ATTEMPTED SYNTHESIS OF EVODONE*

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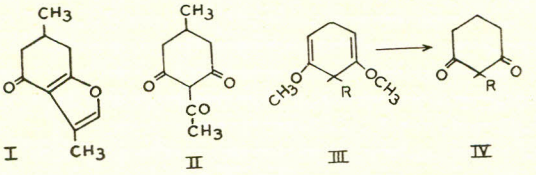
α-Bromoacetal and α-bromopropionacetal were condensed with 1,3-dimethoxy-2,5-dihydrobenzene, and its toluene homologue and the resulting products cyclised.

The product obtained by condensation of dihydroorcinol dimethyl ether with α-bromopropionacetal on cyclisation gave evodone possibly mixed with the cyclic half acetal.

Introduction

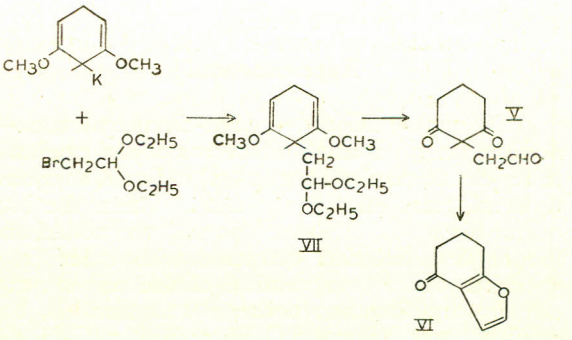
The structure of evodone (I)[1] was based on degradative evidence obtained by van Hulssen[2] (1941) which included ozonolysis to the crystalline compound (II), the structure of which was suggested and the synthesis carried out by Birch and Rickards.[1] The ultra-violet spectrum of evodone was also available. It was not possible, however, to obtain authentic specimens of evodone or its degradation products for comparison purposes and to that extent the structure of evodone is still uncertain. To provide further evidence it was felt that the synthesis of (±) evodone (the natural material is optically active) would enable, in particular, the ultra-violet spectrum to be examined, and the rather unusual ozonolysis to (II) to be repeated.



I II III IV

The synthesis has been based on the reaction discovered by Birch[3] that 2:5 - dihydro - 1:3 - dimethoxybenzene (III) (R = H) forms a potassium salt (III) (R = K) with potassium amide in ammonia, which in turn can be alkylated by an alkyl halide RX to (III) (R = alkyl). Being an enol-ether, on acid hydrolysis this produces (IV) (R = alkyl).

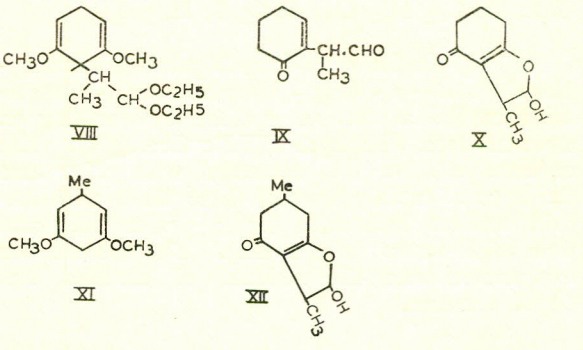
In the present case the type of intermediate desired is (V) which would be expected to ring-close to (VI). The sequence of reactions shown in the diagram was, therefore, examined in the first instance as a model. Alkylation to (VII) appeared to proceed normally, but difficulty was experienced in obtaining (VI). The



VII V VI

product of the reaction analysed rather badly for a content of three oxygens. It did, however, give rise to a semicarbazone, m.p. 195-196°C., and a 2:4 - dinitrophenyl-hydrazone, m.p. 247-248°C., analysing as derivatives of (VI). The crude oil also showed the ultra-violet maximum ($\lambda_{max.}$ 266 mμ, log. $\varepsilon_{max.}$ 3·84) to be expected of (VI) on the basis of the absorption of evodone ($\lambda_{max.}$ 265 mμ; log. $\varepsilon_{max.}$ 3·57).

Condensation of (III) (R = K) with α-bromopropionacetal produced the expected (VIII) which on mild acid treatment gave a product $C_9H_{12}O_3$ which may be (IX) or (X).



VIII IX X XI XII

The action of 2N hydrochloric acid caused some loss of oxygen, the product analysing between $C_9H_{10}O_2$ and $C_9H_{12}O_3$.

*This work was carried out in the School of Chemistry, University of Sydney, Australia.

It was further found that the orcinol derivative (XI) condensed with bromoacetal in the expected manner, and the product of treatment with 2N hydrochloric acid had the expected ultra-violet spectrum ($\lambda_{max.}$ 269 mμ; log. ε max. 4.433). The dihydro-orcinol dimethyl ether (XI) with α-bromopropionacetal produced a substance probably containing some of the expected compound, but analysing badly. Treatment with acid gave a product analysing rather badly for the expected evodone. It may be a mixture of evodone and the cyclic half-acetal (XII), because the ultra-violet spectra of these two substances would not be expected to differ greatly.

Experimental

(*a*) 2:5 - *Dihydro* - 1:3 -*dimethoxybenzene.*—Sodium (12 g.) in small pieces was added gradually to 1:3-dimethoxybenzene (15 g.) in liquid ammonia (400 ml.) and ethanol (40 ml.). When the blue colour disappeared, water (200 ml.) was added and the aqueous solution extracted with ether (2 × 30 ml.). After evaporation of the solvent, 2:5-dihydro-1:3-dimethoxybenzene was distilled, b.p. 49°C./0.9 mm. (Found: C, 68.5; H, 8.7, $C_8H_{12}O_2$ requires: C, 68.5; H, 8.6).

(*b*) *Condensation of* 2:5 - *Dihydro* - 1:3 - *dimethoxybenzene with* α*-Bromoacetal.*—Potassium (5.5 g.) was added in small pieces to liquid ammonia (300 ml.) containing a trace of ferric nitrate. When the blue colour disappeared 2:5-dihydro-1:3-dimethoxybenzene (13 g.) in dry ether (15 ml.) was added and the mixture allowed to stand for ten minutes. α-Bromoacetal (6 g.) in an equal volume of dry ether was added. When the red colour was discharged the mixture was diluted with water (200 ml.) and extracted with ether. After evaporation of the solvent the residual oil was distilled. α-(1:4-dihydro-2:6-dimethoxyphenyl)-acetal had b. p. 62°C./1.0 mm. (Found: C, 65.4; H, 9.1. Calc. for C_{14} H_{24} O_4; C, 65.6; H, 9.4).

(*c*) *Cyclisation of* α-(1:4-*Dihydro*-2:6-*dimethoxyphenyl*)-*acetal.*—α - (1:4 - Dihydro - 2:6 - dimethoxyphenyl) - acetal was cyclised by warming on a water bath with hydrochloric acid (2N). The aqueous solution was extracted with ether and the extract rapidly washed three times with ice-cold sodium hydroxide (2%; 3 × 2 ml.) and then with water (2 × 2 ml.). The solvent was evaporated and the residual oil distilled b.p. 60°C./1.2 mm.

Treatment of this oil with semicarbazide hydrochloride gave a *semicarbazone*, m.p. 195°-6°/C. from absolute ethanol. (Found: C, 55.5; H, 6.3. Calc. for $C_9H_{11}O_2N3$, C, 56.0; H, 5.7).

The oil was regenerated from its semicarbazone and treated with 2:4 - dinitrophenylhydrazine hydrochloride. A dark red derivative, m.p. 247-8°C., from ethyl acetate, was obtained. (Found: C, 53.4; H, 4.2. Calc. for $C_{14}H_{11}O_5N_4$, C, 53.2; H, 3.8).

(*d*) *Condensation of* 2:5 - *Dihydro* - 1:3 - *dimethoxybenzene with* α - *Bromopropionacetal.*—2:5 Dihydro - 1:3 - dimethoxybenzene was condensed with α-bromopropionacetal by the method as described under (b). The condensation product had b.p. 67°C./1.2 mm. (Found: C, 66.2; H, 7.8. Calc. for $C_{15}H_{26}O_4$, C, 66.6; H, 7.6).

(*e*) *Cyclisation of Condensation Product, b.p.* 67°/1.2 *mm.*—Cyclisation of this condensation product was carried out by the method as described under (c). The oily product obtaied after cyclisation was distilled, b.p. 58°C./1.2 mm.

Ultra-violet Absorption Spectrum of Cyclisation Product.—The ultra-violet absorption spectrum of the oil, b. p. 58°C./1.2 m.m., was measured in ethanol.

$\lambda_{max.}$ 274-275 mμ; log. ε_{max}, 3.448.

(*f*) 1:4 - *Dihydro* - 3:5 - *dimethoxytoluene.*—This derivative, b.p. 54°C./1.4 mm. was obtained from 3:5-dimethoxytoluene by the method described under (a).

(*g*) *Condensation of* 1:4 - *Dihydro* - 3:5 - *dimethoxytoluene with* α*-Bromoacetal.*—Potassium (3.7 g.) in small pieces was added to liquid ammonia (300 ml.) containing a trace of ferric nitrate. 1:4 - Dihydro - 3:5 - dimethoxytoluene (10 g.) in dry ether (25 ml.) was added after the blue colour was discharged. The mixture was allowed to stand ten minutes and α-bromoacetal (25 g.) in an equal volume of dry ether added. When the red colour disappeared the mixture was diluted with water (200 ml.) and extracted with ether. Evaporation of the solvent gave α-(1:4-dihydro-2:6-dimethoxy-4-methyl-phenyl)-acetal, b.p. 152°C./1.3 mm. (Found: C, 66.4; H, 9.9. Calc. for $C_{15}H_{26}O_4$, C, 66.6; H, 9.7).

(*h*) *Cyclisation of* α-(1:4-*dihydro*-2:6-*dimethoxy*-4-*methyl-phenyl*)-*acetal.*—Cyclisation of the product, b.p. 152°C./1.3 mm. was carried out by the method as described under (c) above. The oil obtained after cyclisation distilled at 103°C./1.7 mm.

(*i*) *Condensation of* 1:4 - *Dihydro* - 3:5 - *dimethoxytoluene with* α *-Bromopropionacetal.*—1:4 - Dihydro-3:5 - dimethoxytoluene was condensed with α-bromopropionacetal in the presence of potassium

amide in liquid ammonia by the method described above. The crude condensation product distilled at b.p. 85°C./1.4 mm.

(*j*) *Cyclisation of Condensation Product, b.p.* 85°C./1.4 *mm.*—Cyclisation of the oil, b. p. 85°C./1.4 mm. was carried out by the method as described before. The product obtained was distilled, b. p. 76°C./1.5 mm.

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