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NATURAL COUMARINS—VII*

THE CONSTITUTION OF SOME COUMARIN AND COUMARILIC ACID DERIVATIVES

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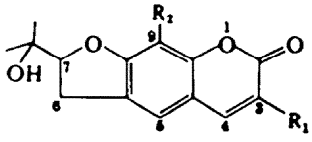
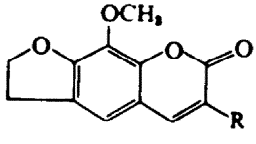
Abstract—A study of the various possibilities of nuclear substitution in a dihydrofurocoumarin (marmesin), its anhydro derivative and the related coumarilic acids is reported. The location of the substituent (bromine) is established by chemical and NMR spectral evidence.

THE behaviour of simple coumarins[1] towards various types of substitution is considerably modified by the fusion of a furan or a dihydrofuran moiety. We have previously demonstrated, on chemical evidence, that bromination or nitration of a linear dihydrofurocoumarin, such as marmesin[2] (I) or 6,7-di-hydroxanthotoxin[3] (II), first engages the C-3 position (III and IV, respectively). In such behaviour the aromaticity is confined to the coumarin part of the molecule and the entering group occupies the same position as in coumarin[4] and 6,7-disubstituted coumarins.[5] We found that treating marmesin with a large excess of bromine (10 moles) affords





I: $R_1 = R_2 = H$
III: R_1 = Br or NO_2; $R_2 = H$
V: $R_1 = R_2$ = Br

II: R = H
IV: R = Br or NO_2

a dibromo derivative in which one bromine atom is located at C-3 since it was also obtained by a similar treatment of III. A support of this assignment was obtained by the transformation of the dibromo derivative into a monobromo coumarilic acid by alkali treatment which is diagnostic for a 3-brominated coumarin constitution. The location of the second bromine atom at C-9 appears to be favoured by a consideration of the known reactivities of 2-alkyl coumaran[6] and coumarin.[1] Bromination of such products leads to substitution at the 5-position in the first and at the

* Part VI, *Canad. J. Chem.*, in press (1966).

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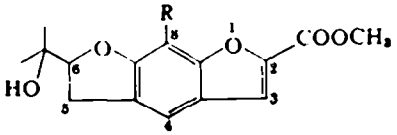
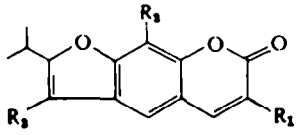
3-, 6- and 8- (but not the 5-) positions in the second. Since marmesin combines the features of both moieties, it appears then that the only sites of attack are the 3- and 9-positions of the nucleus. Moreover, regarding marmesin as a phenol ester, it is reasonable to expect substitution to take place at the vacant position (C-9) *ortho* to the ester group by analogy with the known behaviour of phenol esters.[7] The dihydrofurocoumarilic acid ester (VI), obtainable[2] from 3-bromomarmesin (III) by alkali treatment, may also be regarded, on one side, as a coumarilic acid derivative and, on the other side, as a 2-alkylcoumaran. The bromination of these compounds is known[8] to lead to substitution at the 5-position (*para* to the ethereal oxygen) in both. With such position unavailable in VI, the bromination of this compound would reasonably affect the *ortho* position, namely C-8. The resulting compound (VII) was identical with the monobromocoumarilic acid resulting from V by alkali treatment.





VI: R = H VII: R = Br

VIII: $R_1 = Br$; $R_2 = R_3 = H$ IX: $R_1 = R_2 = Br$; $R_3 = H$

XI: $R_1 = R_2 = R_3 = H$ XII: $R_1 = R_3 = H$; $R_2 = Br$

XIII: $R_1 = R_3 = Br$; $R_2 = H$ XIV: $R_1 = R_2 = R_3 = Br$

The formulation of dibromomarmesin as V finds support from a consideration of the NMR spectral data (cf. Table). We have recently outlined[9] the various proton assignments in the molecule of marmesin (I) and now find the signals attributable to both C-3 and C-9 protons unambiguously absent in the spectrum of V. Additional support appears from a comparison of the spectrum of the anhydro derivative (IX) of V with those of 3-bromo-7-isopropylpsoralene[2] (VIII) and anhydromarmesin[10] (XI) (cf. Table). Dehydration of the coumarilic acid ester (VII) with phosphorus pentoxide gave the monobrominated furocoumarilic acid ester (X) in which the location of the bromine atom was again evidenced from the NMR data.

Attention was next turned to the study of the corresponding anhydro derivatives in which the extension of conjugation brings about a general delocalization of the mobile electrons in the coumarin system. This, besides producing a paramagnetic shift in the location of signals from most protons (for example in anhydromarmesin[10] (XI) as compared with marmesin[9]), creates a fresh aromatic centre in the fused furan moiety. The action of bromine (2 moles) on 7-isopropylpsoralene (XI) led to a monobromo derivative in which the new substituent is, in all probability, located at C-6 (XII). This is not only because of the apparent structural analogy of XI to 2-methylbenzofuran which is reported[1c] to afford the 3-bromo derivative, but also because of the evidence obtained from the NMR spectrum (cf. Table).

This behaviour of XI reflects the enhanced activity at C-6, influenced by the neighbouring alkyl group, among all other centres. Bromination of other products

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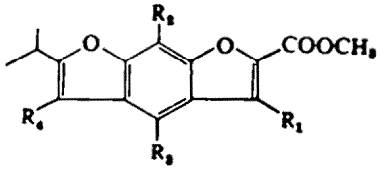
TABLE

No.	Compound	Chemical shifts*							Coupling constants c/s
		δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	δ_9	J_{34}
I	Marmesin	6·22[a]	7·90[a]	7·44	3·22[a]	4·77[b]	—	6·74	10
II	6,7-Dihydroxanthotoxin	6·25[a]	7·71[a]	7·08	3·31[b]	4·79[b]	—	—	10
IV	3-Bromo-6,7-dihydro-xanthotoxin	—	8·04	7·03	3·28[b]	4·73[b]	—	—	—
V	3,9-Dibromomarmesin	—	8·24	7·33	3·38[a]	4·82[b]	—	—	—
VIII	3-Bromo-7-isopropyl-psoralene	—	8·21	7·57	6·49	—	—	7·40	—
IX	3,9-Dibromo-7-isopropyl-psoralene	—	8·18	7·52	6·57	—	—	—	—
X	8-Bromo-6-isopropylfuro-coumarilic acid methyl ester	7·58	7·53	6·43	—	—	—	—	—
XI	7-Isopropylpsoralene†	6·30[a]	7·90[a]	7·66	6·53	—	—	7·37	10
XII	6-Bromo-7-isopropylpsoralene	6·40[a]	8·11[a]	7·72	—	—	—	7·54	10
XIII	3,6-Dibromo-7-isopropyl-psoralene	—	8·01	7·65	—	—	—	7·48	—
XIV	3,6,9-Tribromo-7-isopropylpsoralene	—	8·10	7·74	—	—	—	—	—
XV	6-Isopropylfurocoumarilic acid methyl ester	7·67	7·60	6·42	—	—	7·60	—	—
XVI	4,5-Dibromo-6-isopropyl-furocoumarilic acid methyl ester	7·64	—	—	—	—	7·59	—	—
XIX/ XX	3- or 4-,5,8-Tribromo-6-isopropylfurocoumarilic acid methyl ester	7·61	—	—	—	—	—	—	—

† Reported[10] in acetonitrile

* With reference to tetramethylsilane (zero)

[a] Doublet, [b] Triplet.



X: $R_1 = R_2 = R_4 = H$; $R_3 = Br$ XV: $R_1 = R_2 = R_3 = R_4 = H$

XVI: $R_1 = R_2 = H$; $R_3 = R_4 = Br$ XVII: $R_1 = R_2 = R_3 = H$; $R_4 = Br$

XVIII: $R_1 = R_2 = H$; $R_3 = R_4 = Br$ XIX: $R_1 = R_2 = R_4 = Br$; $R_3 = H$

XX: $R_1 = H$; $R_2 = R_3 = R_4 = Br$

in this series also leads to attack of this position *a priori*. Thus while 3-bromomarmesin (III) is not affected by the action of one mole of bromine, the same treatment of its anhydro analogue (VIII) readily affords a dibromo compound which is different from IX and believed to possess constitution XIII; (see NMR data in the adjoining Table). Also, bromination of IX afforded a tribromo derivative, formulated as XIV, in which the hydrogen atom at C-6 was substituted and the remaining protons (at C-4 and C-5) were easily detected in the NMR spectrum.

The availability of several brominated furo- and dihydrofurocoumarin products

in this series, induced us to extend the present study, of nuclear substitution and correlation with NMR data, to the derived coumarilic acid products. These were always obtained by alkali treatment of the corresponding 3-brominated coumarin precursors. The coumarilic acid ester (XV) was obtained[8] directly from VIII or from III *via* VI followed by dehydration. The action of bromine on this compound afforded a dibromo derivative (XVI) which was also obtained by the action of alkali on XIII, to give the coumarilic acid ester XVII, followed by further bromination. That the new dibromocoumarilic acid derivative (XVI) is actually substituted in the isopropylfuran part of the molecule appears from its origin. The location of the second bromine atom in the benzene ring rather than in the furancarboxylic acid part appears to be favoured by the NMR spectrum (cf. Table) which contains a peak at δ 7·64 attributable[9] to the C-3 proton. This bromine atom is most likely located at C-4 since the alternative structure (XVIII) is certainly possessed by the product resulting from the action of alkali on XIV. The reactivity of the C-5 position in such furocoumarilic acid system, enhanced by the electropositive 6-isopropyl group, has also been demonstrated in the behaviour of the 8-bromo-6-isopropyl derivative (X) towards further bromination. The tribromo derivative which resulted contained one halogen atom at C-5, beside one at C-8, since it was also obtained from XVIII. The location of the third bromine atom, at C-3 or at C-4, gives two possible formulations (XIX and XX) for choice. Owing to the close location of the NMR signals from the C-3 and C-4 protons (δ 7·67 and 7·60 respectively) in the non-brominated parent system[9] (XV), it is difficult to make a definite choice; the spectrum of the new compound (XIX or XX) contains one singlet due to one proton at δ 7·61.

EXPERIMENTAL

The m.ps were taken on a Kofler block and are uncorrected. The NMR spectra were measured on a 60 MC instrument (NMR Specialities, Inc.) in $CDCl_3$, sometimes with addition of DMSO to effect complete dissolution of the sample.

3,9-*Dibromomarmesin* (V). Marmesin (I, 0·5 g) in chf (15 ml) was treated with Br (10 moles, 1·1 ml) in chf (5 ml). The mixture was concentrated and alcohol added to precipitate the dibromo derivative (650 mg) which on crystallization from alcohol gave yellowish plate like needles, m.p. 193–195°. (Found: C, 41·66; H, 2·93; Br, 39·56. $C_{14}H_{12}O_4Br_2$ requires: C, 41·58; H, 2·97; Br, 39·60%.)

This product could also be obtained by treating III[8] with 10 moles Br in a similar manner.

6-(*β-Hydroxyisopropyl*)-5,6-*dihydrofuro*-8-*bromocoumarilic acid methyl ester* (VII). Compound V (500 mg) was refluxed with 6N NaOH (25 ml) for ½ hr. After cooling and acidification, the product (400 mg) was collected and dried. This was dissolved in acetone (100 ml) and refluxed together with MeI (4 ml) and K_2CO_3 (6g) for 20 hr. After filtration, the acetone solution was concentrated and cooled. Water was added to deposit colourless prismatic plates of VII which was also prepared by the bromination of VI[6], m.p. and mixed m.p. 157–159°. (Found: C, 50·54; H, 4·16; Br, 22·34 $C_{15}H_{15}O_6Br$ requires: C, 50·07; H, 4·55; Br, 22·22%.)

3,9-*Dibromo*-7-*isopropylpsoralene* (IX). A soln of V (1 g) in dry benzene (100 ml) was refluxed with P_2O_5 (10 g) for 5 hr. After decantation, the clear benzene soln was concentrated to separate colourless prismatic plates (600 mg) which were crystallized from alcohol, m.p. 202–204°. (Found: C, 43·55; H, 2·66; Br, 41·45. $C_{14}H_{10}O_3Br_2$ requires: IC, 43·52, H, 2·59; Br, 41·45%.)

8-*Bromo*-6-*isopropylfurocoumarilic acid methyl ester* (X). A solution of VII (1 g) in benzene (100 ml) was refluxed with P_2O_5 (10 g) for 5 hr. After working up as usual, the yellow gummy residue was crystallized from EtOH to give X as colourless prisms (600 mg), m.p. 115–117°. (Found: C, 52·97; H, 3·78; Br, 24·16. $C_{15}H_{15}O_6Br$ requires: C, 53·41; H, 3·85; Br, 23·74%.)

6-*Bromo*-7-*isopropylpsoralene* (XII). Compound XI[9] (500 mg) in chf solution was treated with Br (2 moles), at room temp. The mixture was evaporated after standing for a few min and the residue crystallized from EtOH to give the bromo derivative as colourless plates, m.p. 128–130°. (Found: C, 54·57; H, 3·55; Br, 25·48. $C_{14}H_{11}O_3Br$ requires: C, 54·72; H, 3·58; Br, 26·05%.)

3,6-*Dibromo-7-isopropylpsoralene* (XIII). Compound VIII[3] (100 mg) was treated with Br (1 mole) in a chf (2 ml) soln. The solvent was shortly evaporated to dryness and the residue crystallized from alcohol to give pale yellowish needles, m.p. 133–135°. (Found: C, 43·22; H, 2·06. $C_{14}H_{10}O_3Br_2$ requires: C, 43·49; H, 2·59%.)

3,6,9-*Tribromo-7-isopropylpsoralene* (XIV). A soln of IX (50 mg) in chf was treated with 1 mole Br and the product was isolated in the usual manner. The product (colourless felted needles, 50 mg) was crystallized from chf–EtOH, m.p. 182–184°. (Found: C, 36·66; H, 1·93; Br, 51·68. $C_{14}H_9O_3Br_3$ requires: C, 36·12; H, 1·93; Br, 51·61%.)

5-*Bromo-6-isopropylfurocoumarilic acid methyl ester* (XVII). Compound XIII (250 mg) was refluxed in 6N NaOH for ½ hr. After working up in the usual manner, the product was dissolved in acetone, treated with MeI (2·5 ml) and refluxed with K_2CO_3 (2·5 g) for 24 hr. The Me ester (175 mg) was collected as usual and crystallized from alcohol, m.p. 113–114°. (Found: C, 53·64; H, 3·89. $C_{15}H_{13}O_4Br$ requires: C, 53·41; H, 3·85%.)

4,5-*Dibromo-6-isopropylfurocoumarilic acid methyl ester* (XVI). (a) A solution of XV[3] (260 mg) in chf (4·5 ml) was treated with a soln of Br (2 moles) in chf at room temp. The product, isolated after evaporation of the solvent and treatment with alcohol, was crystallized from EtOH to give XVI as clusters of needles, m.p. 156–158°. (Found: C, 34·51; H, 3·03; Br, 38·47. $C_{15}H_{12}O_4Br_2$ requires: C, 34·26; H, 2·85; Br, 38·45%.) (b) Compound XVI was also obtained when XVII (50 mg) was treated with Br in a similar manner.

5,8-*Dibromo-6-isopropylfurocoumarilic acid methyl ester* (XVIII). A mixture of XIV, (300 mg) and a 6N NaOH (20 ml) was refluxed for ½ hr. The product was isolated after acidification and directly methylated as previously described by refluxing its acetone soln with MeI and anhydrous K_2CO_3 for 20 hr. After filtration, the clear soln was concentrated and treated with hot water. Colourless needles (120 mg) were obtained, m.p. 142–145°.

Bromination of XVIII. (a) This compound (75 mg) was treated with 1 mole Br in chf soln in the usual manner. The product was crystallized from alcohol to give a tribromocompound as a mass of colourless needles (70 mg), m.p. 202–204°. (Found: C, 36·49; H, 2·52; Br, 49·08. $C_{15}H_{11}O_4Br_3$ requires: C, 36·36; H, 2·22; Br, 48·48%.) (b) This compound (XIX or XX) was also obtained by the action of 1 mole of Br on X in chf solution as usual.

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