STEREOSPECIFIC CYCLIZATION OF p-QUINOL ACETATES TO HOMOPROAPORPHINES*

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A sole homoproaporphine (Dienone II) not contaminated with another diastereoisomer (kreysiginone) was obtained as a by-product on acid treatment of a p-quinol acetate (4). Absolute configuration of Dienone II was determined by X-ray crystallographic analysis and mechanism of the stereospecific formation of Dienone II was suggested.

In our continued study on the synthesis of isoquinoline alkaloids via p-quinol acetates[1], we obtained three kinds of cyclized products, a homomorphinandienone (1), a homoaporphine (2), and a homoproaporphine (3) by trifluoroacetic acid treatment of the p-quinol acetate (4) from a 7-phenolic-1-phenethyl-

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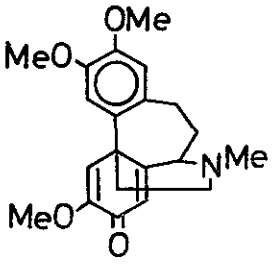
* Dedicated to Prof. R.B. Woodward on the occasion of his sixtieth birthday.



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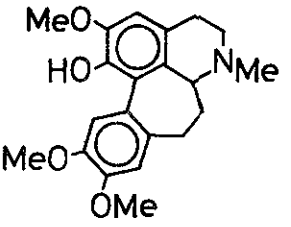

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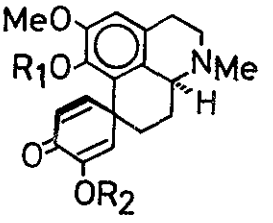
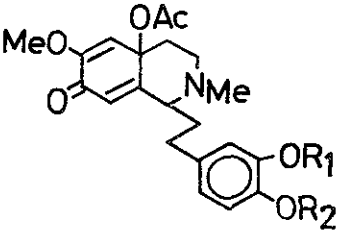
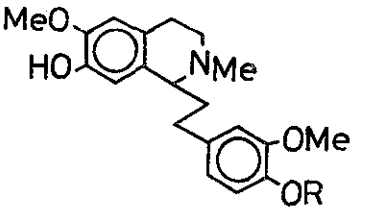


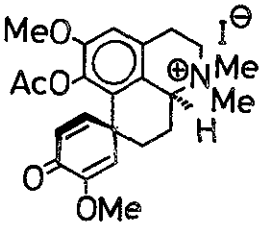
	R_1	R_2
3 :	H	Me
7 :	H	CH_2Ph
10 :	Ac	Me



	R_1	R_2
4 :	Me	Me
8 :	Me	CH_2Ph
9 :	CH_2Ph	Me



	R
5 :	Me
6 :	H



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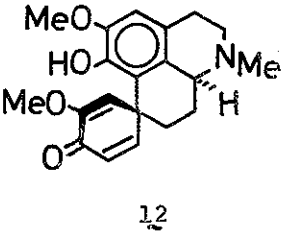


12

Figure 1

tetrahydroisoquinoline (5)[2].

The homoproaporphine (3) was identical with Dienone II, which has already been prepared along with its spiro-isomer, Dienone I, on phenol oxidation of a diphenol (6) independently by Battersby's[3] and Kametani's[4] group. In addition, natural kreysiginone, a minor alkaloid of Kreysigia multiflora, has been known to be identical with Dienone I[3]. According to a recent announcement by Kupchan et al.[5], stereospecific oxidative coupling of a monophenol (5) has proceeded to give Dienone II. In our hand a sole dienone (3 or 7), not contaminated with its spiro-isomer, was yielded when another p-quinol acetate (8 or 9) was treated similarly. Here we wish to report on the stereospecific cyclization and on the absolute configuration of kreysiginone as well.

Though Kametani and co-workers have once postulated that the stereostructure of Dienone II is represented as 3 on the basis of chemical reactions[6], a more direct evidence concerning the matter was still lacking. In order to verify the postulation, X-ray crystallographic determination was undertaken on a crystalline methiodide of its O-acetate which was proved to be most suitable for the X-ray study after several attempts.

Dienone II was treated with acetic anhydride and pyridine to give an acetate (10) [mp 197-199° (dec.); Anal. Calcd. for $C_{22}H_{25}NO_5$ (m.w. 383.43): C, 68.91; H, 6.57; N, 3.65. Found: C, 68.64; H, 6.51; N, 3.92; NMR ($CDCl_3$) δ: 1.98 ($OCOCH_3$), 2.46 (NCH_3), 3.62, 3.73 (each OCH_3), 5.83 (1H, d, J=2.5Hz, 9-H), 6.29 (1H, d, J=10Hz, 12-H), 7.07 (1H, dd, J=2.5, 10Hz, 13-H), 6.68 (1H, s, 3-H); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 ($OCOCH_3$), 1660, 1650, 1635 (dienone)], which was converted as usual to a methiodide

(11) [mp 255-256° (dec.); Anal. Calcd. for $C_{23}H_{28}NO_5I$ (m.w. 525.38): C, 52.58; H, 5.37; N, 2.67. Found: C, 52.35; H, 5.32; N, 2.86].

The X-ray measurement was performed on a Philips PW1100 diffractometer using Mokα radiation monochromated by a graphite plate. Crystal data: $C_{23}H_{28}NO_5I$ (11), m.w. 525.38, monoclinic, space group C $^2/c$, Z=8, Dx=1.467g cm^{-3}; a=20.435 (10), b=11.899 (5), C=21.379 (10) Å, β=113.741 (1)°, U=4758 $Å^3$. A total of 2852 reflexions were measured in a θ range of 3-23° in which 2767 reflexions with $I > 2\sigma$ (I) were used for the structure analysis. Refinement of the structural parameters (anisotropic thermal parameters for heavier atoms were included but no hydrogen atoms assigned) were carried out by the block-diagonal least-squares method giving the final R value of 0.05. Eventually, its stereostructure was defined as illustrated in the Figure 2 by an ORTEP stereoscopic drawing[7] comfirming Kametani's early postulation. This in turn unequivocally determined the absolute configuration of kreysiginone as 12.

The most probable reaction pathway responsible for the stereospecificity was visualized as follows (Scheme 1). Initial removal of the acetoxyl group in 4 was facilitated by a methoxyl at the 6 position leading to an oxonium ion (A), which gave rise to two kinds of carbonium ion (B) and (C); whereas positive charge in the former resided at the 10 position, that in the latter at the 8. The benzene ring of the phenethyl group in the carbonium ion (C) could attack intramolecularly on the positive carbon from either α- or β-side in a formal sense. However, a transition state (D) involving a chair shaped six-membered ring in the case of the β-attack was energetically more favorable

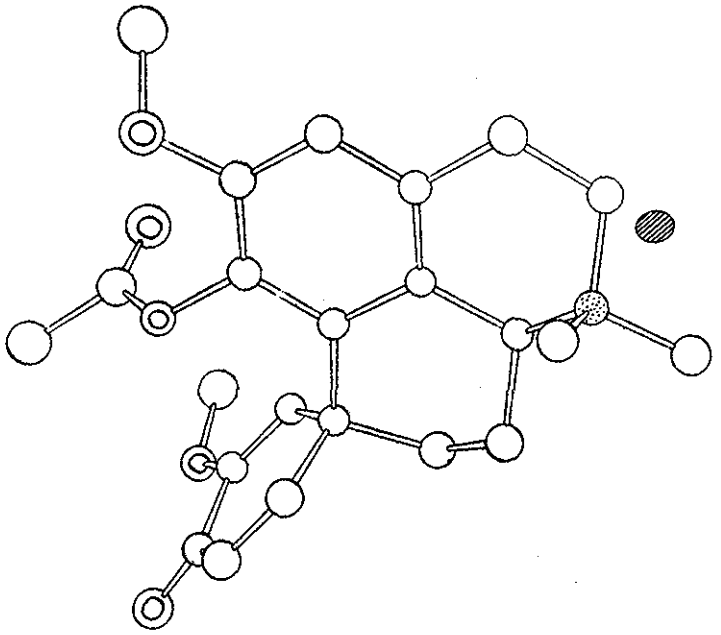
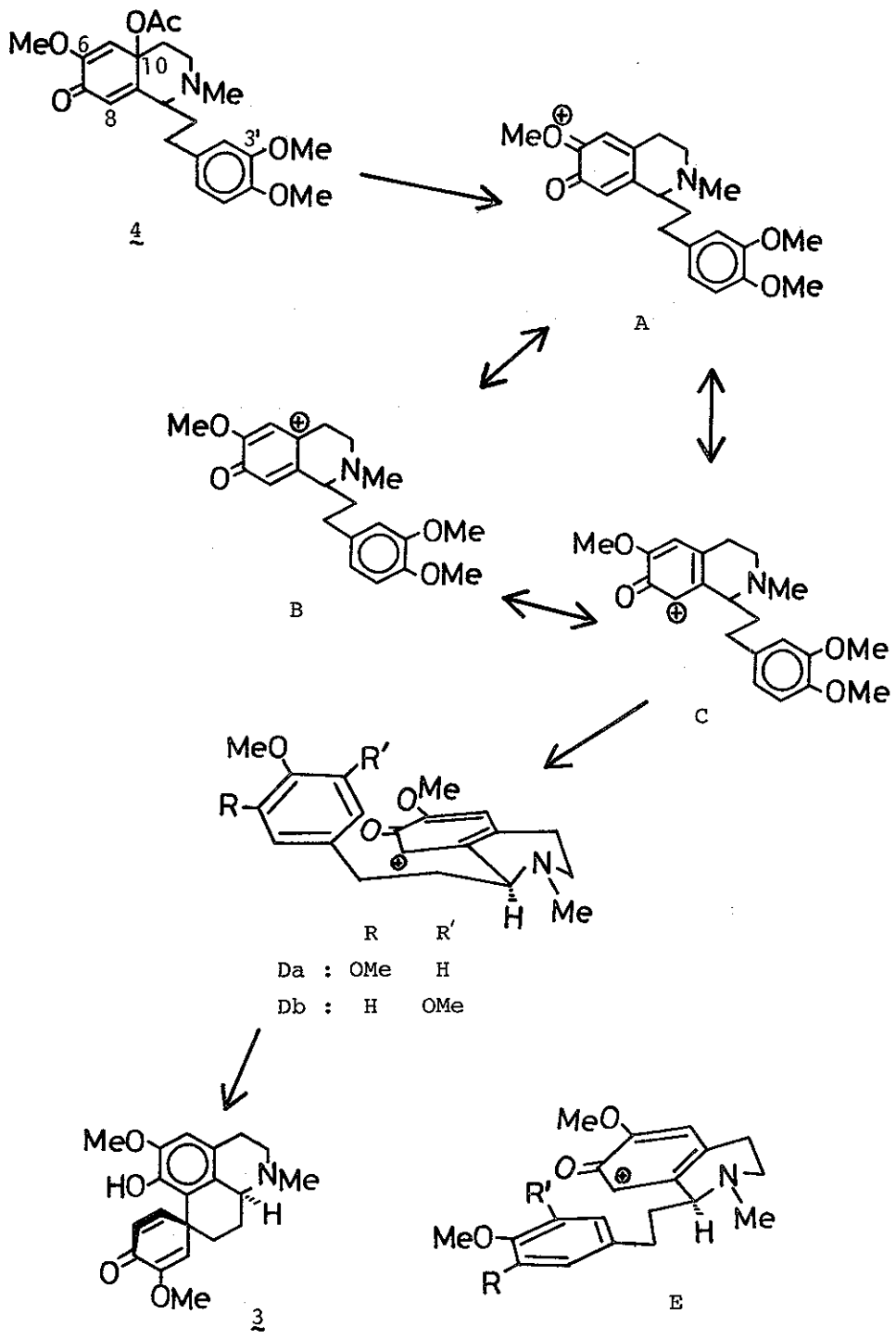


Figure 2. The structure of 11 drawn by the plotter program, ORTEP. Atoms were plotted with the 30% probability ellipsoids. Oxygen atoms are shown by double circles, nitrogen atom by dotted circle and the iodide ion by lined circle.



Scheme 1

than that (E) of the α-attack which contained a boat form[8]. Since steric repulsion imposed by a methoxyl group at the 3' position of the benzene ring played a decisive roll in the stereospecific cyclization, a transition state (Da) having the methoxyl group farthest apart was favored over Db.

Thus the present reaction was in marked contrast to the coupling of a diphenol[3,4,9], whereby a mixture of spiro-isomers were yielded, giving an unnatural isomer as a sole product.

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