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SYNTHESIS OF BENZOFURANOID SYSTEMS. I.
FUROCOUMARINS, BENZOFURANS AND DIBENZOFURANS

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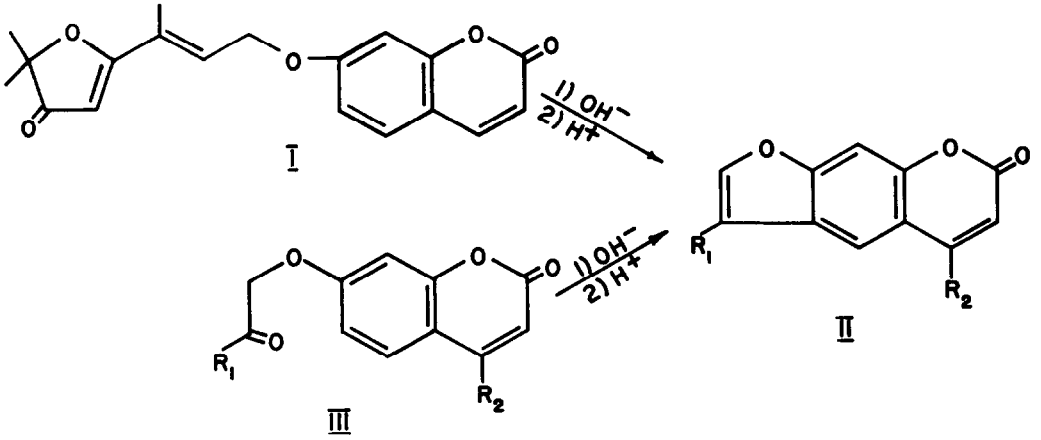
The naturally-occurring coumarin geiparvarin (I) on treatment with mild aqueous base, was shown to undergo a retro-Aldol condensation followed by cyclisation to generate the linear furocoumarin psoralene (II, $R_1 = R_2 = H$: 58%).[1] The postulated intermediate in this cyclisation process, 7-(2-oxoethoxy)coumarin (III, $R_1 = R_2 = H$) was synthesised[2] and on similar base treatment[1] gave psoralene in reasonable yield (30%). Esse and Christensen[2] had previously reported that they were unsuccessful in attempts to cyclise the 4-methyl derivative of 7-(2-oxoethoxy)coumarin (III, $R_1 = H$, $R_2 = CH_3$) to the corresponding furocoumarin (II, $R_1 = H$, $R_2 = CH_3$) under a variety of acidic and basic conditions. Also on repetition of the earlier reported work of Ray[3] on the sodium ethoxide catalysed cyclisation of 7-acetonyloxy-coumarin (III, $R_1 = CH_3$, $R_2 = H$) they obtained the β-methylpsoralene (II, $R_1 = CH_3$, $R_2 = H$) in only 4% yield.

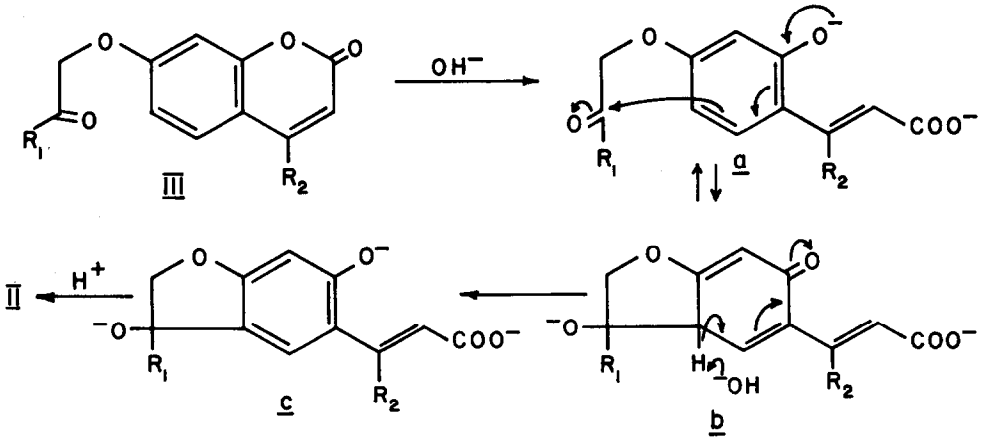


Since our method of synthesis of psoralene involves only four simple steps starting from resorcinol and malic acid (von Pechmann condensation; etherification with allyl bromide; ozonolysis; base-catalysed cyclisation) this offers a considerable improvement over other

published methods of total synthesis of this biologically active compound. We now report the application of this base-catalysed cyclisation process to the preparation of other linear furocoumarins and to the synthesis of benzofurans and dibenzofurans.

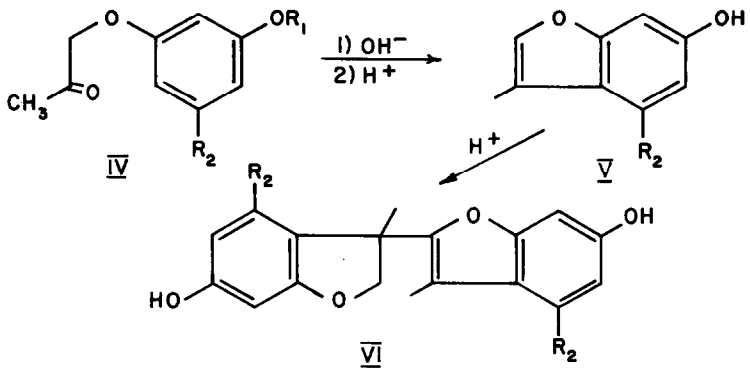
Condensation of chloroacetone or phenacyl bromide with umbelliferone (7-hydroxycoumarin) or its 4-methyl derivative in acetone/K_2CO_3 gave (III, R_1 = CH_3 or C_6H_5, R_2 = H or CH_3) in high yield. Treatment of these four compounds in refluxing 0.1N aqueous KOH for 6 hours followed by cooling and acidification gave the respective β-substituted furocoumarins (II[3], R_1 = CH_3 or C_6H_5, R_2 = H or CH_3) in better than 80% yield of recrystallised product. The PMR spectra of these compounds confirmed that cyclisation had occurred in one direction only to give the linear furocoumarin skeleton.

The mechanism of this reaction can be described as a type of intramolecular aldol condensation in which the phenoxide ion (a), formed on base hydrolysis of the pyrone ring, promotes attack at the exocyclic carbonyl function through the resonance-stabilised carbanion generated at the position para to the phenoxide ion, viz, a → b. The irreversibility of the process is established by abstraction of the proton from the newly formed ring junction to regenerate the coumarinic acid salt c. On acidification the pyrone ring is reformed and following protonation of the alkoxy ion, water is spontaneously eliminated from the labile β-hydroxydihydrofuran ring system to give the psoralene derivative (II).



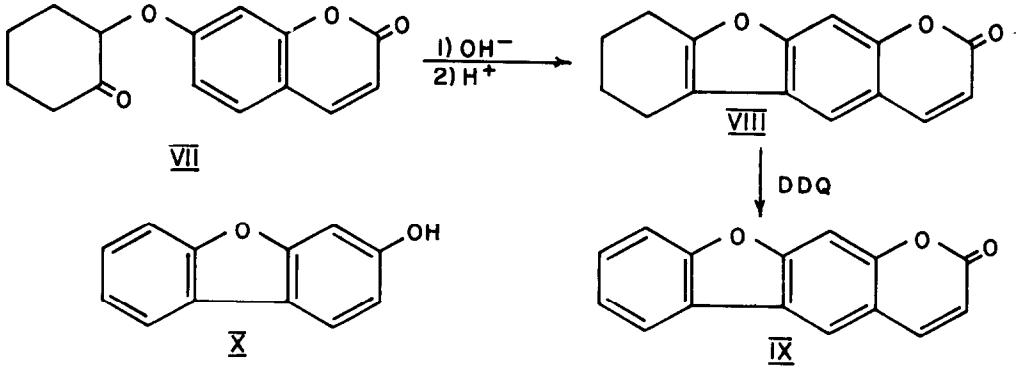
As an extension of the method, we have successfully applied it to the synthesis of 6-hydroxybenzofuran derivatives. The mono-acetonyl ether of resorcinol (IV, R_1 = H, R_2 = H) when treated under reflux with aqueous 0.1N KOH for 4 hours underwent cyclisation to furnish

6-hydroxy-3-methylbenzofuran,[5] m.p. 104-105° (V, R_2 = H; 75%). The mono-methylether (IV, R_1 = CH_3, R_2 = H) did not undergo base catalysed cyclisation and was recovered essentially unchanged.



The acetonyl ether of the mono-benzenesulphonate ester of phloroglucinol mono-methylether[6] (IV, R_1 = $SO_2\emptyset$, R_2 = OCH_3) under similar basic conditions after initial rapid hydrolysis of the ester moiety cyclised cleanly to the benzofuran (V, R_2 = OCH_3), m.p. 102-103° (95%). In both cases cyclisation took place only to the ring position para to the free phenol. The final acidification step had to be carried out cautiously to avoid acid-catalysed formation of the dimer (VI).

To illustrate further the utility of this synthetic method, we prepared in good yield the dibenzofuran derivative (IX) by condensation of 2-bromocyclohexanone with 7-hydroxycoumarin to give (VII), m.p. 169-170°, followed by treatment with aqueous KOH under reflux. The isolated product (VIII), m.p. 148-150°, was readily dehydrogenated with DDQ in benzene to the function-alised dibenzofuran (IX), m.p. 202-203°. Similarly, resorcinol mono-benzenesulphonate, after etherification with 2-bromocyclohexanone, base hydrolysis/cyclisation and dehydrogenation, gave the dibenzofuran (X),[7] m.p. 140-141°.



We are presently engaged in an extensive investigation of the scope of this reaction and its use in the synthesis of other naturally-occurring compounds of biological interest.[8]

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