Tetrahedron, 1967, Vol. 23, pp. 2505 to 2511. Pergamon Press Ltd. Printed in Northern Ireland

A NEW APPROACH TO THE SYNTHESIS OF ROTENOIDS

SYNTHESIS OF DEHYDROMUNDUSERONE AND DEHYDROELLIPTONE*

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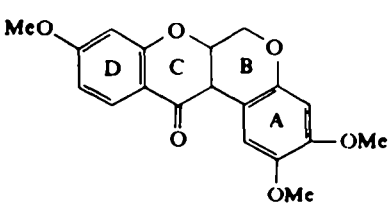
(*Received* 27 *September* 1966)

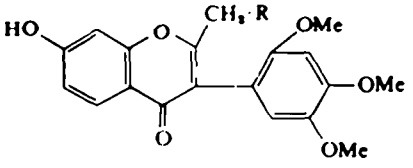
Abstract—A new method for the synthesis of rotenoids has been developed and this has been used for the synthesis of dehydromunduserone and dehydroelliptone.

THE earlier methods of synthesis of rotenoids involving derrisic acids as intermediates have a large number of steps with decreasing yields.[1-5] An alternative synthesis has been in progress in this laboratory following a possible path of biogenesis; this is based on the consideration that the isoflavone part represents the core of the rotenoids and that the 'B' and 'E' rings are added later on. The synthesis[6] of a number of tetracyclic compounds and a simple pentacyclic one, desmethoxydehydroelliptone,[6] was reported earlier.

The extension of this scheme to the synthesis of munduserone (I), the simplest naturally occurring rotenoid, was not successful since the partial demethylation of the 2'-methoxyl group of the appropriate isoflavones II or III could not be effected, probably, due to steric factors arising from the presence of the substituent in the 2-position.

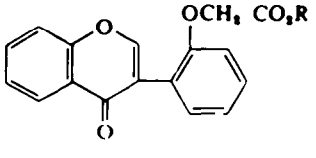


I

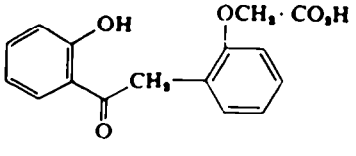


II, R = OEt III, R = H

A different approach to the problem has now been based on the fact that isoflavones undergo ready alkaline hydrolysis to give desoxybenzoins, for example, isoflavone (IV) should give the desoxybenzoin (V) which being also a derrisic acid analogue, would undergo cyclization to yield a dehydrorotenoid.



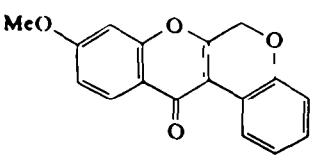
IV



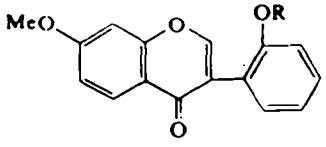
V

* Part of this work appeared as a short communication: V. Chandrashekar, M. Krishnamurti and T. R. Seshadri, *Curr. Sci.* 34, 479 (1965).

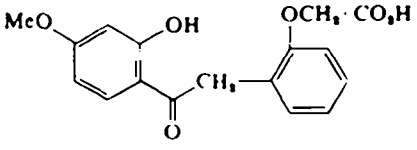
In exploratory experiments the synthesis of 7-methoxychromenochromone (VI), was effected starting from 7,2'-dimethoxyisoflavone (VII)[7] which was partially demethylated at the 2'-position by refluxing with aluminium chloride in acetonitrile.[7a] The 2'-hydroxyisoflavone (VIII) with methyl bromoacetate gave the phenoxyacetic ester IX which was hydrolysed with alcoholic alkali to the derrisic acid analogue X in good yield. It underwent double ring closure to yield VI.



VI

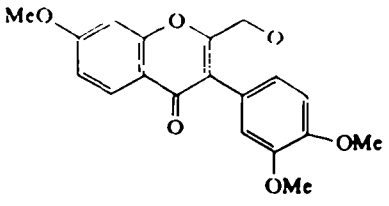


VII R = Me
VIII R = H
IX R = $-CH_2 \cdot CO_2Me$

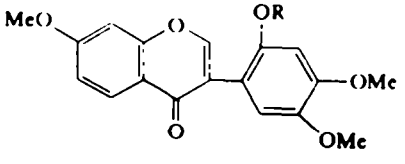


X

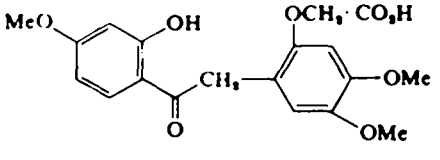
Dehydromunduserone (XI) was made from 7,2',4',5'-tetramethoxyisoflavone (XII).[8] Steps of partial demethylation to XIII, conversion into the phenoxyacetic ester XIV and alkaline hydrolysis gave methyltephrosic acid (XV) in good yield. Subsequent cyclization gave dehydromunduserone (XI) identical in all respects with an authentic sample prepared from natural munduserone, kindly supplied by Prof. W. D. Ollis. As its conversion into munduserone is already known, this procedure forms a convenient total synthesis of (±) munduserone.



XI



XII R = Me
XIII R = H; XIV R = CH_2CO_2Me



XV

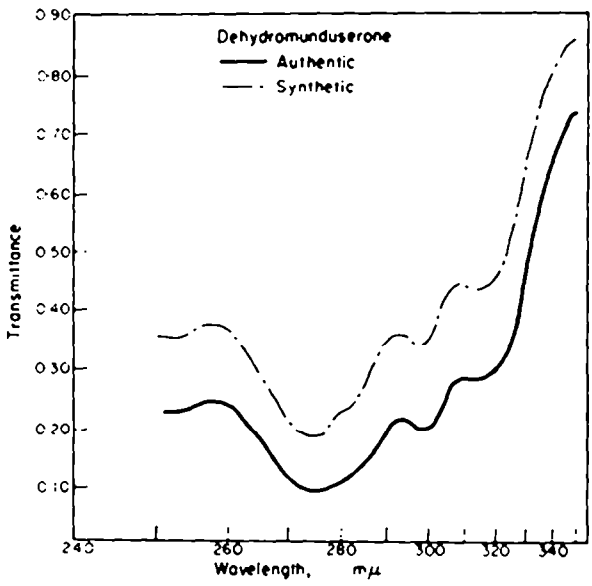


FIG. A.

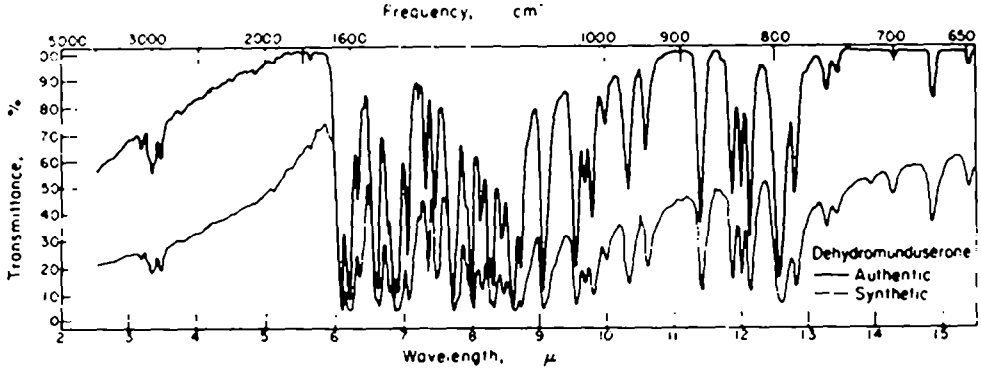
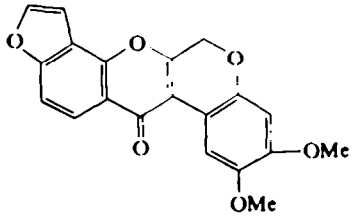


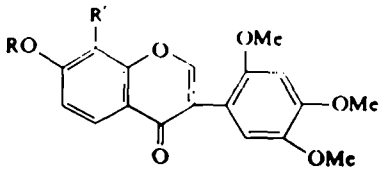
FIG. B.

The general applicability of the above method was further established by the synthesis of dehydroelliptone (XVI), using as intermediate 7-allyloxy-2',4',5'-trimethoxyisoflavone (XVII), which was prepared by two methods: (i) by allylation of 7-hydroxy-2',4',5'-trimethoxyisoflavone[11] (XVIII) and (ii) by isoflavone condensation of 2-hydroxy-4-allyloxyphenyl-2,4,5-trimethoxybenzyl ketone (XIX). Claisen migration of XVII gave the 8-allyl compound XX which was converted into elliptol isoflavone (XXII) by oxidative fission of the allyl group with osmium tetroxide–sodium metaperiodate to the 8-acetaldehyde XXI, followed by ring closure. This isoflavone was synthesized earlier,[9] starting from XVIII but by adopting a different route. The present procedure is far more convenient.

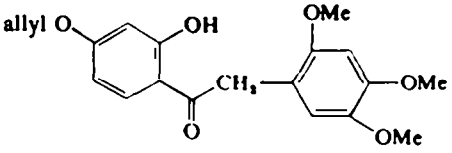
Elliptol isoflavone (XXII) underwent partial demethylation at the 2'-position and the hydroxy compound XXIII was converted into elliptic acid (XXV) in good yield. Final double ring closure yielded dehydroelliptone, identical in all respects with an authentic sample kindly supplied by Prof. S. H. Harper. This constitutes a total synthesis of elliptone since the further steps are already known.[4]



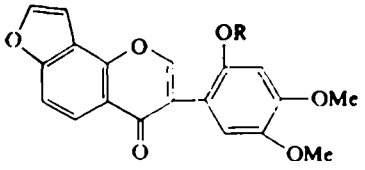
XVI



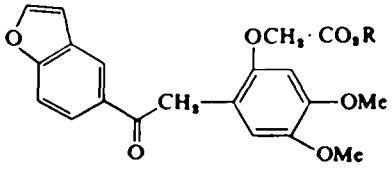
XVII R = allyl, R′ = H XX R = H, R′ = allyl
XVIII R = H, R′ = H XXI R = H, R′ = CH_2CHO



XIX



XXII R = Me
XXIII R = H; XXIV R = $CH_2{\cdot}CO_2Me$



XXV R = H; XXVI R = Me

EXPERIMENTAL

7-Methoxy-2′-hydroxyisoflavone (VIII). A mixture of 7,2′-dimethoxyisoflavone[10] (0·5 g), dry acetonitrile (10 ml) and anhyd $AlCl_3$ (3 g) was refluxed for 6 hr. The acetonitrile was removed, as far as possible, under reduced press and the complex left behind was cooled well in an ice-bath and decomposed by addition of ice-cold conc HCl (10 ml). The soln was heated in a boiling water-bath for a few min and cooled. The separated solid was filtered and macerated well with 2% NaOHaq. The alkaline soln on acidification gave a fluffy ppt of the 2′-hydroxyisoflavone which crystallized from EtOH as colourless needles (0·25 g) m.p. 144° (Lit[7] m.p. 148°).

7-Methoxy-2′-carbomethoxymethoxyisoflavone (IX). A mixture of the above 2′-hydroxyisoflavone (0·2 g), methyl bromoacetate (0·08 ml), dry acetone (15 ml) and anhyd K_2CO_3 (1 g) was refluxed for 20 hr. The K-salts were filtered off and the filtrate concentrated and diluted with water. The separated solid was filtered off, washed and crystallized from EtOH, when the isoflavone separated as globular aggregates (0·2 g), m.p. 134–135°. (Found: C, 67·0; H, 4·9. $C_{19}H_{18}O_6$ requires: C, 67·1; H, 4·8%.)

2-Hydroxy-4-methoxyphenyl-2-carboxymethoxybenzylketone (X). The foregoing phenoxyacetic ester (0·1 g) in alcoholic NaOHaq (5%; 15 ml) was heated under reflux for 2 hr. EtOH was removed under reduced press and the residual yellow soln poured into ice-cold dil HCl (15 ml). The separated solid in AcOEt was washed with water and then extracted with $NaHCO_3$aq. The acidified bicarbonate soln was extracted with AcOEt, the extract dried (Na_2SO_4) and the solvent removed. Crystallization of the residue from MeOH yielded the acid as short needles (0·09 g), m.p. 170° (Found: C, 64·5; H, 5·0. $C_{17}H_{16}O_6$ requires: C, 64·5; H, 5·1%.) It gave a red colour in the $FeCl_3$ test.

7-Methoxychromenochromone (VI). A mixture of the above acid (0·14 g), fused AcONa (0·1 g), freshly distilled Ac_2O (3 ml) and AcOH (0·15 ml) was refluxed at 150° for 10 min. The reaction mixture was cooled, diluted with EtOH (15 ml) and kept overnight in an ice-chest. The contents were poured into ice-cold water (100 ml) and extracted with AcOEt. The extract was washed with

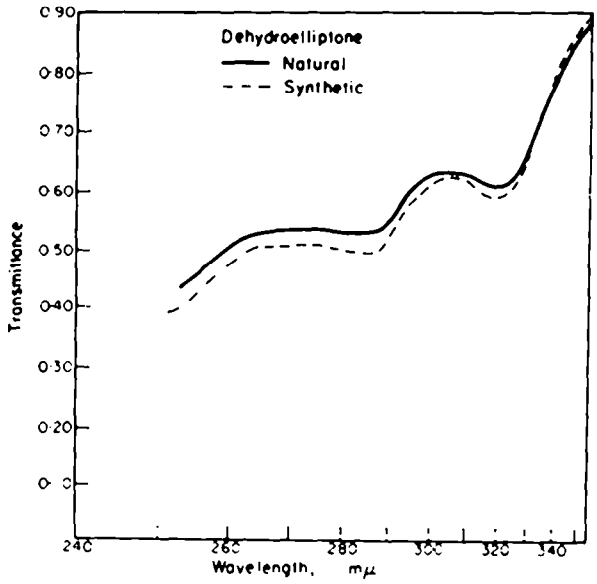


FIG. C.

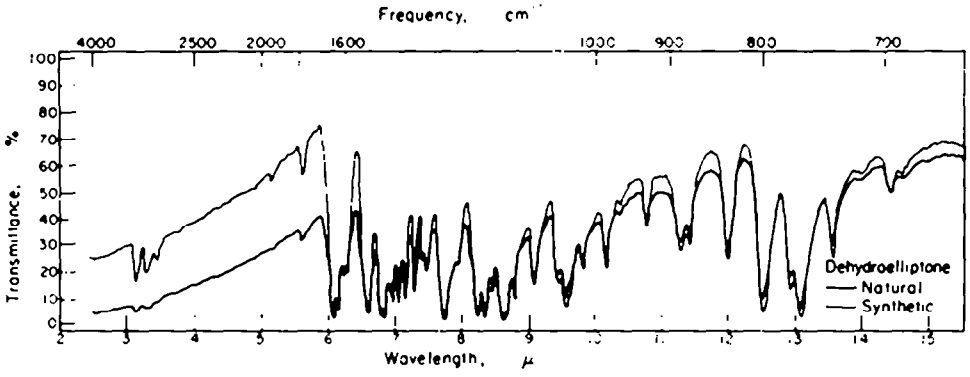


FIG. D.

$NaHCO_3$aq, water, dried (Na_2SO_4) and the solvent removed. The oily residue was dissolved in benzene and passed through a short column of alumina using dry benzene as eluant. The eluate was concentrated to a small volume, diluted with a little pet. ether and kept in a refrigerator. The colourless solid was crystallized from ether (0·02 g), m.p. 161–162°. (Found: C, 72·2; H, 4·3. $C_{17}H_{18}O_4$ requires: C, 72·9; H, 4·3%), λ_{max}^{EtOH} 224 (4·42), 270 (4·43), 297·5 (4·14) mμ.

2'-Hydroxy-7,4',5'-trimethoxyisoflavone (XIII). Compound XII (0·2 g) was added to a soln of anhyd $AlCl_3$ (2·5 g) in dry acetonitrile (15 ml) and the mixture refluxed for 8 hr. The product was worked up as described for the simpler member. The isoflavone separated from EtOH as colourless needles (0·15 g), m.p. 203–204°. (Found: C, 65·7; H, 4·9. $C_{18}H_{16}O_6$ requires C, 65·9; H, 5·2%.)

7,4',5'-Trimethoxy-2'-carbomethoxymethoxyisoflavone (XIV). A mixture of the above 2'-hydroxyisoflavone (1 g), methyl bromoacetate (0·035 ml), anhyd K_2CO_3 (2 g) and dry acetone (50 ml) was refluxed for 18 hr and the product worked up as described earlier. The isoflavone separated as needles from EtOH (0·12 g), m.p. 174–175°. (Found: C, 62·8; H, 5·4. $C_{21}H_{20}O_8$ requires: C, 63·0; H, 5·0%.)

Methyltephrosic acid (XV). The above 2'-carbomethoxymethoxyisoflavone (0·25 g) in alcoholic NaOHaq (5%, 25 ml) was refluxed for 2½ hr. EtOH was removed, as far as possible, under reduced press. The residual soln was cooled, diluted with water (50 ml), acidified and extracted with AcOEt.

The extract was washed with water, dried (Na_2SO_4) and the solvent removed. Crystallization of the residue from EtOH yielded the acid as cubes (0·2 g) m.p. 206–207° (lit[10] m.p. 204–205°). (Found: C, 60·1; H, 5·7. $C_{16}H_{20}O_6$ requires: C, 60·6; H, 5·4%.) It gave a deep red $FeCl_3$ test.

Dehydromunduserone (XI). A mixture of methyltephrosic acid (0·25 g) fused AcONa (0·2 g), Ac_2O (5 ml) and AcOH (0·5 ml) was refluxed for 10 min, cooled, diluted with EtOH (10 ml) and left overnight in a refrigerator. The soln was poured over crushed ice and the separated solid filtered off. It was boiled with EtOH, the EtOH insoluble residue was dissolved in Chf and passed through a short column of alumina. The eluate on concentration and dilution with EtOH deposited yellow crystals of dehydromunduserone (0·04 g) m.p. 209° undepressed by admixture with an authentic sample prepared from munduserone. (Found: C, 66·7; H, 4·7. $C_{16}H_{16}O_6$ requires: C, 67·1; H, 4·8%.) The UV and IR spectra of synthetic and natural samples were identical.

7-Allyloxy-2',4,5'-trimethoxyisoflavone (XVII). A mixture of 7-hydroxy-2',4',5'-trimethoxyisoflavone (1 g)[9], allyl bromide (0·3 ml), anhyd K_2CO_3 (5 g) was refluxed for 8 hr. The K- salts were filtered off and washed with hot acetone. The filtrate was concentrated to a small volume and diluted with water. The separated solid was crystallized from EtOH, and the isoflavone was obtained as short needles (1·1 g), m.p. 139–140°. (Found: C, 68·4; H, 5·9. $C_{21}H_{20}O_6$ requires: C, 68·5; H, 5·5%.)

4-Allyloxy-2-hydroxyphenyl-2,4,5-trimethoxybenzylketone (XIX). A mixture of 2,4-dihydroxyphenyl-2,4,5-trimethoxybenzylketone[11-14] (2 g), allyl bromide (0·6 ml), anhyd K_2CO_3 (8 g) and dry acetone (70 ml) was heated under reflux for 8 hr and worked up as above. The ketone crystallized from EtOH in long needles (1·8 g), m.p. 105–106°. (Found: C, 67·0; H, 6·5. $C_{20}H_{22}O_6$ requires: C, 67·0; H, 6·2%.) It gave a deep red $FeCl_3$ test.

7-Allyloxy-2',4',5'-trimethoxyisoflavone (XVII) *from* XIX. A mixture of the foregoing ketone (0·03 g), dry pyridine (1 ml), freshly distilled ethyl orthoformate (0·3 ml) and piperidine (3 drops) was refluxed for 12 hr. The cooled reaction mixture was acidified with 2N HCl and the separated solid crystallized from EtOH as short needles of the isoflavone, m.p. 139–140° undepressed on admixture with the one obtained from XXVII.

7-Hydroxy-8-allyl-2',4',5'-trimethoxyisoflavone (XX). Compound XVII (1 g) was heated under reduced press at 220° for 2 hr and the product extracted with 1% NaOHaq. The alkaline soln on acidification gave a white solid which crystallized from Chf as colourless crystals (1 g) m.p. 229°. (Found: C, 69·0; H, 5·5. $C_{21}H_{20}O_6$ requires: C, 68·5; H, 5·5%.) In subsequent experiments it was found that the product could be purified by simply boiling with EtOH which dissolved the unchanged 7-allyloxyisoflavone.

Elliptolisoflavone (XXII). The foregoing 8-allylisoflavone (0·5 g) in Chf (20 ml) to which water (20 ml) was added, was vigorously agitated in a vibroshaker with OsO_4 (0·08 g) for ½ hr, when the reaction mixture turned deep black. Powdered $NaIO_4$ (3 g) was added in small portions (2 hr), and the mixture allowed to stand overnight, during which time the colour turned yellow and some solid separated. The solid was filtered off and washed with water. The Chf layer of the filtrate was separated and evaporated to dryness and the residue mixed with the above solid. It was warmed with polyphosphoric acid [prepared from syrupy phosphoric acid (10 ml) and P_2O_5 (15 g)] over a boiling water-bath for 10 min and poured over crushed ice. The separated solid was extracted with AcOEt. The extract was washed successively with water, K_2CO_3aq, water, dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in benzene and passed through a short column of alumina. The eluate on evaporation gave a colourless solid which on crystallization from EtOH yielded colourless flakes of elliptol isoflavone (0·3 g), m.p. 185° (Lit[9] m.p. 185°). Found: C, 67·7; H, 4·8. $C_{20}H_{16}O_6$ requires: C, 68·2; H, 4·5%.)

Norelliptolisoflavone (XXIII). A mixture of elliptolisoflavone (0·5 g), anhyd $AlCl_3$ (1·5 g) and acetonitrile (15 ml) was refluxed for 6 hr and the product was worked up as described in the earlier cases. The isoflavone crystallized from MeOH as colourless needles (0·3 g), m.p. 204–205°. (Found: C, 67·1; H, 4·4. $C_{19}H_{14}O_6$ requires: C, 67·5; H, 4·2%.)

7,8,2',3'-Furano-2'-carbomethoxymethoxy-4',5'-dimethoxyisoflavone (XXIV). A mixture of norelliptolisoflavone (0·2 g), methyl bromoacetate (0·08 ml), anhyd K_2CO_3 (1·5 g) and dry acetone (50 ml) was refluxed for 24 hr. The acetone soln, filtered free from the K-salts, was concentrated to a small volume (1 ml) and water (20 ml) added. The solid obtained crystallized from EtOH as colourless crystals (0·2 g) m.p. 182–183°. (Found: C, 64·2; H, 4·5. $C_{23}H_{18}O_8$ requires: C, 64·4; H, 4·4%.)

Elliptic acid (XXV). The above phenoxyacetic ester (0·2 g) in alcoholic NaOHaq (5%, 25 ml) was heated under reflux for 2 hr. EtOH was removed under reduced press and the residue diluted

with water and acidified. The ppt in AcOEt was washed with water, dried (Na_2SO_4) and evaporated to dryness. Crystallization of the residue from EtOH gave the acid as needles (0·18 g), m.p. 190° (Lit[18] m.p. 190°). (Found: C, 61·7; H, 5·0. $C_{20}H_{18}O_6$ requires: C, 62·2; H, 4·7%.) It gave a bluish green $FeCl_3$ test. The methyl ester XXVI ($MeOH-H_2SO_4$) crystallized from EtOH as silky needles, m.p. 142° (Lit[19] m.p. 142°). (Found: C, 63·0; H, 5·5. $C_{21}H_{20}O_6$ requires: C, 63·0; H, 5·0%.)

Dehydroelliptone (XVI). A mixture of elliptic acid (0·4 g), anhyd AcONa (0·02 g), Ac_2O (5 ml) and AcOH (0·5 ml) was refluxed for 10 min, cooled and diluted with EtOH. After standing overnight a small amount of pale yellow crystals separated. These were filtered and washed with EtOH. From the filtrate a little more of compound was obtained and this was added to the main bulk. The solid in Chf was passed through a short column of alumina and eluted with Chf. The eluate was concentrated and diluted with MeOH when pale yellow transparent crystals (0·018 g) were obtained, m.p. 262°, undepressed on admixture with an authentic sample. (Found: C, 68·8; H, 3.9. $C_{20}H_{14}O_6$ requires: C, 68·6; H, 4·0%.) The UV and the IR spectra of the two samples were identical.

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