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CLAISEN REARRANGEMENTS IN THE XANTHONE SERIES AND SYNTHESIS OF DIHYDROISOJACAREUBIN

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Allyl aryl ethers usually undergo thermal Claisen rearrangements to give exclusively _ortho_ allylphenols[1] and this fact has been used in synthesis of extended xanthones in high yield[2]. Rearrangement to the _para_ position is expected only when the _ortho_ positions are already substituted although there are some exceptions[1a]. The recent report that γ-phenylallyl and γ-methylallyl _meta_ substituted phenyl ethers undergo Claisen rearrangement to yield mixtures of _ortho_ and _para_ allylated phenols[3] prompts us to give a preliminary account of similar work in the xanthone series which has led to the synthesis of dihydroisojacareubin.

The reaction of 1-hydroxy-3,5,6-trimethoxyxanthone[4] (Ia) in presence of

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[1] (a) D. S. Tarbell, The Claisen Rearrangement, in R. Adams, "Organic Reactions", Vol. _II_, chap. 1, John Wiley & Sons, Inc., New York, 1944.
(b) H. Schmid, _Gazzetta_, _92_, 968, (1962)

[2] (a) F. Scheinmann and H. Suschitzky, _Tetrahedron_, _7_, 31, (1959)
(b) A. Mustafa, M. M. Sidky, S.M.A.D. Zayed, and F. M. Soliman, _ibid_, _19_, 1335, (1963)

[3] J. Borgulya, H. J. Hansen, R. Barner and H. Schmid, _Helv. Chim.Acta_, _46_, 2444, (1963)

[4] (a) F. E. King, T. J. King and L. C. Manning, _J. Chem. Soc_. 3932, (1953)
(b) G. D. Shah, and R. C. Shah, _J. Sci. Ind. Res., India_, _15б_, 630, (1956)

potassium carbonate and acetone with allyl bromide gave the allyl ether (Ib) m.p. 143 - 144°. Similarly with γ,γ-dimethylallyl bromide the γ,γ-dimethylallyl ether (Ic) m.p. 142° was prepared. Rearrangement of the allyl ether (Ib) in boiling dimethylaniline proceeded normally to give the 2-allyl derivative (Id) m.p. 194°, since ozonolysis yielded formaldehyde, isolated as the dimedone derivative, and the xanthylacetaldehyde (Ie) m.p. 224 - 226°, ν 1718 cm^{-1} (aliphatic aldehyde), which gave a 2,4-dinitrophenylhydrazone derivative m.p. 256°. The orientation of the xanthylacetaldehyde (Ie) was proved by cyclisation, with polyphosphoric acid to the furanoxanthone (II) m.p. 245°, and by the nuclear magnetic resonance spectrum of the product which shows the α-furano-proton at 2.31τ and the β-furano proton at 3.21τ as doublets (J 2.0 c/s).

In contrast the γ,γ-dimethylallyl ether (Ic) in dimethylaniline rearranged abnormally and the chief isomeric product did not cyclise in presence of formic acid, and gave the same hydrogen bromide adduct m.p. 146° when addition was carried out in presence or in absence of peroxides[5]. This adduct failed to cyclise in presence of sodium ethoxide but instead underwent elimination of hydrogen bromide. The chief rearrangement product was proved to be 4-γ,γ-dimethylallyl-1-hydroxy-3,5,6-trimethoxyxanthone (If), m.p. 162°, by ozonolysis and nuclear magnetic resonance spectroscopy. Ozonolysis yielded acetone and a xanthylacetaldehyde (Ig), 1718 cm^{-1} (alphatic aldehyde), m.p. 210 - 212°, depressed on admixture with the 2-xanthylaldehyde (Ie) and which yields a 2,4-dinitrophenylhydrazone m.p. 266 - 268° (decomp.). The nuclear magnetic resonance spectrum confirmed the nature of the side chain and its orientation by showing the presence of three aromatic protons two of which are adjacent (Table 1)[6] thus eliminating the possibility of migration to the other aromatic nucleus.

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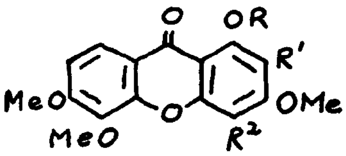
[5] C. D. Hurd and W. A. Hoffman, J. Org. Chem., 5, 212, 1940

[6] The nuclear magnetic resonance spectra were measured on a Varian HR-100 spectrometer. M. L. Wolfrom et al Tetrahedron Letters, No.12, 749, (1963) quote nuclear magnetic resonance data for xanthone analogues which are in agreement with our results.

By chromatography on silica gel three additional products were isolated: 1-hydroxy-3,5,6-trimethoxyxanthone (Ia), the furanoxanthone (III) m.p. 155 - 156° and, the normal Claisen rearrangement product (Ih) m.p. 122° whose structure is supported by presence of three vinyl protons consistent with an ABX system linked to a tertiary carbon atom (Table 1)[6]. In another experiment 2,4-di-γ,γ-dimethylallyl-1-hydroxy-3,5,6-trimethoxyxanthone (Ii) m.p. 120° was also isolated.

The 2-α,α-dimethylallylxanthone (Ih) cyclises to the furanoxanthone (III) by refluxing with formic acid or with dimethylaniline. In contrast to the results of Schmid *et al.*[3], it is significant that dimethylaniline does not cause further migration of the side chain from C - 2 to C - 4 because it proves that in this case the *p*-Claisen rearrangement does not proceed by prior formation of the *ortho* isomer (Ih). However, it is still possible that both *ortho* and *para* rearrangement products (Ih and If) are irreversibly formed from the same transient cyclohexadienone intermediate.



I

a; $R = R^1 = R^2 = H$

b; $R = CH_2.CH:CH_2$, $R^1 = R^2 = H$

c; $R = CH_2.CH:C(CH_3)_2$, $R^1 = R^2 = H$

d; $R = R^2 = H$, $R^1 = CH_2.CH:CH_2$

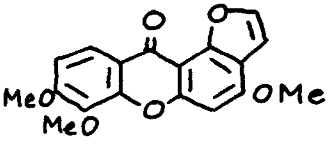
e; $R = R^2 = H$, $R^1 = CH_2.CHO$

f; $R = R^1 = H$, $R^2 = CH_2.CH:C(CH_3)_2$

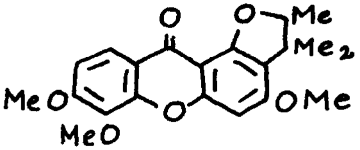
g; $R = R^1 = H$, $R^2 = CH_2.CHO$

h; $R^1 = C(CH_3)_2\ CH:CH_2$, $R = R^2 = H$

i; $R = H$, $R^1 = R^2 = CH_2.CH:C(CH_3)_2$



II



III

TABLE 1[6]

Proton magnetic resonance absorptions, τ (p.p.m.) and J(c.p.s.) in $CDCl_3$ (Id, If and Ii), and $C.Cl_4$ (Ih and III) using tetramethylsilane as internal reference.

Aromatic protons

Compound	H - 2	H - 4	H - 7	H - 8	J(H - 7/H - 8)
Id	-	3.55 s	3.12 d	2.14 d	9.0
If	3.68 s	-	3.06 d	2.08 d	9.0
Ii	-	-	3.10 d	2.10 d	9.0
Ih	-	3.63 s	3.15 d	2.12 d	9.0
III	-	3.63 s	3.20 d	2.16 d	9.0

γ,γ-Dimethylallyl side chain

	$.CH_2$	.CH:	$:C\ (CH_3)_2$
If	6.51 d	4.78 t	8.14 s 8.34 s
Ii	6.46 d 6.64 d	4.74 t*	8.14 s 8.21 s 8.31 s*

α,α-Dimethylallyl side chain

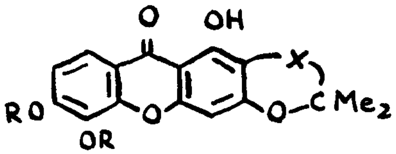
		ABX Vinyl				
	$C\ (CH_3)_2$	.CH:(X)	:CH(A)	:CH(B)	J(AX)	J(BX)
Ih	8.44 s*	3.82 q	5.24 t	5.30 t	17.8	10.3

Heterocyclic ring in 2,3,3-trimethylcoumaran system

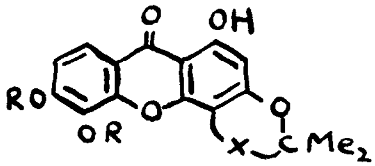
	2-.CH	$2\text{-}.CH_3$	$3,3\text{-}(CH_3)_2$
III	5.52 q	8.54 d	8.86 s 8.61 s

s = singlet d = doublet t = triplet q = quartet * double intensity

Jacareubin, a pyranoxanthone isolated from the heartwood of *Calophyllum brasiliense* (Guttiferae) was given either structure (IVa) or structure (Va) on the basis of degradative evidence[4a]. Structure (IVa) was favoured[7] by a positive Gibbs test on the dimethyl ether of jacareubin (IVb or Vb), but it was admitted that the recent synthesis of dihydrojacareubin is equivocal[8]. Since the Gibbs reaction may give conflicting results[9], further experimental evidence is required to confirm the structure of jacareubin.



IV



V

a; X = CH:CH, R = H

b; X = CH:CH, R = Me

c; X = $CH_2.CH_2$, R = H

4-γ,γ-Dimethylallyl-1-hydroxy-3,5,6-trimethoxyxanthone (If) on refluxing with hydriodic acid in acetic acid undergoes demethylation with simultaneous cyclisation. The product, m.p. 288°, depresses the melting point of dihydrojacareubin[8] and is the dihydropyranoxanthone (Vc) and which we have named dihydroisojacareubin. Its structure is confirmed by the nuclear magnetic resonance spectrum in trifluoracetic acid with cyclohexane as internal reference

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[7] F. E. King, T. J. King and L. C. Manning, *J. Chem. Soc.*, 563, (1957)

[8] H. B. Bhat and K. Venkataraman, *Tetrahedron*, 19, 77, (1963)

[9](a) H. Inouye, Y. Kanaya and Y. Murata, *Chem. Pharm. Bull. Japan*, 7, 573, (1959); *Chem. Abs.*, 54, 19,559, (1960)

(b) A. Jefferson and F. Scheinmann, unpublished work.

which shows the presence of a single methyl peak at 8.48τ, and two triplets at 7.94τ and at 6.85τ due to the two methylene groups of the dihydropyran ring. The three aromatic protons appear as two doublets at 2.66τ and 1.93τ (J 9.5 c.p.s.) for the two adjacent protons at C - 7 and C - 8 while the isolated proton at C - 2 is a singlet at 3.29τ.

The synthesis of dihydroisojacareubin (Vc) thus provides additional evidence that jacareubin has structure (IVa).

Correct analyses were obtained for all compounds, and the ultra-violet and infra-red spectra are in accord with proposed structures.

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