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NEW SYNTHETIC ROUTES TO 3-ETHYLIDENE-2′,4-6 TRIMETHYLGRIS-2′-EN-4′-ONE.

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Abstract—3-Ethylidene-2′,4,6-trimethylgris-2′-en-4′-one has been synthesized by two alternative routes in the proof of the spiran nature of the compounds IV ($R = COOC_2H_5$ and $R = H$) derived from the cyclization of diketobenzofurans (V, $R = COOC_2H_5$ and $R = H$).

CYCLIZATION of diketobenzofurans (V, $R = COOC_2H_5$ and $R = H$) with sulphuric acid, furnished the products (A) and (B), which by analogy of similar conversion of the diketoesters (I) to usnolic acid analogues (II) were expected to possess structures IV($R = COOC_2H_5$ and $R = H$) respectively.[1] The spiran nature of usnolic acid analogues such as II has been established mainly on the formation of spiro-coumaranone (III) and formaldehyde on ozonolysis. The products (A) and (B), however, did not furnish the expected coumaranones (VI) and acetaldehyde under similar conditions, the dioxadibenzo(a,d)pentalenes (VII) being obtained instead. In contrast, the compound VIII, obtained from diketoester (IX) by Dawkins and Mulholland[2] behaved in the normal manner with ozone furnishing the coumaranone (X) and formaldehyde. Since the method of ozonolysis could not provide evidence of the spiran nature of the products (A) and (B), their structures (IV, $R = COOC_2H_5$ and IV, $R = H$) are dubious. A compound of structure IV ($R = H$) has been synthesized by two alternative routes and is identical with product (B), thus providing proof that the structure IV ($R = H$) suggested originally for this compound is correct.

The first successful synthesis is indicated in Fig. 1. The reaction of 2-acetyl-3-ethyl-4,6-dimethylbenzofuran[3] (XI) with ethyl bromoacetate under Reformatsky conditions afforded ethyl β-(3-ethyl-4,6-dimethyl-2-benzofuryl)crotonate (XII, $R = OC_2H_5$) which hydrolysed to the acid XII ($R = OH$). Its acid chloride (XII, $R = Cl$) reacted with cadmium methyl, furnishing the ketone (XIII), which on Mannich reaction afforded the compound XIV. When its quaternary salt (XV) was treated with a base, a compound identical with product (B) was produced. The two benzofuran derivatives (V and XV) would, however, yield identical products only when the reaction proceeds in such a way that the $C_{(w)}$ and $C_{(z)}$ atoms of the respective moities

$$—\overset{(Z)}{CH_2}—CH_2—CO—CH_2—\overset{(W)}{CO}—CH_3$$

and

$$H_3C—\overset{(Z)}{C}=CH—CO—CH_2—\overset{(W)}{CH_2}—N^+(CH_3)_3I^-$$

join at a common point i.e., position −2, as shown in Fig. 2, resulting in the formation of a spiro ring.

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[1] F. M. Dean, T. Francis and K. Manunapichu, *J. Chem. Soc.* 4551 (1958).

[2] A. W. Dawkins and T. P. C. Mulholland, *J. Chem. Soc.*, 2211 (1959).

[3] D. S. Deorha and P. Gupta, *Chem. Ber.* **97**, 616 (1964).

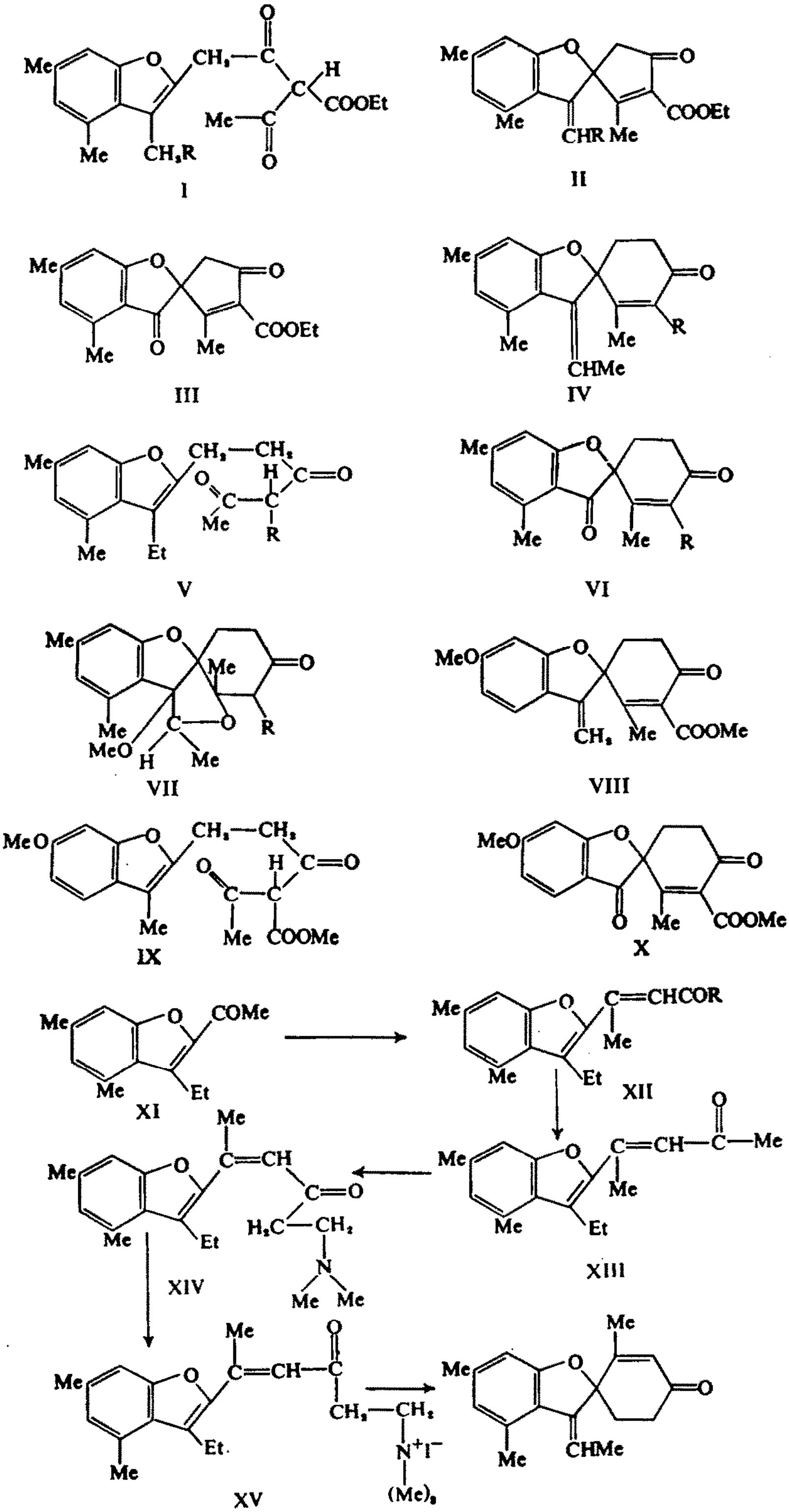

FIG. 1.

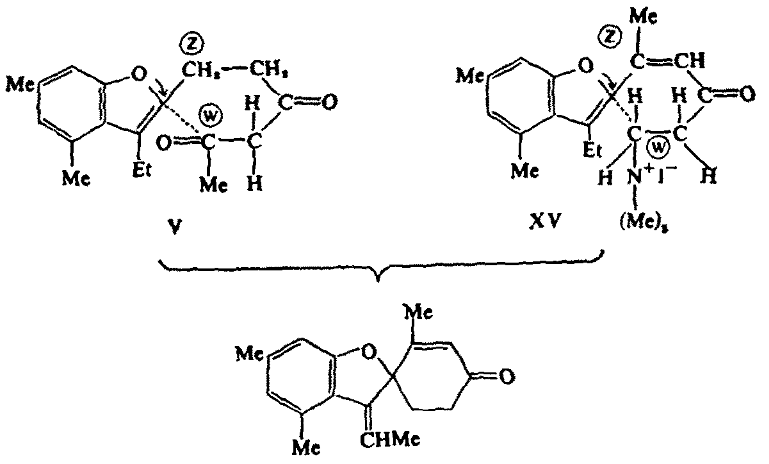

FIG. 2.

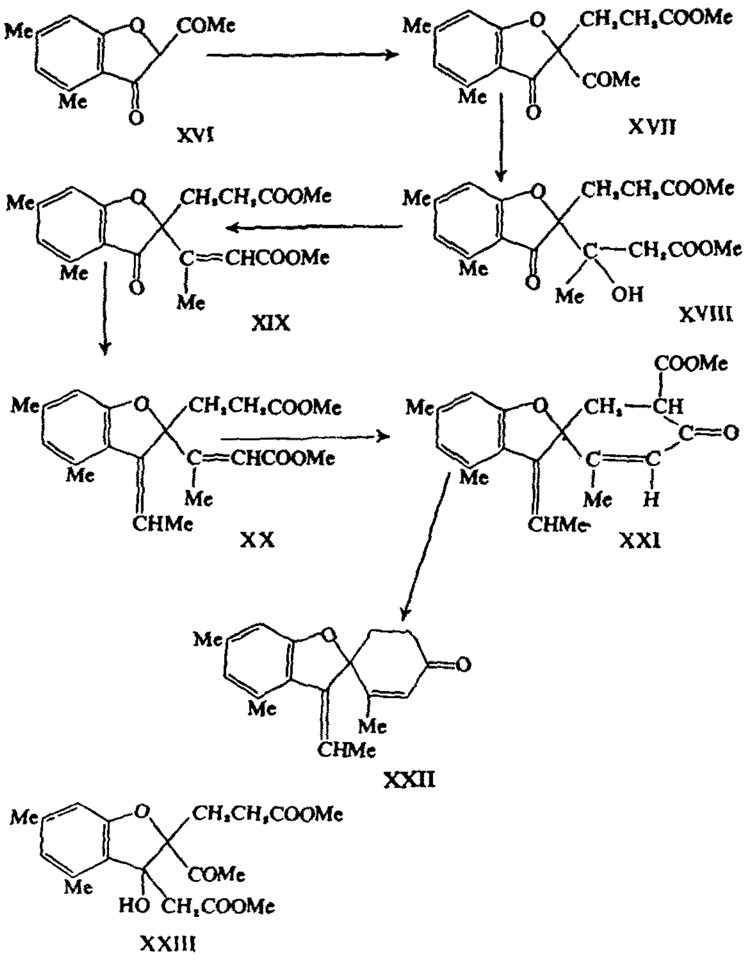

FIG. 3.

In the second synthesis as shown in Fig. 3, the Micheal reaction of 2-acetyl-4,6-dimethylcoumaran-3-one[4] (XVI) with methyl acrylate afforded the compound XVII. The reaction of methyl bromoacetate with the coumaranone (XVII) under Reformatsky conditions should produce XVIII or XXIII or both depending on the carbonyl group involved in the reaction. In practice, a compound in accord with structure XIX chemically and spectroscopically was obtained. The reaction with ethyl triphenylphosonium iodide in presence of sodium methoxide converted the coumaranone (XIX) into its derivative XX. Reaction of the latter with sodium in toluene followed by hydrolysis of the derived product (XXI) afforded a ketone (XXII) identical with compound (B).

As the grisene (IV, R = H) was derived from the product (A) by hydrolysis followed by decarboxylation, the structure of the latter is unambiguous.

EXPERIMENTAL

β-(3-Ethyl-4,6-dimethyl-2-benzofuryl)crotonic acid (XII, R = OH). To a solution of 2-acetyl-3-ethyl-4,6-dimethylbenzofuran (4·3 g) heated under reflux in dry benzene (40 ml) containing ethyl bromoacetate (3·5 g) activated Zn dust (1·5 g) was added. After heating 6 hr, the mixture was cooled. The complex formed was decomposed with ice cold 2N H_2SO_4. The organic layer was separated and washed with $NaHCO_3$aq and dried over $MgSO_4$. Evaporation of benzene and distillation of the residue provided ethyl-β(3-ethyl-4,6-dimethyl-2-benzofuryl)crotonate (4·5 g) as a colourless liquid, b.p. 182°/2 mm. (Found C, 75·70; H, 7·85; $C_{18}H_{22}O_3$ requires: C, 75·51; H, 7·74%.)

The foregoing crude ester (4·5 g) was heated under reflux with 2N NaOH (40 ml) and EtOH (15 ml) for 2 hr. Acidification of the cooled and filtered solution furnished a solid, which when crystallized from benzene afforded β-(3-ethyl-4,6-dimethyl-2-benzofuryl)crotonic acid (3·7 g) as light yellow needles, m.p. 210°, λ_{max} (log ε) 248 (3·75), 339 (4·48) mμ, ν_{max} 1701 cm^{-1} (COOH). (Found C, 74·50; H, 7·15; $C_{16}H_{18}O_3$ requires: C, 74·36; H, 7·02%.)

β-Oxo-δ-methyl-δ-(3-ethyl-4,6-dimethyl-2-benzofuryl)but-γ-ene (XIII). To dry $CHCl_3$ (50 ml) containing PCl_5 (1 g), was added the crotonic acid (1·1 g). The solution was kept at room temp for 15 min and then heated under reflux on a water bath for 30 min. Removal of $CHCl_3$ left an oil which was purified by distillation with dry benzene (150 ml).

A mixture of dimethyl-cadmium (0·6 g) in dry ether (25 ml) and the preceding acid chloride was heated under reflux on a water bath for 2 hr. It was cooled and shaken with dil AcOH. The organic layer was washed with $NaHCO_3$aq and water, dried over $MgSO_4$, and concentrated. The product crystallized from EtOH to furnish β-oxo-δ-methyl-δ-(3-ethyl-4,6-dimethyl-2-benzofuryl)but-γ-ene in colourless needles (1·0 g), m.p. 60°, ν_{max} 1678 cm^{-1} (conjugated C═O), 1360 cm^{-1} (methyl ketone). (Found C, 79·80; H, 7·98; $C_{17}H_{20}O_2$ requires: C, 79·67; H, 7·87%.)

It formed a 2,4-dinitrophenylhydrazone as brown needles, m.p. 219°, λ_{max} (log ε) 228 (4·28), 378 (4·36) mμ. (Found N, 13·02; $C_{23}H_{24}N_4O_5$ requires: N, 12·84%.)

3-Ethylidene-2′,4,6-trimethylgris-2′-en-4′-one. A mixture of dimethylamine hydrochloride (1·65 g), the aforesaid ketone (2·1 g), paraformaldehyde (0·85 g), and EtOH (10 ml) was heated under reflux for 20 hr. The milky solution was filtered and concentrated under red. press. After adding water (5 ml) and excess 45% KOHaq, the solution was saturated with $KHCO_3$ and extracted with ether. The extract was washed with water and dried over Na_2SO_4. Removal of ether left an oil which was distilled under red. press. as a colourless liquid (1·5 g), b.p. 150°/2 mm.

A mixture of this amine (1·5 g) and MeI (1 g) in benzene was allowed to stand ½ hr at 0° and then for 1 hr at room temp. The methiodide was used in the subsequent step without purification due to its hygroscopic nature.

The methiodide with MeOH (10 ml) and 45% KOHaq (0·5 ml) was heated under an inert atm for 20 hr. After cooling, the mixture was diluted and extracted with benzene. When concentrated, the benzene extract deposited the 3-ethylidene-2′,4,6-trimethylgris-2′-en-4′-one[1] as colourless prisms (0·4 g), m.p. 106° undepressed on admixture with the compound obtained from V (R = H), λ_{max} (log) 230 (4·52), 238 (4·57), 256 (4·23), 264 (4·11), 268 (4·15), 306 (4·03), 314 (4·06), 318 (4·09) mμ,

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[4] F. M. Dean and K. Manunapichu, *J. Chem. Soc.* 3112 (1957).

ν_{max} 1678 cm^{-1} (conjugated C═O). (Found C, 80·79; H, 7·20; calc. for $C_{18}H_{20}O_2$ C, 80·70; H, 7·40%.)

Its 2,4-dinitrophenylhydrazone separated from EtOH in orange crystals, m.p. and mixed m.p. with that obtained from IV (R = H) derived from V (R = H) 250°. (Found N, 12·63; calc. for $C_{24}H_{24}N_4O_5$ N, 12·50%.)

Methyl β-(2-acetyl-4,6-dimethyl-3-oxo-coumaran-2-yl)propionate (XVII). A mixture of Triton B (1·5 ml), 2-acetyl-4,6-dimethyl-coumaran-3-one[4] (6·2 g), and methyl acrylate (6 ml) in dioxan (18 ml) was allowed to stand 3 days at 2°. The product resulting from acidification and dilution was isolated with ether.

The ethereal solution was washed with $NaHCO_3$aq, water and then dried over $MgSO_4$. Removal of ether left an oil which was distilled under red. press. The fraction, b.p. 143°/0·1 mm was purified from benzene on alumina and when redistilled, gave the 3-oxo-coumaran-2-ylpropionate as a yellowish oil (7·2 g), b.p. 145°/0·1 mm, λ_{max} (log ε) 272 (4·14), 330 (3·81) mμ, ν_{max} 1736 cm^{-1} (ester), 1721 cm^{-1} (ketone), 1698 cm^{-1} (coumaranone —C═O).

Its 2-chloro-4,6-dinitrophenylhydrazone separated from EtOH in orange yellow needles, m.p. 142°. (Found Cl, 7·23; $C_{22}H_{21}N_4O_8Cl$ requires: Cl, 7·02%.)

Methyl β-(2-2′-carbomethoxyethyl-4,6-dimethyl-3-oxo-coumaran-2-yl)crotonate (XIX). To a solution of the crotonic ester (5·8 g) in dry benzene (40 ml) containing methyl bromoacetate (3·1 g) heated under reflux, was added activated Zn dust (1·5 g). After heating for 6 hr, the mixture was cooled. The complex formed was decomposed with ice-cold 2N H_2SO_4. The organic layer was separated, washed with $NaHCO_3$aq and dried over Na_2SO_4. Evaporation of benzene left a solid which crystallized from dil MeOH as needles (5·6 g), m.p. 102°, λ_{max} (log ε) 232 (4·11), 275 (4·25), 320 (3·98) mμ, ν_{max} 1739 cm^{-1} (saturated ester), 1718 cm^{-1} (unsaturated ester), 1701 cm^{-1} (coumaranone —C═O). (Found C, 65·73; H, 6·26; $C_{19}H_{22}O_6$ requires: C, 65·89; H, 6·40%.)

Methyl β-(2-2′-carbomethoxyethyl-3-ethylidene-4,6-dimethylcoumaran-2-yl)-crotonate (XX). Sodium methoxide (prepared from 0·53 g Na) in MeOH (15 ml) was added to a solution of ethyl triphenylphosphonium iodide (14 g) and the preceding crotonate (10 g) in MeOH (20 ml), with stirring and under an atm of N_2 during a period of 15 min maintaining the temp at 55–60°.

The contents were stirred at 60° for another 5 hr during which the colour changed from red to yellow. After removing the MeOH *in vacuo*, the residue was extracted with pet. ether (b.p. 40–60°). Evaporation of pet. ether left an oil which solidified after 2 days. Crystallization of the solid from dil MeOH furnished the 3-ethylidene-coumaran-2-yl-crotonate in needles (8·1 g), m.p. 92°, λ_{max} (log ε) 245 (4·12), 268 (4·24), 325 (3·94) mμ, ν_{max} 1736 cm^{-1} (saturated ester), 1720 cm^{-1} (unsaturated ester). (Found C, 70·50; H, 7·20; $C_{21}H_{26}O_5$ requires: C, 70·35; H, 7·31%.)

Perphthalic acid titrations showed the presence of 2·02 double bonds.

Methyl-3-ethylidene-2′,4,6-trimethyl-4′-oxogris-2′-ene-5′-carboxylate (XXI). This ester (1 g) in boiling toluene (25 ml) containing powdered Na (0·7 g) and a drop of MeOH was boiled for 6 hr. The mixture was cooled and treated with 2N H_2SO_4. The organic layer was extracted with ice-cold 0·1N NaOH.

The alkaline extracts were acidified to furnish a solid which was extracted into ether. The extract was washed with water and dried over $MgSO_4$. Removal of ether furnished a solid which separated from aqueous MeOH in needles of 4′-oxogris-2′-ene-5′-carboxylate (0·35 g), m.p. 128°. (Found C, 73·70; H, 7·95; $C_{20}H_{22}O_4$ requires: C, 73·60; H, 7·79%.)

The compound gave a purple ferric reaction.

3-*Ethylidene*-2′,4,6-*trimethylgris*-2′-*en*-4′-*one* (XXII). The preceding compound (1·0 g) was heated under reflux with 2N NaOH (10 ml) for 1 hr. The insoluble material formed was isolated with ether and chromatographed on silica from pet. ether (b.p. 60–80°). The product was recrystallized from the same solvent, affording 3-ethylidene-2′,4,6-trimethylgris-2′-en-4′-one as prisms (0·2 g), m.p. 106° not depressed by admixture with specimens obtained by the first route or by Dean's method.[1] (Found C, 80·56; H, 7·28; Calc. for $C_{18}H_{20}O_2$; C, 80·70; H, 7·40%.)

The 2,4-dinitrophenylhydrazone separated from EtOH in orange crystals, m.p. and mixed m.p. with that obtained from IV (R = H) 250°. (Found N, 12·72; Calc. for $C_{24}H_{24}N_4O_5$: N, 12·50%.)

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