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β-PHENOXYETHYL ALKYL(ARYL) KETONES. REARRANGEMENT AND CONVERSION INTO BENZOPYRYLIUM SALTS

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Abstract—The rearrangement of some β-phenoxyethyl alkyl(aryl) ketones to 4-hydroxyphenoxyethyl alkyl(aryl) ketones has been studied. The latter undergo rearrangement under oxidative conditions to flavilium salts such as 0-trimethylapigeninidin chloride or 0-tetramethylluteolinidin chloride. The mechanism of these changes has been discussed.

IN CONNECTION with our studies on the synthesis of chromenes, β-*m*-methoxyphenoxyethyl methyl ketone (I) and related phenyl ketone (II) were prepared in moderate yields from β-*m*-methoxyphenoxypropionitrile[1] by the action of methylmagnesium iodide and phenylmagnesium bromide respectively. The main by-product in these preparations was *m*-methoxyphenol arising on account of *retro*-Michael reaction presumably occuring in the magnesium complex or the resulting ketone. Indeed when the ketones (I and II) were treated with alcoholic sodium ethoxide, *m*-methoxyphenol was formed in nearly quantitative yields. However, when ketone I was heated with piperidine in benzene, the rearranged ketone III was formed. This was confirmed by the unambiguous synthesis† of the ethyl derivative (V) from 2-methoxy-4-ethoxyphenylpropionitrile and methylmagnesium iodide. Similarly the ketone II on rearrangement gave IV, the orientation of which was confirmed by conversion into VI which was also synthesized.†

Both the rearranged products of III and IV were also obtained in fair yield by Michael condensation† of *m*-methoxyphenol with methiodide of 4-diethylaminoethylbutan-2-one (VII)[2] and β-diethylaminoethyl phenyl ketone (VIII)[3] respectively. The rearrangement of the phenoxy ketones obviously involves *retro*-Michael reaction followed by recombination of the vinyl ketone with the phenolate anion giving thermo-dynamically more stable C-alkylated products as shown below:

The Michael adducts (IX and X), derived from phloroglucinol dimethyl ether and methiodides of β-diethylaminoethyl anisyl ketone and gallyl ketone respectively, on treatment with alcoholic hydrogen chloride in presence of chloranil gave good yields of O-trimethylapigeninidin chloride[4] (XVIII) and O-tetramethylluteolinidin chloride[4] (XIX). A quantitative yields of corresponding perchlorates were obtained on treating the ketones (IX, X and XI) with trityl perchlorate in boiling acetic acid. The reagent is found to be eminently suitable for the synthesis of benzo-pyrylium salts from O-hydroxychalcones† or flav-2-enes[5] from which they are derived. Thus 2-hydroxy-

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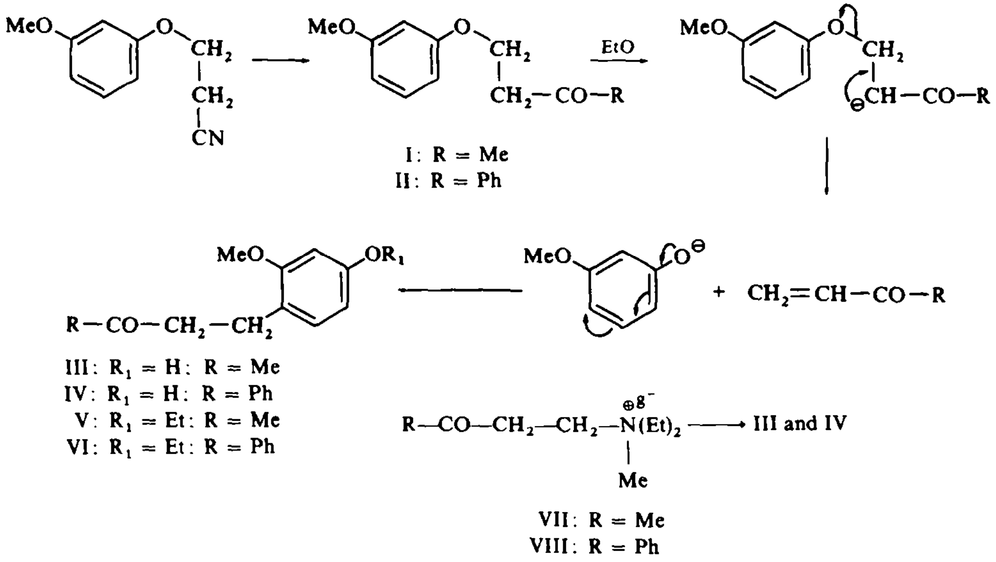
†The Michael condensation of Mannich base methosalts with phenols has been studied in detail and the results are in press.



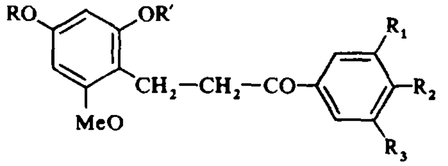
I: $R = Me$
II: $R = Ph$

III: $R_1 = H$: $R = Me$
IV: $R_1 = H$: $R = Ph$
V: $R_1 = Et$: $R = Me$
VI: $R_1 = Et$: $R = Ph$

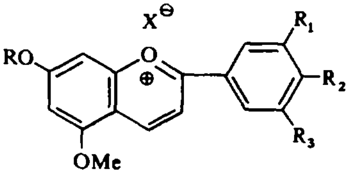
VII: $R = Me$
VIII: $R = Ph$

4,6,4′-trimethoxy-, 2-hydroxy-4,6,3′,4′-tetramethoxy- and 2-hydroxy-4,6,3′,4′,5′-pentamethoxy-α:β-dihydrochalcones (XII, XIII and XIV) respectively gave the corresponding pyrylium perchlorates (XX, XXI and XXII). The above three perchlorates were also obtained from the flavenes (XV, XVI and XVII) in quantitative yields.

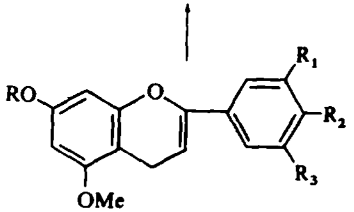
O-Trimethylpelargonidin chloride (XXIV) was prepared from 5,7,4′-trimethoxyflavene (XV) using the procedure of Johnson *et al.*[5] and found identical with an authentic sample.[6]



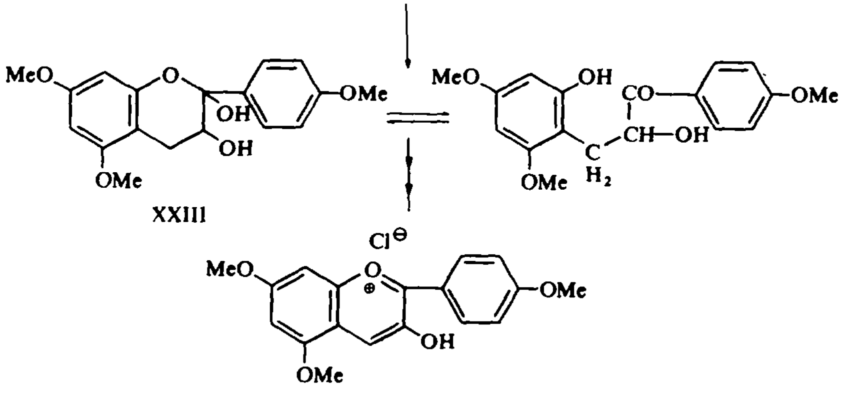
IX: $R = R_1 = R_3 = H$: $R' = Me$: $R_2 = OMe$
X: $R = R_3 = H$: $R' = Me$: $R_1 = R_2 = OMe$
XI: $R = H$: $R' = Me$. $R_1 = R_2 = R_3 = OMe$
XII: $R' = R_1 = R_3 = H$: $R = Me$: $R_2 = OMe$
XIII: $R' = R_3 = H$: $R = Me$: $R_1 = R_2 = OMe$
XIV: $R' = H$: $R = Me$; $R_1 = R_2 = R_3 = OMe$



XVIII: $R_1 = R_3 = H$: $R = Me$: $R_2 = OMe$: $X = Cl$
XIX: $R_3 = H$: $R = Me$: $R_1 = R_2 = OMe$: $X = Cl$
XX: $R_1 = R_3 = H$: $R = Me$: $R_2 = OMe$; $X = ClO_4$
XXI: $R_3 = H$: $R = Me$: $R_1 = R_2 = OMe$; $X = ClO_4$
XXII: $R = Me$: $R_1 = R_2 = R_3 = OMe$; $X = ClO_4$



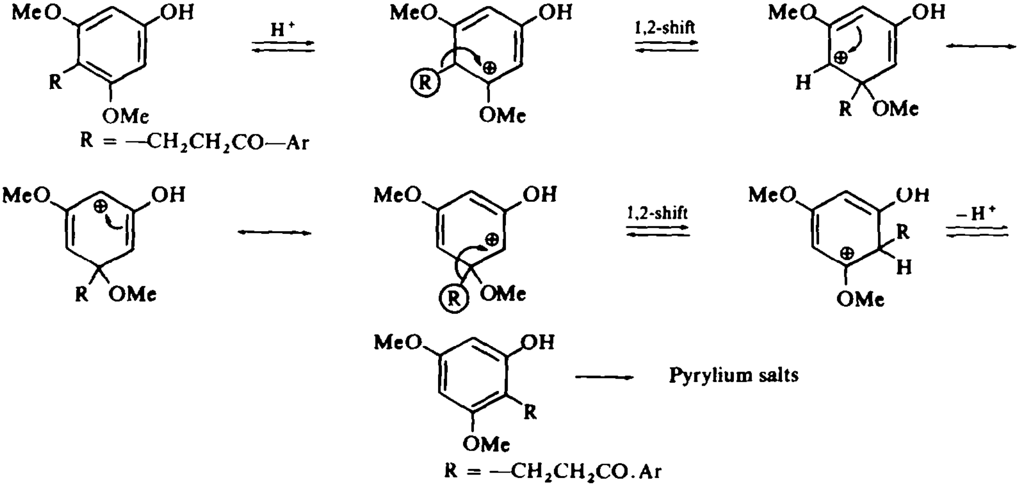
XV: $R_1 = R_3 = H$; $R = Me$; $R_2 = OMe$
XVI: $R_3 = H$; $R = Me$; $R_1 = R_2 = OMe$
XVII: $R = Me$; $R_1 = R_2 = R_3 = OMe$



XXIII

XXIV

Two mechanisms may be considered to explain the formation of pyrylium salts from *p*-hydroxy ketones of the type of IX as described above. These are (i) an intermolecular rearrangement by an acid-catalysed reverse Michael reaction followed by the addition of the vinylketone *ortho*- to the OH group. Cyclization and oxidation stabilizes the product as the pyrylium salt, and equilibrium is thus displaced to give good yields of the salt or (ii) an intramolecular rearrangement as shown below involving a double 1,2-shift of the side chain to the *ortho*-position of the OH group.



R = —CH_2CH_2CO—Ar

R = —$CH_2CH_2CO.Ar$

EXPERIMENTAL

All m.p. are uncorrected. The IR spectra were recorded with Perkin–Elmer Infracord, model 237.

β-m-*Methoxyphenoxyethyl methyl ketone (I)*

An ethereal soln of β-*m*-methoxyphenoxypropionitrile (5·2 g) was added dropwise with stirring to an ice-cooled ethereal soln of MeMgI (Mg, 2·2 g and MeI, 6·3 ml). The mixture was gently refluxed for 2 hr, cooled, decomposed with 5N H_2SO_4 and extracted with ether. The ethereal soln was washed with 5% NaOH, water and dried ($MgSO_4$). The *ketone*, obtained on removal of solvent, distilled at (bath temp) 165–70°/0·1 mm as colourless oil (1 g). (Found: C, 67·92; H, 7·17. $C_{11}H_{14}O_3$ requires: C, 68·02; H, 7·27%). The IR showed sharp peak for CO at $\nu_{\text{neat}}^{\text{max}}$ 1715 cm^{-1}. The 2,4-*DNP* crystallized in orange needles from EtOAc, m.p. 161–2°. (Found: N, 15·25. $C_{17}H_{18}O_6N_4$ reauires: N, 14·97%).

β-m-*Methoxyphenoxyethyl phenyl ketone (II)*

The title compound was obtained, similarly, using β-*m*-methoxyphenoxypropionitrile (1·7 g) and PhMgBr (Mg, 0·5 g and PhBr, 2 ml). The *ketone* crystallized from MeOH as colourless tiny needles (0·12 g), m.p. 97–98°. (Found: C, 74·95; H, 6·09. $C_{16}H_{16}O_3$ requires: C, 74·98; H, 6·29%). The IR showed peak for CO at $\nu_{\text{KBr}}^{\text{max}}$ 1690 cm^{-1}. The 2,4-*DNP* crystallized in orange plates from EtOAc, m.p. 200°. (Found: N, 12·55. $C_{22}H_{20}O_6N_4$ requires: N, 12·84%).

Rearrangement of β-m-*methoxyphenoxyethyl methyl ketone (I)*

A mixture of *ketone* (I) (0·97 g, 1 mole), piperidine (1·5 g, 3 moles) and dry benzene (25 ml) were refluxed for 36 hr. Removal of benzene left a residue which was taken up in NaOH (20 ml, 10%). Unchanged 0-ketone and polymerized product were removed by ether extraction. The residual alkaline soln was acidified with 2N HCl and extracted with ether. The ether extract was washed with water and dried ($MgSO_4$). On evaporation of ether, a thick brown oil (0·8 g) was obtained. As the desired phenol (III) was likely to be accompanied by *m*-methoxyphenol, the compound was purified by distillation, whereupon *m*-methoxyphenol separated as yellow oil (bath temp) 140°/10 mm, (*ca* 0·5 g). The residue, a thick brown oil, was ethylated with Et_2SO_4 and baked K_2CO_3 in acetone as usual. After removal of acetone, the mixture was steam distilled to remove last traces of *m*-methoxyphenol as steam volatile *m*-methoxyethoxybenzene. The alkaline soln was cooled, extracted with ether, washed with water and dried ($MgSO_4$). The residue, on removal of solvent, was distilled at (bath temp) 172–80°/1 mm as colourless oil (0·1 g) characterized as V by comparing with authentic sample† (superimposable IR spectra). The 2,4-*DNP* crystallized from EtOAc in yellow orange needles, m.p. 139–40°. (Found: N, 13·83. Calc. for $C_{19}H_{22}O_6N_4$: N, 13·92%).

Rearrangement of β-m-*methoxyphenoxyethyl phenyl ketone (II)*

Like above, the rearrangement of β-*m*-methoxyphenoxyethyl phenyl ketone in benzene piperidine, followed by ethylation and removal of *m*-methoxyethoxybenzene, left a thick brown oil. It was distilled at (bath temp) 250–55°/0·1 mm as colourless oil. The product was identified as VI by comparing with authentic sample.† The 2,4-*DNP* crystallized in shining red needles from EtOAc, m.p. 200°. (Found: N, 12·28. Calc. for $C_{24}H_{24}O_6N_4$: N, 12·06%).

O-Trimethylapigenidin chloride (XVIII)

Dry HCl was passed through a mixture of 4-hydroxy-2,6,4'-trimethoxy-α:β-dihydrochalcone† (0·1 g), chloranil (25 mg) and abs EtOH (2 ml) till saturation (3 hr). The mixture was chilled, dilution with dry ether (25 ml) afforded a dark brown solid. It was collected and crystallized from 6N HCl as brown red needles (25 mg), m.p. 133–34° (lit.[4] 135°). The IR spectrum showed bands at $\nu_{\text{KBr}}^{\text{max}}$ 1645, 1605, 1535, 1505, 1435, 1380, 1315, 1290, 1245, 1055, 913, 820, 762 and 630 cm^{-1}. It is found to be identical with authentic sample (undepressed m.m.p. and superimposable IR spectra).

O-*Trimethylapigenidin perchlorate* (XX)

(a) A mixture of 4-hydroxy-2,6,4'-trimethoxy-α:β-dihydrochalcone† (35 mg) and trityl perchlorate (*ca* 25 mg) in extra pure glacial AcOH (2 ml) was heated for 15 min. The mixture, on cooling, afforded dark red granular crystals (15 mg), m.p. 255° (d).

(b) A soln of 2-hydroxy-4,6,4'-trimethoxy-α:β-dihydrochalcone[5] (25 mg) in glacial AcOH (2 ml) was treated with trityl perchlorate. The mixture, on cooling, afforded orange red needles (25 mg), m.p. 254–56° (d).

(c) Similarly 5,7,4'-trimethoxyflav-2-ene[5] on treatment with trityl perchlorate in glacial AcOH gave orange red crystals, m.p. 255° (d).

The three perchlorates, obtained from different starting materials, were found to be identical. (mixed m.p. and superimposable IR).

O-Tetramethylluteolinidin chloride (XIX)

A mixture of 4-hydroxy-2,6,3',4'-tetramethoxy α:β-dihydro-chalcone† (0·1 g), chloranil (25 mg) and abs EtOH (2 ml) was taken and dry HCl was passed into it for 3 hr at room temp and kept in freezer for 2 days. On adding dry ether a blackish brown solid precipitated which was crystallized from 6N HCl as dark brown needles (25 mg), m.p. 160–61° (lit.[4] m.p. 160–62°). The IR showed bands at ν_{KBr}^{max} 1645, 1572, 1500, 1365, 1150, 1055, 1000, 950 and 755 cm^{-1}. This pyrylium salt was found to be identical with the authentic sample (undepressed mixed m.p. and superimposable IR spectra).

O-Tetramethylluteolinidin perchlorate (XXI)

(a) A mixture of 4-hydroxy-2,6,3',4'-tetramethoxy α:β-dihydro-chalcone† (25 mg), trityl perchlorate (*ca* 25 mg) and extra pure glacial AcOH (2 ml) was heated for 15 min. The mixture, on cooling, afforded dark red granular crystals (15 mg), m.p. 260–61° (d).

(b) Similarly 2-hydroxy-4,6,3',4'-tetramethoxy α:β-dihydro-chalcone and 5,7,3',4'-tetramethoxyflav-2-ene[5], separately, on treatment with trityl perchlorate in glacial AcOH afforded dark red granular crystals, m.p. 260° (d). The perchlorates (from three different starting compounds) were found to be identical in all respects (undepressed mixed m.p. and superimposable IR spectra).

5,7,3',4',5'-Pentamethoxyflavylium perchlorate

(a) A solution of 4-hydroxy-2,6,3',4',5'-pentamethoxy α:β-dihydrochalcone† (25 mg) in glacial AcOH (2·0 ml) was treated with trityl perchlorate (*ca* 25 mg). The mixture, on cooling, afforded dark red woolly needles (15 mg), m.p. 248–49°.

(b) Similarly, 2-hydroxy-4,6,3',4',5'-pentamethoxy α:β-dihydrochalcone and 5,7,3',4',5'-pentamethoxy-flav-2-ene,† separately, on treatment with trityl perchlorate in AcOH, afforded dark red woolly needles (20 mg), m.p. 248–50°.

The three perchlorates obtained from three different starting substances were found to be identical in all respects (undepressed mixed m.p. and superimposable IR spectra). The main peaks in IR at ν_{KBr}^{max} 1712, 1643, 1585, 1518, 1495, 1433, 1350, 1300, 1225, 990, 845, 738 and 708 cm^{-1}.

α:β-Dihydro-α:2-dihydroxy-4,6,4'-trimethoxychalcone (XXIII)

5,7,4'-Trimethoxyflav-2-ene[5] (0·18 g) was added to an ethereal soln of monoperphthalic acid (0·35 g in 250 ml). The mixture was kept at 20° for 4 hr with occasional shaking. Excess of acid was neutralized by adding just sufficient amount of $NaHCO_3$ aq and the ether layer was separated and dried (Na_2SO_4). A pale yellow solid was obtained on removal of ether, which crystallized from benzene as colourless small needles (50 mg), m.p. 202–03°. (Found: C, 64·83; H, 5·98. $C_{18}H_{20}O_6$ requires: C, 65·05; H, 6·07%). The IR showed bands at ν_{KBr}^{max} 3420, 1778, 1745, 1708, 1495, 1118, 883, 765, 720, 705 and 405 cm^{-1}.

O-Trimethylpelargonidin chloride (XXIV)

Above *hydroxychalcone* (50 mg) was heated with a mixture of i-PrOH HCl (50 ml; 19:1 ratio) in a sealed tube at 100° for 3 hr. After cooling, i-PrOH was removed under *vacuum*. A red silky mass together with some black tarry material was obtained. The whole material was taken in ethanolic HCl (25 ml; 1:1), boiled and filtered. The filtrate, on concentration and cooling, furnished a red brown solid along with some undesired tarry material. The second crystallization from same solvent afforded reddish orange needles (4 mg), m.p. 210–12° (d) (lit.[5] m.p. 213° d). The product was found to be identical with an authentic sample prepared by the method of King *et al.*[6] (mixed m.p., TLC in several solvents). The IR spectra of the two samples were superimposable, showed bands at ν_{KBr}^{max} 1715, 1630, 1600, 1575, 1325, 1260, 1218, 1018 and 835 cm^{-1}.

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