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ALKYLATION OF THE CHRYSIN DIANION

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Abstract—Alkylation of the disodium salt of chrysin in liquid ammonia with methyl iodide gave a mixture of the 6- and 8-monomethyl derivatives, while with prenyl bromide the 6-mono- and the 6,8-diprenyl derivatives were obtained. Nuclear methylation was also achieved by means of dimethyl sulphate. With benzyl chloride as alkylating agent benzylation did not occur under similar conditions, but the 6-C, 7-O-dibenzyl derivative was obtained when the liquid ammonia was replaced by dioxan.

A RECENT publication[1] on the prenylation of chrysin (**1**) has prompted us to report the results of some alkylation reactions of the same compound carried out in this laboratory.

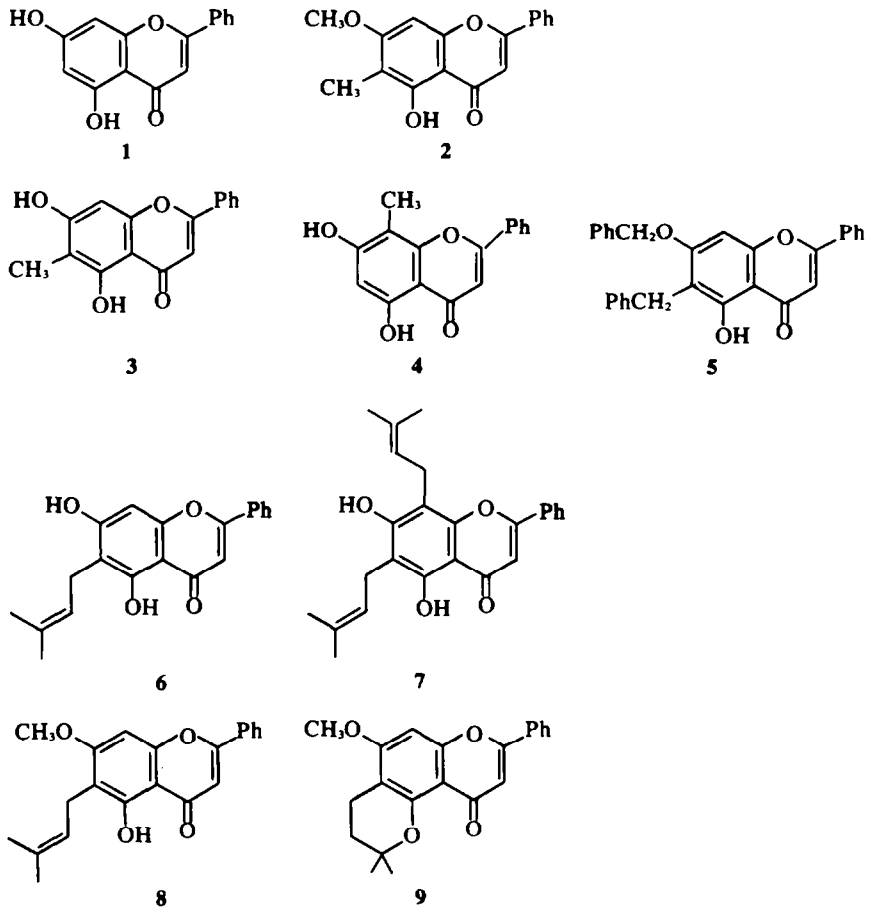
Base catalysed nuclear methylations of 5,7-hydroxy substituted flavonoids are generally effected by means of methanolic potassium hydroxide, or sodium methoxide, and methyl iodide.[2] Nuclear methylation has invariably been found to take place at the 6-position, and all hydroxy groups except, under the usual conditions, that at the 5-position are also methylated.[2] For example, chrysin in methanol on reaction with sodium methoxide and methyl iodide afforded 5 - hydroxy - 6 - methyl - 7 - methoxyflavone (**2**).[3,4] Chopin and Justin[5] in a similar reaction isolated 5,7 - dihydroxy - 6 - methylflavone (**3**) in addition to flavone **2**.

We now report that nuclear methylation occurs at the 8-position as well as at the 6-position when the disodium salt of chrysin is treated with methyl iodide in liquid ammonia or in monoglyme. The structures of the products **3** and **4** were established by their identity with authentic samples prepared by other routes previously described.[3] In contrast to earlier reported methylations of chrysin, no O-methylated products were isolated from these reactions. The disodium salt was prepared by the addition of one molecular equivalent of chrysin to two molecular equivalents of sodium amide in liq ammonia. That the dianion of I had formed completely was indicated by the absence of a purple colouration in the liquid ammonia solution on the addition of a drop of benzyl chloride.[6]

When the disodium salt of **1**, suspended in dioxan, was treated with dimethyl sulphate, the products were 5 - hydroxy - 6 - methyl - 7 - methoxyflavone **2** and 5 - hydroxy - 7 - methoxyflavone in 31% and 9% respectively. That O-methylation occurred in this reaction was not unexpected since dimethyl sulphate is known to favour this mode of reaction with phenols, but nuclear methylation of a 5,7-dihydroxyflavonoid with this reagent was unpredicted.[2]

No benzylation products were isolated on reaction of the chrysin dianion with benzyl chloride in liquid ammonia; chrysin was recovered almost quantitatively. A small amount of 1,2-diphenylethane (5%) was detected in the product by GLC. Benzylation of the disodium salt of chrysin suspended in dioxan yielded 6 - benzyl - 7 - benzyloxy - 5 - hydroxyflavone **5** in 42% yield. This product had been obtained previously by reaction of chrysin with potassium hydroxide and benzyl bromide in ethanolic solution.[7]

Reaction of the disodium salt of chrysin with prenyl bromide in liquid ammonia afforded two products which were assigned structures, 5,7 - dihydroxy - 6 - prenylflavone **6** and 5,7 - dihydroxy - 6,8 - diprenylflavone **7** on the basis of elemental analyses, NMR spectra and chemical reactions (Experimental). Study of this reaction was in the course of completion when Jain and Sharma[1] described the prenylation of chrysin by means of sodium methoxide and prenyl bromide in methanol to give the same products **6** and **7**. The main difference in results arising from the two reactions is that the diprenyl derivative **7** is the major product in the former reaction while the monoprenyl derivative **6** is the major product in the latter. Substitution of the two isoprenyl groups at the 6- and 8-positions in the diprenylated product was indicated by the absence of the two A-ring proton signals in the NMR spectrum of the product. The presence of only one A-ring proton in the spectrum of the monoprenylated product showed it to be a C-alkylated derivative. That substitution had occurred at the 6- rather than at the 8-position was demonstrated by the cyclisation of the partially methylated derivative **8** to the chroman **9** by means of formic acid. The mono methyl ether **8** was produced by the reaction of one equivalent of dimethyl sulphate with chrysin in acetone in the presence of potassium carbonate. The NMR spectrum of the product **8** had a OMe signal at τ6·10 and an OH signal at τ − 2·75. The low τ-value of the latter may be attributed to chelation between the 5-hydroxy and the ketone groups, and consequently methylation must have occurred at the 7-position. A strong positive ferric chloride test on the product also indicated that the OH group at the 5-position had not been methylated. The NMR spectrum of the cyclised product **9** showed triplets characteristic of the chroman system and a singlet for the two equivalent Me



groups. The formation of a chroman ring from the 7-O-Me derivative is only possible when the prenyl group is located at the 6-position.

Prenylation of the disodium salt of chrysin with prenyl bromide was also carried out using monoglyme as solvent. Flavones **6** and **7** were again the products; however, in this case flavone **6** was obtained in much reduced yield.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on a Perkin-Elmer IR 700 spectrometer. NMR spectra were recorded on a Perkin-Elmer R12 spectrometer operating at 60 MHz. Samples were run as solutions in the solvents indicated using TMS as internal reference.

The methylation of chrysin **1**

1. *With methyl iodide in liq ammonia.* Chrysin (1·28 g, 0·005 mole) was slowly added to a stirred soln of sodium amide (0·01 mole) in liq ammonia (100 ml). The resulting suspension was stirred for 30 min. No red colouration was observed when one drop of benzyl chloride was added. A soln of MeI (0·709 g, 0·005 mole) in anhyd ether (5 ml) was added dropwise and the stirring of the mixture was continued for a further hr. Ammonium chloride (0·32 g, 0·06 mole) was added and the ammonia allowed to evaporate. The residue was treated with iced water (5 ml), neutralised with dil HCl and extracted repeatedly with ether. Removal of the solvent from the dried ethereal extract gave a brown solid which on fractional crystallisation from MeOH afforded **1** (0·83 g; 65%), mp and mmp 278°; **3**, (1·153 g; 12%) mp 308–310° (lit.[3] mp 308–310°); and **4**, (0·192 g; 12%) mp 255–256° (lit.[3] mp 255–256°). Mixture mp determinations of **3** and **4** with authentic samples of these compounds prepared by the methods described by Mukerjee and Seshadri[3] were undepressed.

2. *With methyl iodide in monoglyme.* A soln of the disodium salt of **1** (0·005 mole) in liq ammonia was prepared as in the previous expt. The ammonia was evaporated (steam bath) and replaced by anhyd monoglyme (100 ml). A soln of MeI (0·709 g; 0·005 mole) in anhyd ether (5 ml) was added dropwise and stirring was continued for 2 hr. The monoglyme was removed and the solid residue was worked up as in the previous expt to give **1** (0·973; 76%) mp and mmp 277–278°; **3**, (0·077 g; 6%), mp and mmp 308–310°, and **4**, (0·102; 8%), mp and mmp 255–256°.

3. *With dimethyl sulphate in liq ammonia.* A suspension of the disodium salt of **1** (0·64; 0·0025 mole) in liq ammonia (50 ml) was prepared as in the previous expt. After 1 hr the ammonia was replaced by anhyd dioxan. Me_2SO_4 (0·316 g; 0·0025 mole) was added and the mixture heated under reflux for 1 hr. The brown residue obtained on removal of the solvent was treated with ice and 10% HCl. The product was fractionally crystallised from MeOH to give **1** (0·356; 55%) mp and mmp 277–278°; **2**, (0·22 g; 31%), mp 170–172° (lit.[4] mp 170–171°); a mixture mp determination with an authentic sample[4] was undepressed; and 5 - hydroxy - 7 - methoxyflavone (0·054 g; 9%), mp 165° (lit.[7] mp 165°), a mixture mp determination with an authentic sample[7] was undepressed.

The benzylation of chrysin

1. *With benzyl chloride in dioxan.* A suspension of the disodium salt of **1** (0·0025 mole) in dioxan (50 ml) was prepared as in the previous expt. Benzyl chloride (0·315 g, 0·0025 mole) was added and the mixture heated under reflux for 1 hr. The orange solid obtained on removal of the solvent from the mixture was treated with ice and 10% HCl. The product obtained crystallised from acetone in pale yellow needles of **5**, (0·458 g; 42%), mp and mmp 205° (lit.[7] mp 205°).

2. *Attempted benzylation of disodiochrysin in liquid ammonia.* A soln of benzyl chloride (0·630 g, 0·005 mole) in anhyd ether (5 ml) was added dropwise to a stirred soln of disodiochrysin (0·005 mole) in liq. ammonia (100 ml) and stirring was continued for a further hr. Ammonium chloride (0·32 g, 0·06 mole) was added and the ammonia was allowed to evaporate. Work up of the residue* treated with iced water gave yellow needles (from MeOH) **1** (1·15 g; 91%), mp and mmp 278°.

The prenylation of chrysin

1. *With prenyl bromide in liq ammonia.* A soln of prenyl bromide* (0·745 g, 0·005 mole) in anhyd ether (5 ml) was added dropwise to a stirred suspension of disodiochrysin (0·005 mole) in liq ammonia (100 ml) and stirring was continued for a further 1 hr. The residue was treated with water (100 ml), neutralised with dil HCl and extracted with ether (5 × 100 ml). Removal of the solvent from the dried ethereal extracts gave a yellow-brown residue which was chromatographed, (silica gel/$CHCl_3$) collecting 100 ml fractions. Fractions 4 and 5 yielded, yellow crystals (from MeOH) of **7**, (0·31 g; 2%), mp 170° (Jain and Sharma[1] report mp 196° for this compound); ν_{max} (KBr), 1645, 1610 cm^{-1}; NMR (DMSO-d_6), τ 8·33 and 8·21 (singlets, 12H, two $(CH_3)_2C$=groups), 6·62 (incompletely resolved m, 4H, two CH_2 groups), 4·78 (incompletely resolved m, 2H, two –CH=groups), 2·99 (s, 1H, 3-H) 2·30 and 1·93 (ms, 3H and 2H, 2-Ph groups). (Found: C, 76·91; H, 6·50; $C_{25}H_{26}O_4$ requires: C, 76·90; H, 6·71%).

Fractions 6–11 yielded, yellow crystals (from $CHCl_3$) of **6**, (0·406 g; 24%), mp 213–214°; ν_{max}(KBr), 1635, 1620, 1450, 1355 cm^{-1}; NMR (DMSO-d_6), τ 8·34 and 8·24 (two sls, 6H, Me_2C=group), 6·72 (d, J = 7H_z, 2H, CH_2), 4·74 (t, J = 7 Hz, 1H, –CH=groups), 3·34, 3·03 (sls, 1H and 1H, 8-H and 3-H), 2·32 and 1·89 (m, 3H and 2H, 2-Ph group), −0·85 (s, 1H, 7-OH), −3·10 (s, 1H, 5-OH). The two latter peaks diminish on addition of D_2O. (Found: C, 74·32; H, 5·63. $C_{20}H_{18}O_4$ requires: C, 74·52; H, 5·63%).

2. *With prenyl bromide in monoglyme.* Chrysin (1·23 g, 0·005 mole) was added to a stirred soln of sodium amide (0·01 mole) in liq ammonia (100 ml). The ammonia was slowly evaporated and replaced by anhyd monoglyme (100 ml). A soln of prenyl bromide (0·745 g, 0·005 mole) in anhyd ether (5 ml) was added slowly and the mixture sitrred at room temp for 2 hr. Work up of the solid obtained on removal of the solvent gave **7** (0·108 g; 5%), mp and mmp 170°; **6** (0·069 g; 4%), mp and mp 214° and **1** (0·69 g; 54%) mp and mmp 278°.

The methylation of flavone **6**

A mixture of **6** (0·150 g, $0·465 \times 10^{-3}$ mole), Me_2SO_4 (0·044 ml, $0·465 \times 10^{-3}$ mole), K_2CO_3 (0·90 g) and acetone (30 ml) was heated under reflux for 4 hr. The yellow solid (0·141 g) obtained on work-up of the mixture separated on PLC (silica/$CHCl_3$) to give yellow crystals of **8**, (0·124; 79%), mp 168°, ν_{max} (KBr) 1610 (broad), 1450 cm^{-1}, NMR ($CDCl_3$), τ 8·31 and 8·21 (sls, 6H, $(CH_3)_2C$=group), 6·64 (d, J = 7 Hz, 2H, CH_2), 6·10 (s, 3H, 3-H), 4·71 (t, J = 7 Hz, 1H, =CH–), 3·50 and 3·35 (sls, 1H and 1H, 3-H and 8-H), 2·42 and 2·09 (ms, 3H and 2H, 2-Ph), −2·75 (s, 1H, 5-OH). The compound gave a dark grey-green colouration with ethanolic $FeCl_3$. (Found: C, 75·30; H, 5·80. $C_{21}H_{20}O_4$ requires: C, 74·98; H, 5·99).

The cyclisation of flavone **8**

Flavone **8** (0·115 g) in formic acid (20 ml) was heated under reflux for 2 hr. The mixture was cooled, treated with a mixture of ice and water (100 ml) and extracted with chloroform. The residue obtained on removal of the solvent from the dried extract was recrystallised from MeOH to give yellow needles of **9**, (0·110 g; 96%), mp 249–250°; ν_{max} (KBr) 1590 (broad), 1440 cm^{-1}, NMR ($CDCl_3$), 8·55 (s, 6H, $(CH_3)_2C$), 8·16 (t, J = 7 Hz, 2H, CH_2), 7·31 (t, J = Hz, 2H, CH_2), 6·04 (s, 3H, OCH_3), 3·44 and 3·29 (sls, 1H and 1H, 3-H and 8-H), 2·43 and 2·05 (mls, 3H and 2H, 2-Ph). (Found: C, 74·86; H, 5·69. $C_{21}H_{20}O_4$ requires: C, 74·98; H, 5·99%).

*Examination of the product by GLC showed the presence of diphenylethane (5%).

REFERENCES

[1]A. C. Jain and B. N. Sharma, *J. Org. Chem.* **39**, 1149 (1964)

[2]T. R. Seshadri in *The Chemistry of Flavonoid Compounds*, Ed. T. A. Geissman, Pergamon Press, p. 180 (1962); J. C. Jain and T. R. Seshadri, *Quart Rev.* **10**, 169 (1956)

[3]S. K. Mujerjee and T. R. Seshadri, *Proc. Ind. Acad. Sci.* **38A**, 207 (1953)

[4]D. Pillon and C. Mentzer, *Bull. Soc. chim. France*, 30 (1954)

[5]J. Chopin and M. Justin, *Compt. rend.* **248**, 3307 (1959)

[6]C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor and A. E. Brodhag, *J. Am. Chem. Soc.* **78**, 1653 (1956)

[7]K. C. Gulati and K. Venkataraman, *J. Chem. Soc.* 267 (1936)