ester group was released in 30 min whilst the second equivalent of methanol was released in a slower reaction over 12 h, after which time the characteristic GP spectrum was present and formation of methanol was complete.

The UV spectrum of dimethyl xanthophanic enol **1** (R = Me) in concentrated sulfuric acid was also studied. Monitored immediately, the absorptions corresponding to the starting material rapidly disappeared and were no longer present after 30 min. The absorptions of an intermediate or intermediates were now present and these decayed slowly so that after 12 h a chromophore closely resembling that of GP1 was present (Fig. 1). We suggest that ring-A is formed first, and fairly rapidly, whilst ring-B is closed more slowly giving opportunity for the deuteriation to occur on the pre-ring-B intermediates: this deuterium ultimately emerges at 5′ in **15**.

As mentioned earlier, treatment of GP1 itself in D_2SO_4 results in deuteriation only of the acetyl methyl of ring-B, the acetyl of ring-A remaining unaffected. This conclusion that unchelated acetyls are easy to deuteriate in strong acid media, whilst chelated acetyls are highly resistant, was borne out by experiments on some simple cases. Thus, acetophenone **17** and *p*-hydroxyacetophenone **18** were substantially deuteriated on their acetyl methyls after dissolution in deuteriotrifluoroacetic acid for 12 h, but the methyl group of chelated *o*-hydroxyacetophenone **19** remained undeuteriated after 3 days. An interesting test case was 2,4-diacetyl-5-hydroxytoluene[8] with one chelated and one unchelated acetyl attached to the same benzene nucleus. The unchelated acetyl δ 2.48 had essentially disappeared from the ^{1}H NMR spectrum after 24 h whilst the chelated acetyl δ 2.54 remained completely unaffected

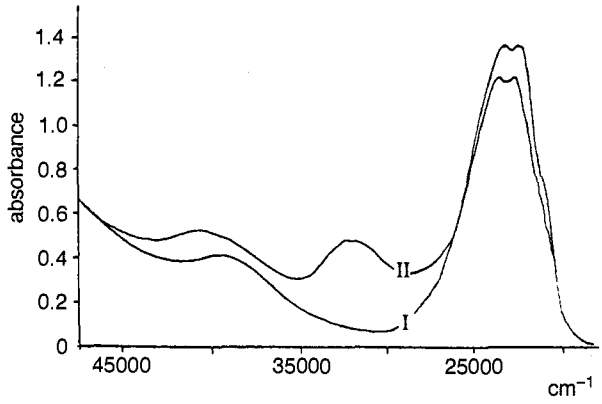
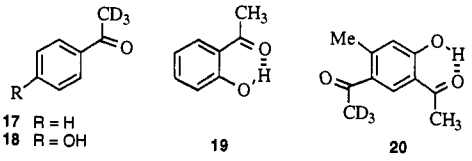


Fig. 1 Formation of GP1 in concentrated H_2SO_4: UV data. I, GP1 **2** dissolved in concentrated H_2SO_4; II, dimethyl xanthophanic enol **1** (R = Me) after 12 h in concentrated H_2SO_4

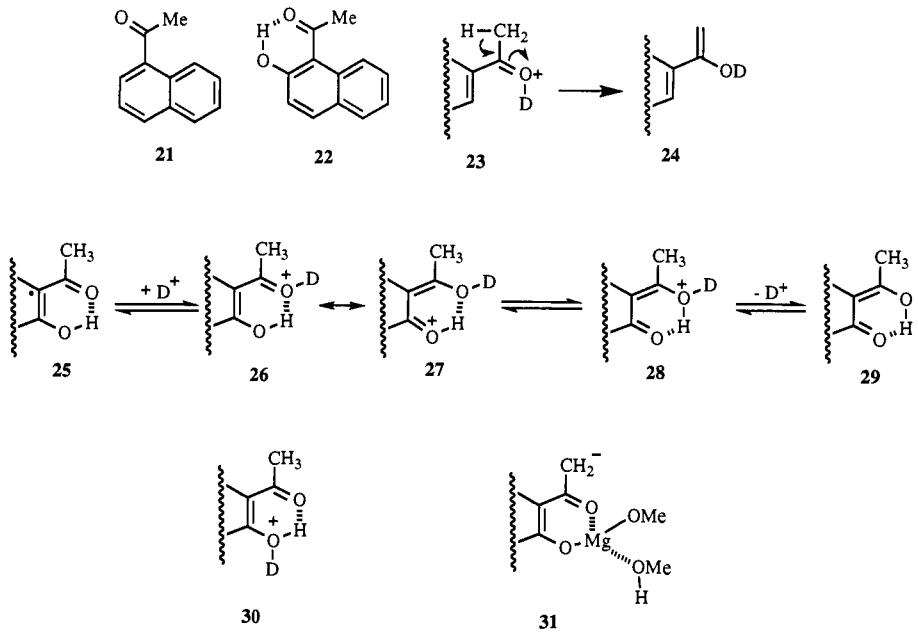


after 6 days in CF_3CO_2D giving **20**. The ^{13}C spectrum of 2,4-diacetyl-5-hydroxytoluene (solvent CF_3CO_2H containing 10% C_6D_6 for lock purposes) is also of interest. In the region δ 20–30 there are three signals: 23.4 (ArMe), 28.4 and 26.1 (two acetyl methyls). If the solvent is now changed to CF_3CO_2D the carbon signal at δ 28.4 slowly disappears from the spectrum. This can be explained as a consequence of the greatly increased relaxation time of the trideuteriomethyl carbon, combined with septet splitting, which makes the signal disappear into the baseline noise.

Extension of the examples to the pair 1-acetylnaphthalene **21** and 1-acetyl-2-hydroxynaphthalene **22** met with difficulties caused by deacylation–reacylation in the strongly acid media (F_3CO_2D), presumably *via* the acylium ion. Scrutiny of the aromatic multiplets in the earlier benzenoid examples showed that no detectable isomerisation had occurred, but in the case of 1-acetylnaphthalene changes gradually occurred in the aromatic ^{1}H NMR pattern and a new signal emerged at δ 2.77 near the original acetyl resonance at 2.82. In the case of 1-acetyl-2-hydroxynaphthalene, isomerisation was still more marked. New multiplets emerged in the aromatic pattern and two new acetyl resonances appeared at δ 2.28 and 2.51 near the original acetyl at 3.02. Repositioned away from the chelating hydroxyl, the new acetyls can deuteriate and deuterium is also introduced into the naphthalene ring. Strong acid isomerisation thus sets limits on the usefulness of the procedure.

An explanation for the non-deuteriation of chelated acetyls in stable structures is suggested as follows. The deuteriation of a non-chelated acetyl involves the usual acid-catalysed enolisation mechanism **23** with the deuteron being inserted into the methyl from the external deuterio-acid solvent *via* the enol **24**: ultimately, all three methyl positions are replaced. The situation with regard to the chelated acetyl is different. Here the chelated system **25** is again conceived as deuterionated at the carbonyl oxygen **26**/**27**, allowing transfer of the chelated proton from the hydroxyl to the carbonyl oxygen **28** to give an orthoquinone type of structure **28**, the deuteron diffusing away **29**. The process can now reverse itself. Only the proton or deuteron held between the two oxygens is formally involved: external exchange between a proton and a deuteron does not affect the issue of deuterium non-incorporation. The possibility of enolisation into the methyl is thwarted and reaction is confined within the chelate ring. Initial deuteriation at the hydroxyl oxygen can bring about a similar process **30**.

The chelated acetyl group in a compound such as **19** can, of



course, be deuteriated under base conditions with, for example, D_2O–NaOMe. A convenient way is to treat it with 1.5 mol of $Mg(OMe)_2$ in MeOD (1 mol equiv. to complex, 0.5 mol equiv. to provide base) when deuterium exchange proceeds *via* the anion **31**.

Experimental

Preparation of GP1 2 using H_2SO_4

Dimethyl xanthophanic enol **1** (R = Me) (500 mg) was shaken with concentrated H_2SO_4 (3 cm^3) and set aside at room temperature (24 h) and then poured onto ice. The product was washed with water and chloroform (1 cm^3) and recrystallised from acetone (charcoal) to give GP1 **2** (220 mg, 52%) as golden yellow plates, mp 280 °C (lit.,[3] mp 282 °C decomp.) (Found: M^+, 290.043. Calc. for $C_{14}H_{10}O_7$: *M*, 290.043); ν_{max}(KBr)/cm^{-1} 1715 and 1680; λ_{max}(EtOH or 0.01 M ethanolic H_2SO_4)/nm 251i (ε 3600), 309i (2600), 398 (17 600), 408i (16 800) and 438i (7600); λ_{max}(0.01 M ethanolic KOH)/nm 237i (13 700), 301 (14 200), 467 (33 800), 495 (33 600) and 546 (5400); $\delta_H([^2H_6]$-DMSO) 8.45 (1 H, s, CH=), 8.24 (1 H, d, *J* 8, CH=), 7.52 (1 H, d, *J* 8, CH=) and 2.70 (3 H, s, MeCO); $\delta_H(F_3CCO_2H)$ 9.00 (1 H, s, CH=), 8.64 (1 H, d, *J* 8, CH=), 7.94 (1 H, d, *J* 8, CH=), 2.90 (3 H, s, MeCO) and 2.84 (3 H, s, MeCO); $\delta_H(CDCl_3)$ 8.68 (1 H, s, enolic hydroxyl), 8.28 (1 H, d, *J* 7.5, CH=), 8.01 (1 H, s, CH=) and 7.65 (1 H, d, *J* 7.5, CH=); $\delta_C(F_3CCO_2H)$: ring A 162.2 (C, 6-enol), 112.5 (C, C-5), 154.2 (CH, C-4), 123.9 (C, C-3), 170.4 (C, C-2 carbonyl), 163.4 (C, acetyl carbonyl), 21.8 (CH_3, acetyl Me); ring **B** 160.7 (C, C-6'), 109.9 (CH, C-5'), 148.6 (CH, C), 115.0 (C, C-4'), 179.0 (C, C-2', C=O), 203.0 (C, acetyl C=O) and 21.8 (CH_3, acetyl Me); *m*/*z* 290 (40%), 275 (23), 262 (22), 247 (20), 231 (6), 219 (4), 191 (8), 181 (14), 163 (5), 137 (15), 109 (29), 95 (33), 53 (7), 44 (17), 43 (100) and 39 (16).

Preparation of Tetradeuterio-GP1 15 (R = Me) using D_2SO_4

Treated as above, but using concentrated D_2SO_4, dimethyl xanthophanic enol gave tetradeuterio-GP1 **15** (R = Me); $\delta_H(F_3C{\cdot}CO_2H)$ 8.99 (1 H, s, CH=), 8.63 (1 H, s, CH=) and 2.88 (3 H, s, MeCO); *m*/*z* 294 (52%), 276 (33), 266 (27), 247 (14), 232 (9), 220 (7), 192 (13), 181 (21), 164 (7), 141 (17), 113 (37), 97 (17), 53 (13), 46 (100), 45 (50), 44 (37), 43 (67), 41 (17) and 39 (15).

Trideuterio-GP1 16 (R = Me) by dissolution of GP1 in D_2SO_4

GP1 (500 mg) was dissolved in concentrated D_2SO_4 (3 cm^3) and set aside (24 h) at room temperature. Work-up with ice as before gave trideuterio GP1 **16** (R = Me); $\delta_H(F_3CCO_2H)$ 9.10 (1 H, s, CH=), 8.73 (1 H, d, *J* 8, CH=), 8.04 (1 H, d, *J* 8, CH=) and 2.94 (3 H, s, MeCO); *m*/*z* 293 (27%), 275 (18), 265 (10), 248 (24), 231 (6), 219 (4), 191 (8), 181 (12), 163 (6), 140 (10), 112 (19), 96 (33), 53 (12), 46 (100), 45 (37), 43 (66), 40 (18) and 39 (13).

GP1 was set aside in F_3CCO_2D for 12 h at 20 °C. ^1H NMR monitoring showed the formation of trideuterio-GP1.

Preparation of GP2 8 using H_2SO_4

(Experiment by Dr M. Eskins) 3'-Acetyl-3,3',5-trimethoxycarbonylxanthyrone **7** (500 mg) was kept at room temperature (24 h) in concentrated sulfuric acid and then poured into ice. Work-up gave *GP2* **8** (240 mg, 55%), brownish crystals from acetone, mp 135 °C (Found: M^+, 306.039. $C_{14}H_{10}O_8$ requires *M*, 306.038); ν_{max}(mull)/cm^{-1} 1750 (pyrone carbonyl), 1695 (acetyl carbonyl), 1640 (bonded ester) and 1595; λ_{max}(EtOH and 0.01 M ethanolic sulfuric acid)/nm 258 (9100), 330 (8300) and 475 (48 400); λ_{max}(0.01 M ethanolic KOH)/nm 260 (18 900), 340 (15 500), 412 (26 700), 485 (34 500) and 538 (8600); $\delta_H(F_3CCO_2H)$ 9.07 (1 H, s, CH=), 8.45 (1 H, d, *J* 8, CH=), 7.91 (1 H, d, *J* 8, CH=), 4.11 (3 H, s, MeO) and 2.80 (3 H, s, MeCO); $\delta_H([^2H_6]$-DMSO) 8.65 (1 H, s, CH=), 8.18 (1 H, d, *J* 8, CH=), 7.32 (1 H, s, *J* 8, CH=), 3.70 (3 H, s, MeO), 2.47 (3 H, s, MeCO); *m*/*z* 306 (35%), 274 (60), 259 (22), 246 (12), 215 (6), 202 (5), 187 (8), 174 (8), 160 (8), 147 (12), 137 (8), 134 (18), 119 (6), 109 (27), 95 (29), 53 (13), 44 (85), 43 (100), 40 (28) and 39 (18). The compound gave a strong red Fe^{III} colour and dilute solutions in alcohol, acetone or chloroform showed an intense fluorescence.

In similar experiments with concentrated sulfuric acid 3,5-dimethoxycarbonyl-3',3'-diacetylxanthyrone **5** and 3,3',3'-triacetyl-5-methoxycarbonylxanthyrone **6** gave amorphous black products having no discernible UV and IR spectra. On the other hand 3-methoxycarbonyl-5,3',3'-triacetylxanthyrone **3** and 3,5,3',3'-tetraacetylxanthyrone **4** were recovered unchanged from concentrated sulfuric acid at room temperature.

Treatment of GP1 and GP2 with magnesium methoxide in methanol

(With Dr M. Eskins). Magnesium methoxide solution [from magnesium (2.5 g) and dry methanol (100 cm^3)] was added to a solution of GP1 (3.0 g) in 1 : 1 chloroform–methanol (50 cm^3). After 4 days at room temperature it was poured into water and acidified with 4 M-hydrochloric acid. Extraction with chloroform gave a gum which was chromatographed on neutral

alumina, eluting with benzene to give dimethyl 4-hydroxyisophthalate **9** (310 mg), mp 94 °C (lit.,[3] mp 96–97 °C) (Found: C, 57.05; H, 5.15. Calc. for $C_{10}H_{10}O_5$: C, 57.15; H, 4.80); ν_{max}(mull)/cm^{-1} 1735 (ester), 1683 (chelated ester) and 1618, 1587 (Ar); λ_{max}/nm (EtOH) 225 (ε 22 000), 253 (12 800) and 303 (3800); δ_H 3.95 (6 H, s, 2 × OMe), 7.00 (1 H, d, *J* 8.6, ArH), 8.40 (1 H, dd, *J* 8.6, 1.9, ArH), 8.52 (1 H, d, *J* 1.9, ArH) and 11.16 (1 H, chelated OH). In a similar way GP2 (840 mg) gave dimethyl 4-hydroxyisophthalate (230 mg) mp and mixed mp 94 °C.

Preparation of tetradeuterio-GP2 15 (R = OMe) using D_2SO_4

Xanthyrone **7** (500 mg) was dissolved in concentrated deuteriosulfuric acid (3 cm^3), set aside for 7 h, and then worked up as before. The ^{1}H NMR spectrum indicated the presence of two compounds **15** (R = OMe) and **16** (R = OMe) in approximately equal quantities. Compound **15** (R = OMe) had $\delta_H(F_3CCO_2H)$ 9.13 (1 H, s, CH=), 8.47 (1 H, s, CH=), 4.12 (3 H, s, OMe); and compound **16** (R = OMe) had δ_H 9.13 (1 H, s, CH=), 8.47 (1 H, d, *J* 8, CH=), 7.97 (1 H, d, *J* 8, CH=) and 4.13 (3 H, s, OMe).

Trideuterio-GP2 by dissolution of GP2 8 (R = OMe) in D_2SO_4

GP2 was treated as before with concentrated deuteriosulfuric acid at room temperature for 24 h. Work-up gave structure **16** (R = OMe) having the unchelated methyl trideuteriated, but no deuterium at 5′. The NMR spectrum had $\delta_H(F_3CCO_2H)$ 9.15 (1 H, s, CH=), 8.49 (1 H, d, *J* 8, CH=), 7.97 (1 H, d, *J* 8, CH=) and 4.13 (3 H, s, MeO). GP2 **8** when kept in F_3CCO_2D for 12 h caused complete deuteriation of the acetyl group (by NMR).

Deuteriation of acetophenones in acidic media

Acetophenone was dissolved in F_3CCO_2D: the initial NMR spectrum showed δ_H 8.10 (2 H, m, aromatic H's), 7.8 (3 H, m, aromatic H's) and 2.75 (3 H, s, MeCO). After the solution had been maintained at room temperature for 12 h, the signal at δ 2.75 had almost disappeared.

p-Hydroxyacetophenone was similarly treated and initially had $\delta_H(F_3CCO_2D)$ 8.09 (2 H, d, *J* 9, 2 × CH=), 7.07 (2 H, d, *J* 9, 2 × CH=) and 2.73 (3 H, s, MeCO). After 24 h at room temperature the signal at δ 2.73 had been almost completely removed by deuteriation.

o-Hydroxyacetophenone was similarly treated and initially had $\delta_H(F_3CCO_2D)$ 7.75 (2 H, m, aromatic H's), 7.1 (2 H, m, aromatic H's), 2.79 (3 H, s, MeCO). After 3 days at room temperature in the deuterio-acid the signals showed no change. 2,4-Diacetyl-5-hydroxytoluene,[8] had $\delta_C(F_3CCO_2H$ containing 20% hexadeuteriobenzene) 23.35 (ArMe), 26.11 (chelated MeCO), 28.41 (unchelated MeCO), 113.6, 123.0, 129.6, 137.3, 153.4, 166.4 (aromatics), 206.7, 208.7 (2 × C=O). When the compound was kept in F_3CCO_2D for 24 h, the unchelated signal at δ_C 28.4 had largely disappeared from the spectrum (see text). The ^{1}H spectrum (F_3CCO_2D) showed initially three methyl signals at δ_H 2.36, 2.48 and 2.54: the two aromatic protons were at 6.7 and 8.2. When the solution was kept for 24 h, the unchelated methyl at 2.48 had declined very substantially and at 6 days it had essentially disappeared giving **20**.

Deuteriation of acetylnaphthalenes in acidic media

In the case of 1-acetylnaphthalene **21** dissolved in F_3CCO_2D at room temperature the initial ratio of ArH to $COCH_3$ (7:3) had fallen to 7:1.6 after 1 day though with only the slightest observable changes in the ^{1}H spectrum. After 3 days, however, there were changes in the ArH multiplets and a new acetyl resonance (δ 2.77) emerged near the old one at 2.82. These progressive changes were followed over 8 days when the ArH to $COCH_3$ ratio was 7:0.5.

The initial ratio of ArH:$COCH_3$ protons is 2:1 in 1-acetyl-2-hydroxynaphthalene **22** but after 1 day in F_3CCO_2D new multiplets had emerged in the aryl region and there were now two new acetyl resonances at δ 2.28 and 2.51 as well as at the original position at 3.02. The ratio of ArH:$COCH_3$ protons had become 2:0.73. Acetyl signal heights changed progressively and at 6 days the intensity of the δ 2.28 resonance was much stronger than the original at 3.02.

Deuteriation of *o*-hydroxyacetophenone in basic media

A trace of sodium methoxide was added to a solution of *o*-hydroxyacetophenone in deuteriomethanol and the solution was examined by NMR spectroscopy. The acetyl peak (δ_H 2.80) was rapidly removed by deuterium exchange (within 30 min).

o-Hydroxyacetophenone (1.00 g) was added to magnesium methoxide solution [from magnesium (265 mg) and deuteriomethanol (5 cm^3)] and kept for 1 h after which it was shaken with chloroform (50 cm^3) and an excess of 1 M-hydrochloric acid. The chloroform solution was washed with water (2 × 10 cm^3), dried ($MgSO_4$), and evaporated. Examination of the product by ^{1}H NMR showed that the acetyl peak at δ_H 2.80 had virtually disappeared.

Acknowledgements

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