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SYNTHESIS OF NATURAL KETOLS OF THE PYRETHRIN SERIES

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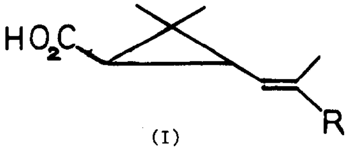
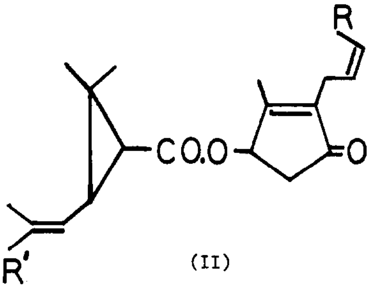
The rethrolones cinerolone (IXa), jasmolone (IXb) and pyrethrolone (IXc) constitute the alcohol components of the six insecticidally active constituents of the flower heads of Chrysanthemum cinerariaefolium. Severally combined with chrysanthemic acid (Ia) and pyrethric acid (Ib) they form the six active principles, cinerin I (IIa), cinerin II (IIb), jasmolin I (IIc), jasmolin II (IId), pyrethrin I (IIe) and pyrethrin II (IIf).[1] The cis geometry of the side chain, in natural rethrolones, has been established by synthesis and spectral (i.r. and n.m.r.) studies.[1,7] The cis linkages in cinerolone (IXa) and pyrethrolone (IXc) were introduced by partial hydrogenation of acetylenic intermediates,[2,3] but in the case of pyrethrolone (IXc) hydrogenation of the corresponding enyne was not completely selective.[3] Jasmolone (IXb) has been synthesised from "leaf alcohol" (cis-n-hex-3-en-1-ol).[4] We now report a much superior synthesis of pyrethrolone (IXc) via a novel Wittig synthesis which is completely stereoselective and gives pyrethrolone in an overall yield of 21%.

Wittig reaction between the phosphorane (III) and acrolein (IVc), under controlled 'salt-free' conditions,[5] gave (50%) the cis diene (Vc) almost exclusively. The configuration followed from spectral properties, from comparison with authentic trans diene,[6] and from its recovery unchanged (spectrally) on treatment with p-benzoquinone. The n.m.r. properties of the olefinic protons on the cis diene (Vc) are summarised in (X).[7] Hydrolysis of (Vc) provided (89%) the ketone (VIc) which gave an essentially quantitative yield (titrimetric control) of the β-keto acid (VIIc; R'=H) on treatment with magnesium methyl carbonate (M.M.C.)[8] The use of M.M.C. for the carboxylation of saturated acyclic methyl ketones has not previously been investigated. The method constitutes a considerable improvement over previous methods, using diethyl carbonate, for such conversions. Condensation of the potassium salt (VIIc; R'=K) of the β-keto acid with pyruvaldehyde gave (68%) the hydroxy-dione (VIIIc) which was cyclised in ethanolic NaOH to give (70%) racemic pyrethrolone (IXc). The pyrethrolone obtained was chromatographically and spectrally (i.r., u.v., n.m.r.) indistinguishable from natural



(I)

a R=Me: b R=$-CO_2Me$



(II)

a R=R'=Me

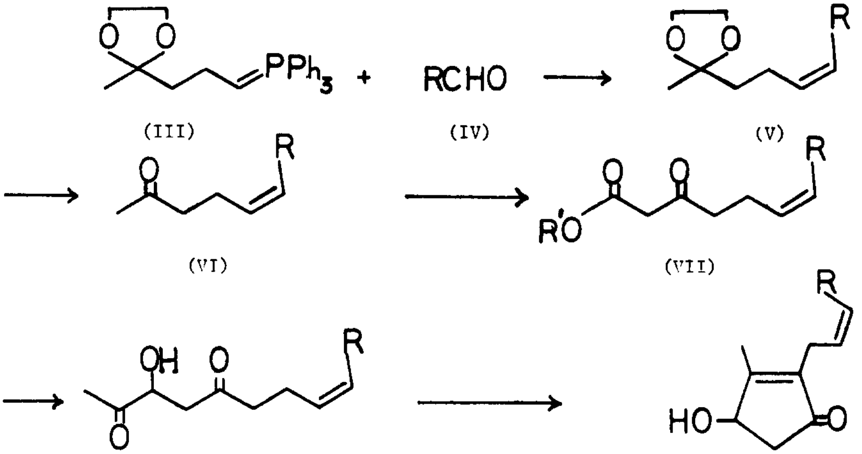
b R=Me; R'=$-CO_2Me$

c R=Et; R'=Me

d R=Et; R'=$-CO_2Me$

e R=$-CH=CH_2$; R'=Me

f R=$-CH=CH_2$; R'=$-CO_2Me$

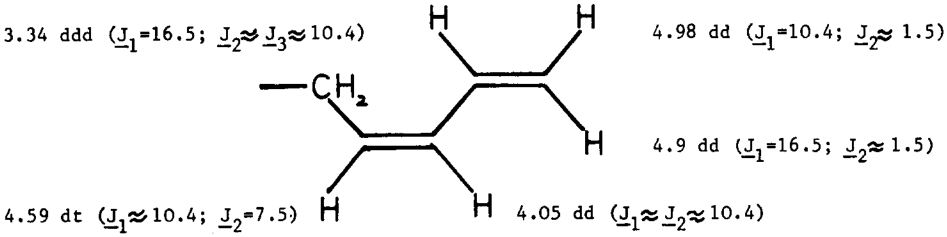


(III) (IV) (V) (VI) (VII) (VIII) (IX)

a R=Me; b R=Et; c R=$-CH=CH_2$.

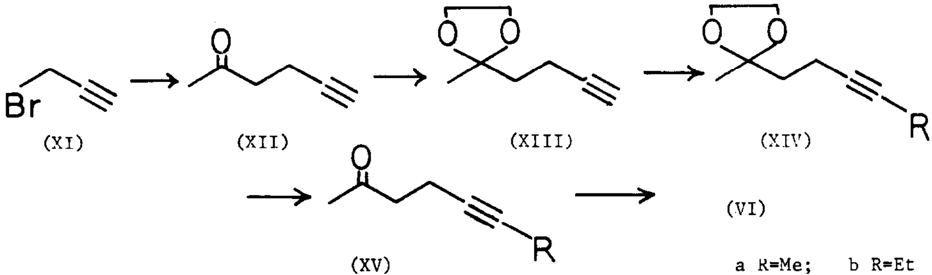
(+)-pyrethrolone, isolated according to the method of Elliott.[9]

Wittig reactions between (III) and either acetaldehyde or propionaldehyde, under 'salt-free' conditions,[5] gave (Va) and (Vb) respectively, each containing not more than 6% of the corresponding <u>trans</u>-olefins; hydrolysis of the dioxolones (Va) and (Vb) then gave the ketones (VIa) and (VIb) respectively. The cis ketones (VIa) and (VIb) were more conveniently obtained, however, by selective hydrogenation (Lindlar's catalyst) of the corresponding acetylenes (XVa) and (XVb) respectively. Alkylation (MeI and EtI) of the acetylene (XIII)[10] gave (∿75%) (XIVa) and (XIVb) respectively. Hydrolysis of the dioxolones followed by hydrogenation of the ketones (XVa) and (XVb) furnished the pure (>98% by g.l.c.; 5% $AgNO_3$/ethylene glycol- 25°) ketones (VIa)



(X)

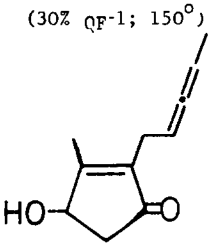
and (VIb) respectively. The ketones (VIa) and (VIb) were then converted [ca. 16% overall yield from (XIII)] into racemic cinerolone (IXa) and racemic jasmolone (IXb) respectively, by transformations similar to those used previously in the synthesis of racemic pyrethrolone. The synthetic racemic cinerolone (IXa) which could be purified by g.l.c. (30% QF-1; 150°), had spectral (i.r. and n.m.r.) and physical properties similar to those reported previously for the natural (+) material and for a sample of (±) material obtained by an earlier synthesis.[2,4]



a R=Me; b R=Et

The jasmolins I (IIc) and II (IId) have only recently[11] been recognised as minor active constituents of pyrethrum extract, but jasmolone (IXb) and jasmolin I (IIc) were synthesised much earlier in an investigation of the insecticidal activity of cinerin homologues.[4] Jasmolone (IXb) has not been isolated from the hydrolysis of pyrethrum extract, principally because it is present only in small quantity and also because it is separated only with difficulty from cinerolone (IXa). The synthetic (±) jasmolone (IXb), purified finally by g.l.c. (30% QF-1; 150°), had n_D^{24} 1.5100, $\lambda_{max.}$ (95% EtOH) 230mμ, ε 11,200; $\nu_{max.}$ (film) 3400, 1700, 1645 cm.$^{-1}$

In the earlier literature,[12] pyrethrolone was formulated as an allene (cf. XVI). This structure has now been synthesised by converting the trans olefin (V R=Me) into the corresponding allene, using the von Doering method, and completing the synthesis by methods parallel to those mentioned above.



(XVI)

The allenolone separated from natural pyrethrolone on mixed g.l.c. (30% QF-1; 150°) and the two materials were spectrally non-identical.

Satisfactory analytical and spectral data have been obtained for all compounds mentioned above.

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