The Oxidation of Chromanones and Flavanones with Lead Tetra-acetate.

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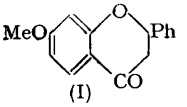
Oxidation of a number of flavanones with lead tetra-acetate has been found to give complex mixtures in which the corresponding flavone is invariably present. The reaction mixtures from flavanone and from 7-methoxy- and 7 : 4′-dimethoxy-flavanone also contain the respective 3-acetoxy-derivative and the related *iso*flavone, whilst 7 : 3′ : 4′-trimethoxyflavanone furnished 7 : 3′ : 4′-trimethoxy*iso*flavone. Under similar conditions the chromanones yield only the 3-acetoxy-derivatives.

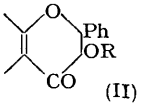
The acetoxylation of reactive methylene groups with lead tetra-acetate, developed by Dimroth and Schweizer (*Ber.*, 1923, **56**, 1375), Criegee (*Annalen*, 1930, **481**, 263), Cavill, Robertson, and Whalley (*J.*, 1949, 1567), and others, has now been extended to a number of flavanones. With this reagent in acetic acid at 80—90° (reaction did not occur at room temperature) flavanone, and 7-methoxy- and 7 : 4′-dimethoxy-flavanone, each furnished mixtures of three products, *viz.*, the 3-acetoxyflavanone (*O*-acetyldihydroflavanol), the flavone, and the *iso*flavone. From the products from 7 : 3′ : 4′-trimethoxyflavanone, 7 : 3′ : 4′-trimethoxyflavone and the isomeric *iso*flavone, but not the expected 3-acetoxy-flavanone, were isolated; 3′ : 4′-dimethoxy- and 7-methoxy-3′-nitro-flavanone gave only the flavones; 7-methoxy-3′ : 4′-methylenedioxyflavanone formed an intractable tar, owing, presumably, to the initial attack of the methylenedioxy-group; and 7 : 2′-dimethoxy-flavanone gave an irresolvable mixture. When these studies were well advanced Oyamada's work (*J. Chem. Soc. Japan*, 1943, **64**, 331, 471) became available to us, first as abstracts (*Chem. Abstracts*, 1947, **41**, 3797) and ultimately in full. In the five examples recorded, this author obtained the 3-acetoxyflavanone accompanied in the cases of flavanone and 7-methoxy- and 7 : 4′-dimethoxy-flavanone by products which he was unable to identify but which from their descriptions seem to have been the *iso*flavones.

The crude mixtures obtained in the present work were difficult to purify and were not quantitatively separated. Fractional crystallisation was successful only with the products from 7-methoxyflavanone (I), but this served to show that flavone and *iso*flavone are not artefacts due to the action of aluminium oxide when it was found subsequently that chromatography gave more complete results. The complexity of the reaction may be due in part to the tendency of the flavanone system to revert to the flavanone–chalkone equilibrium mixture, as well as to the attack at the 2-position of the flavanone.

The 3-acetoxyflavanones (II; R = Ac) were readily hydrolysed with warm mineral acids, giving the corresponding 3-hydroxyflavanones, the orientation of which follows from the negative ferric reaction and their behaviour as α-hydroxy-ketones in readily reducing warm Fehling's solution and in reacting with *o*-phenylenediamine to give dihydroquinoxalines; attempts to dehydrate the 3-hydroxyflavanone to the flavones were unsuccessful. The orientation of 3-hydroxy-7-methoxyflavanone (II; R = H) is supported by its forma-



(I)



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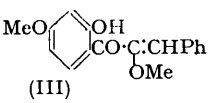


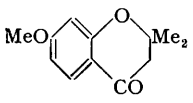
(III)

tion on cyclisation, with partial demethylation of the chalkone (III) by hot hydrochloric acid, and from 2′-hydroxy-4′-methoxychalkone under the conditions employed by Reichel and Steudel (*Annalen*, 1942, **553**, 83; cf. Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, *B* **42**, 1) for the conversion of chalkone into 3-hydroxyflavanone. On oxidation with alkaline hydrogen peroxide or with a boiling mixture of 2N-sulphuric acid and dioxan (aerial oxidation) this

flavanone gave 7-methoxyflavonol which was also obtained from 2'-hydroxy-4'-methoxychalkone by Reichel and Steudel's procedure (*loc. cit.*). In this connection it is of interest that the deacetylation of 3-acetoxy-7-methoxyflavanone with methanolic ammonia at room temperature was accompanied by oxidation to 7-methoxyflavonol.

The mechanism of the novel conversion of, *e.g.*, 7-methoxyflavanone into 7-methoxy*iso*flavone by lead tetra-acetate is open to a number of interpretations which are complicated by the ambiguity regarding the mode of action of the oxidising agent. On the view that the initial step is acetoxylation at position 3 it appears that the *iso*flavones are formed from the acetates by a Wagner–Meerwein type of rearrangement. The difficulties involved in fitting the naturally occurring *iso*flavones into a self-consistent biological scheme, together with the co-occurrence of structurally similar flavanones, flavones, and *iso*flavones, have already led Geissmann and Hinreiner (*Bot. Review*, 1952, **18**, 165) to suggest that *iso*flavones might arise by Wagner–Meerwein rearrangement of 3-hydroxyflavanones or equivalent precursors, although a reaction of this nature had not been observed at that time. However, the results of the lead tetra-acetate oxidation of chromanones, when combined with those in the flavanone series, do not support this simple explanation.

Chromanone, and 7-methoxy- and 7-methoxy-2 : 2-dimethyl-chromanone (IV), gave only single (racemic) 3-acetoxy-derivatives, whereas 7-methoxy-2-methylchromanone (V) gave *trans*- (VI) and *cis*-racemates (VII), m. p. 118° and m. p. 120°. In accordance with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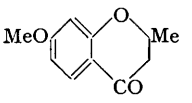
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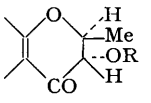
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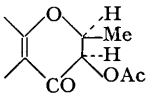
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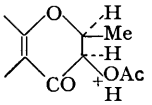

(VIII)

the well-known stereochemical instability of the system R·CO·CHR'R'' acid hydrolysis of both racemates yielded the same alcohol which with acetic anhydride regenerated only the acetate, m. p. 120°. This result indicated that the difference between the racemates was stereochemical and not structural. Taken in conjunction with the principle of *trans*-elimination, failure to extrude the elements of water from the alcohol or of acetic acid from the acetate, m. p. 120°, suggested that these compounds have the *trans*-configuration (VI; R = H or Ac) and this assignment was confirmed by the conversion of the other (*cis*-)racemate, m. p. 118°, into 7-methoxy-2-methylchromone by sulphuric acid, presumably by way of an ion (VIII). The single acetate obtained from 2-methylchromanone is considered to have the *trans*-configuration because it resisted conversion into a chromone.

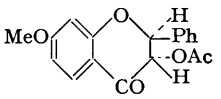
Kharasch, Friedlander, and Urry (*J. Org. Chem.*, 1951, **16**, 533) found that di*iso*propyl ether is converted into the diacetate (IX) by lead tetra-acetate, so the 2-position of a chromanone must also be considered to be a site for attack; hence it is not surprising that 7-methoxy-2 : 2-dimethylchromanone, with the 2-position blocked, gave the best yields of a 3-acetoxy-derivative. In no case was a 2- or a 3-methylchromone isolated from the product of a lead tetra-acetate oxidation.

Reaction at position 2 would be facilitated by the aryl groups of flavanones but the products, being esters of β-hydroxy-ketones, would readily generate the unsaturated ketones, *i.e.*, flavones. Yields of flavones were higher when 3-acetoxyflavanones were not isolated, which suggests that the flavones are produced chiefly by this method and discloses the competitive nature of the attack at the two available positions. In efforts to acquire further evidence of oxidation at the 2-position benzyl (X; R = H) and *m*-nitrobenzyl phenyl ether (X; R = NO_2) were treated with lead tetra-acetate: although the products could not be freed from the parent ethers they undoubtedly contained the α-acetoxy-derivatives (XI) because acid hydrolysis gave the aldehydes and phenol whilst the product from (X; R = NO_2) showed only one carbonyl frequency at 1754 $cm.^{-1}$, corresponding to that of an aliphatic ester.

As with 7-methoxy-2-methylchromanone, acetoxylation at position 3 of a flavanone should give two racemates but in the favourable cases examined only one has been isolated. If the *iso*flavones are indeed produced by a Wagner–Meerwein rearrangement, this can take place only with a racemate of the *trans*-type (XII). The surviving racemate would then

have the *cis*-configuration (XIII), but a number of considerations militate against this interpretation: (*a*) The surviving racemates cannot be converted into flavones by the method which generated 7-methoxy-2-methylchromone from *cis*-3-acetoxy-7-methoxy-2-methylchromanone. (*b*) The surviving racemates can be regenerated from their parent

$Me_2CH{\cdot}O{\cdot}CMe(OAc){\cdot}CH_2{\cdot}OAc$ (IX) $PhO{\cdot}CH_2{\cdot}C_6H_4R\text{-}m$ (X) $PhO{\cdot}CH(OAc){\cdot}C_6H_4R\text{-}m$ (XI)



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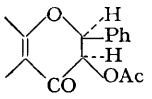
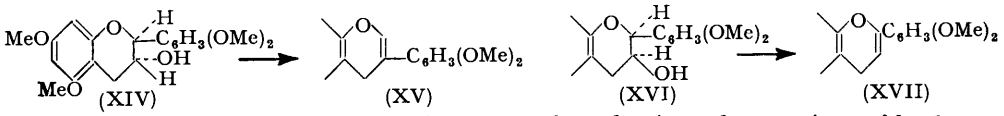


(XIII)

alcohols, and hence these alcohols and their acetates must have the same configuration, but in the chromanone series the stable configuration appears to be *trans* and not *cis*. (*c*) No rearrangement was observed in the chromanone series, even with 2 : 2-dimethylchromanone where the stereochemistry must be favourable to migration. (*d*) The polar character of the carbonyl group of chromanones and flavanones would oppose the development on the neighbouring carbon atom of the positive charge necessary for the initiation of the Wagner–Meerwein rearrangement or elimination. In contrast it may be noted that tetra-*O*-methylcatechin (XIV) has the *trans*-configuration and with acidic reagents gives 5 : 7 : 3′ : 4′-tetramethoxy*iso*flav-2-en (XV) whereas the corresponding *cis*-compound, tetra-*O*-methyl*epi*catechin (XVI) is dehydrated normally, giving 5 : 7 : 3′ : 4′-tetramethoxyflav-2-en (XVII) as established by Freudenberg and his collaborators and by Baker (*J.*, 1929, 1593) who gives the bibliography.

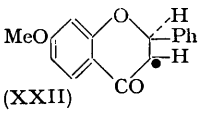


(XIV) (XV) (XVI) (XVII)

In spite of the absence of any precise accepted mechanism, the reactions of lead tetra-acetate present the chief features of radical activity, and we prefer to interpret the present observations in terms of radicals instead of ions. In a study of the reactions of the radical (XIX) formed from (XVIII), Urry and Kharasch (*J. Amer. Chem. Soc.*, 1932, **54**, 3274) obtained products which showed that (XIX) could isomerise to (XX) by migration of phenyl, but they were not able to obtain evidence of a similar migration of methyl which would have given (XXI). In other work, Kharasch, Poshkus, Forio, and Nudenberg

$Ph{\cdot}CMe_2{\cdot}CH_2Cl$ (XVIII) $Ph{\cdot}CMe_2{\cdot}CH_2{\cdot}$ (XIX) $Me_2\dot{C}{\cdot}CH_2Ph$ (XX) $Ph{\cdot}\dot{C}Me{\cdot}CH_2Me$ (XXI)

(*J. Org. Chem.*, 1951, **16**, 1458) noted that in certain radicals phenyl migrated from carbon to oxygen, whereas with methyl in place of phenyl, elimination occurred without rearrangement. These observations are entirely consistent with the formation of *iso*flavones from radical intermediates of type (XXII) and the non-formation of 3-methylchromones from the corresponding radicals (XXIII). Further, flavones could arise directly from radicals of type (XXIV) by loss of hydrogen in any of several possible ways. Because methyl



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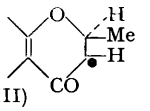

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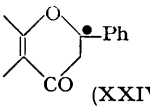

(XXIV)

and allied radicals are planar, any stereospecificity in radicals of types (XXII) and (XXIII) would disappear and with it any grounds for supposing that the surviving racemates from flavanone oxidations have the *cis*-configuration. Indeed, radicals of type (XXII) would be able to adopt the more stable *trans*-configuration when combining with acetate radicals. The apparent discordance between the acetates and alcohols in the flavanone series and those in the chromanone series would then be resolved.

Experimental

The light petroleum employed had b. p. 60—80°.

Oxidation of Flavanone.—A solution of flavanone (8 g.) and lead tetra-acetate (16 g., 1 mol.) was kept at 90° for 2½ hr., then giving a negative test for quadrivalent lead. The cooled mixture was diluted with water, and, on isolation with ether (extracts being washed with aqueous sodium hydrogen carbonate), the product was a viscous oil which was dissolved in benzene (100 ml.) and poured on aluminium oxide (70 × 2·5 cm.). The column was washed with benzene (6 × 200 ml.). Combined and evaporated, the first and second eluates gave a product (1·2 g.), m. p. 80—85°, which on fractional crystallisation from benzene gave (less soluble) *iso*flavone in white plates (0·5 g.), m. p. 132° (Found : C, 81·0; H, 4·5. Calc. for $C_{15}H_{10}O_2$: C, 81·1; H, 4·5%) (Joshi and Venkataraman, *J.*, 1934, 513). The product left on evaporation of the benzene liquors from *iso*flavone combined with the benzene eluates (3—6) was crystallised from ethyl acetate and had m. p. 88—92° (yield, 1·3 g.). Repeated recrystallisation of this from methanol ultimately gave 3-acetoxyflavanone in colourless needles (0·6 g.), m. p. 97° (Found : C, 72·4; H, 5·1. Calc. for $C_{17}H_{14}O_4$: C, 72·4; H, 5·0%) (cf. Oyamada, *loc. cit.*, who gives m. p. 94—94·5°).

The aluminium oxide column was then washed with methanol, the brown solution was evaporated, and the residue was extracted with boiling light petroleum, giving flavone in colourless needles (0·4 g.) (Found : C, 81·1; H, 4·5%), a solution of which in concentrated sulphuric acid exhibited the characteristic blue fluorescence.

3-Hydroxyflavanone.—Hydrolysed with boiling methanol (20 ml.) and concentrated hydrochloric acid (2 ml.) for ½ hr., 3-acetoxyflavanone (0·5 g.) gave 3-hydroxyflavanone which separated from methanol in needles (0·3 g.), m. p. 184° (Found : C, 74·9; H, 5·3. Calc. for $C_{15}H_{12}O_5$: C, 75·0; H, 5·0%) (Oyamada, *loc. cit.*, gives m. p. 183—184°, and Reichel and Steudel, *loc. cit.*, m. p. 176—178°). Interaction of this compound (0·2 g.) with *o*-phenylenediamine (0·15 g.) in boiling alcohol (5 ml.) and acetic acid (3 ml.) for 15 min. gave 1 : 2-*dihydroflavano*(3′ : 4′-2 : 3)-*quinoxaline* which formed bright yellow plates, m. p. 177°, from alcohol (Found : C, 80·6; H, 4·8; N, 9·1. $C_{21}H_{16}ON_2$ requires C, 80·8; H, 5·1; N, 9·0%). On dilution with water the dark orange-brown solution of this in concentrated sulphuric acid became royal blue.

Oxidation of 7-Methoxyflavanone.—(*A*) This flavanone (Kostanecki and Stoppani, *Ber.*, 1904, **37**, 1180) (2 g.) was oxidised with 1 mol. of lead tetra-acetate in acetic acid for 3 hr., and the mixed product isolated with ether by the method employed for flavanone. Fractional crystallisation from ethyl acetate gave 7-methoxy*iso*flavone in needles (0·25 g.), m. p. and mixed m. p. 157° (Found : C, 76·3; H, 5·0. Calc. for $C_{10}H_{12}O_3$: C, 76·2; H, 4·8%) (Venkataraman, *J.*, 1934, 1120). The residual liquors furnished the more soluble 3-acetoxyflavanone which separated from methanol in needles (0·3 g.), m. p. 161° (Found : C, 69·3; H, 5·2; OMe, 9·8. Calc. for $C_{17}H_{13}O_4$·OMe : C, 69·2; H, 5·1; OMe, 9·9%) (Oyamada, *loc. cit.*, gives m. p. 159—161°).

(*B*) The reaction mixture from 7-methoxyflavanone (10 g.) was separated by the chromatographic procedure employed for the product from flavanone. The benzene eluates (1) and (6) contained only traces of material. Evaporation of the eluate (2) left 3-acetoxy-7-methoxyflavanone (1·8 g.), m. p. and mixed m. p. 161° after purification, whilst eluates (3) and (4) gave a mixed product (4·5 g.), m. p. 124—136°. Eluate (5) gave 7-methoxy*iso*flavone (0·6 g.), m. p. and mixed m. p. 157° after purification. The residue left on evaporation of the light brown methanolic eluate, which had a blue fluorescence, was extracted with light petroleum, giving 7-methoxyflavone in colourless needles (0·4 g.), m. p. 109—110°, undepressed on admixture with an authentic specimen, m. p. 110° (Löwenbein, *Ber.*, 1924, **57**, 1515) (Found : C, 75·7; H, 4·8; OMe, 12·1. Calc. for $C_{15}H_9O_2$·OMe : C, 76·2; H, 4·8; OMe, 12·3%). That 7-methoxyflavone did not arise from the decomposition of 3-acetoxy-7-methoxyflavanone by the aluminium oxide was established by the fact that the oily residues left from the separation of the oxidation products by method (*A*) yielded a small amount of the flavone, m. p. and mixed m. p. 110°.

3-Hydroxy-7-methoxyflavanone.—(*A*) Deacetylation of 3-acetoxy-7-methoxyflavanone (0·1 g.) by boiling hydrochloric acid–methanol or by 80% sulphuric acid at room temperature gave 3-hydroxy-7-methoxyflavanone, forming needles (0·8 g.), m. p. 150°, from methanol, with a negative ferric reaction (Found : C, 70·9; H, 5·2; OMe, 9·7. Calc. for $C_{15}H_{11}O_3$·OMe : C, 71·1; H, 5·2; OMe, 11·5%) (Oyamada, *loc. cit.*, gives m. p. 146—147°). Treatment of this compound (0·1 g.) with acetic anhydride (10 ml.) and concentrated sulphuric acid (2 drops) for 10 min. regenerated the acetate (0·08 g.), m. p. and mixed m. p. 160°. Attempts to dehydrate 3-hydroxy-7-methoxyflavanone with cold 80% or boiling 15% sulphuric acid or with boiling acetic anhydride were unsuccessful; more drastic conditions led to decomposition.

With *o*-phenylenediamine 3-hydroxy-7-methoxyflavanone gave a *dihydroquinoxaline* derivative, forming yellow needles, m. p. 163° (from methanol and then light petroleum), which had a violet sulphuric acid reaction subsequently becoming blue (Found: C, 77·7; H, 4·9; N, 8·6; OMe, 11·8. $C_{21}H_{15}ON_2 \cdot OMe$ requires C, 77·2; H, 5·3; N, 8·2; OMe, 9·1%).

A mixture of 3-hydroxy-7-methoxyflavanone (0·3 g.), alcohol (20 ml.), 2N-aqueous sodium hydroxide (1·5 ml.), and perhydrol (1 ml.) was heated on the steam-bath for ½ hr., cooled, and acidified. Crystallised from methanol, the yellow precipitate gave 7-methoxyflavonol in pale yellow needles (0·2 g.), m. p. 179°, having the characteristic violet ferric reaction (Found: C, 71·7; H, 4·6; OMe, 11·7. Calc. for $C_{15}H_9O_3 \cdot OMe$: C, 71·6; H, 4·5; OMe, 11·5%) (cf. Kostanecki, *Ber.*, 1904, **37**, 1181, who gives m. p. 180°). The flavonol (0·3 g.) was also formed by (*a*) heating 3-hydroxy-7-methoxyflavanone (0·4 g.) with a boiling mixture of 2N-sulphuric acid (5 ml.) and dioxan (6 ml.) for 12 hr. and on purification had m. p. and mixed m. p. 179, and (*b*) keeping 3-acetoxy-7-methoxyflavanone (0·12 g.) in methanol (100 ml.) saturated with ammonia for 3 days at 0°, removing the solvent in a current of air, and crystallising the product from methanol. On isolation the compound formed yellowish needles, m. p. and mixed m. p. 179° (0·06 g.), having a violet ferric reaction and forming an acetate, m. p. 176°. Some yellow amorphous material was also formed.

7-Methoxyflavonol was prepared (cf. Reichel and Steudel, *loc. cit.*) by boiling a solution of 2′-hydroxy-4′-methoxychalkone (1·5 g.) in methanol (200 ml.), containing perhydrol (5 ml.) and 2N-aqueous sodium hydroxide (4 ml.), for ¼ hr. Acidification of the cooled mixture gave the flavonol, m. p. and mixed m. p. 178—180°. The acetate had m. p. 175—176° (Kostanecki, *loc. cit.*).

(*B*) A solution of 2′-hydroxy-4′-methoxychalkone (1 g.) in alcohol (100 ml.), containing perhydrol (5 ml.) and 2N-aqueous sodium hydroxide (2·5 ml.), was gently heated for a few minutes, kept for *ca.* 18 hours, and acidified (cf. Reichel and Steudel, *loc. cit.*). Crystallised from alcohol, the precipitate gave 3-hydroxy-7-methoxyflavanone in needles (0·25 g.), m. p. 148—150°, undepressed by the foregoing specimen, m. p. 150°.

(*C*) On adding boiling 60% aqueous potassium hydroxide (10 ml.) to a mixture of 2-hydroxy-ω : 4-dimethoxyacetophenone (Slater and Stephen, *J.*, 1920, 309) (2 g.), benzaldehyde (1·1 g.), and methanol (5 ml.) a vigorous reaction ensued and the mixture set to a bright yellow solid. Treatment of this solid with dilute acids gave pale yellow oils which did not solidify. The product was triturated with water (150 ml.) and the resulting pale yellow solid (1·8 g.), which undoubtedly consisted of the chalkone (III), was heated under reflux with methanol (150 ml.) containing concentrated hydrochloric acid (8 ml.) and water (20 ml.) for 6 hr., the methanol was evaporated, and the residue was extracted with ether. Evaporation of the extracts, which had been washed with aqueous sodium hydrogen carbonate and water, left an oil which crystallised from ethyl acetate–light petroleum and then methanol, giving 3-hydroxy-7-methoxyflavanone, m. p. and mixed m. p. 150°.

Oxidation of 7 : 4′-*Dimethoxyflavanone.*—The crude product (7·8 g.) from the oxidation of 7 : 4-dimethoxyflavanone (Juppen and Kostanecki, *Ber.*, 1904, **37**, 4161) (8 g.) and lead tetra-acetate (13·6 g., 1 mol.) in acetic acid (100 ml.) at 80—90° for 4 hr. was resolved by the chromatographic method into (*a*) 3-acetoxy-7 : 4′-dimethoxyflavanone, needles (0·5 g.), m. p. 140°, from methanol [Found: C, 66·4; H, 5·5; OMe, 18·1. Calc. for $C_{17}H_{12}O_4(OMe)_2$: C, 66·7; H, 5·3; OMe, 18·1%], (*b*) 7 : 4′-dimethoxy*iso*flavone, m. p. and mixed m. p. 161° (cf. Anderson and Marrian, *J. Biol. Chem.*, 1939, **127**, 649, who give m. p. 158—159°) [Found: C, 72·5; H, 5·0; OMe, 22·1. Calc. for $C_{15}H_8O_2(OMe)_2$: C, 72·3; H, 5·0; OMe, 22·0%], and (*c*) 7 : 4′-dimethoxyflavone, m. p. 145° (Found: C, 72·4; H, 5·2; OMe, 21·5%) (Tambor, *Ber.*, 1916, **49**, 1710).

Deacetylation of 3-acetoxy-7 : 4′-dimethoxyflavanone with 80% sulphuric acid at room temperature for 1 hr. gave 3-hydroxy-7 : 4-dimethoxyflavanone, forming needles, m. p. 130°, from light petroleum (Found: C, 68·0; H, 5·5. Calc. for $C_{17}H_{16}O_5$: C, 68·0; H, 5·3%) (Oyamada, *loc. cit.*, gives m. p. 124—126° for this compound, and m. p. 143—144° for its acetate).

Oxidation of 3′ : 4′-*Dimethoxyflavanone.*—One mol. of lead tetra-acetate furnished a product which, separated by the chromatographic method, appeared to consist of unchanged flavanone (yield 26%) and 3′ : 4′-dimethoxyflavone, forming needles (yield, 22%), m. p. 155°, from methanol [Found: C, 72·3; H, 5·1; OMe, 21·4. Calc. for $C_{15}H_8O_2(OMe)_2$: C, 72·3; H, 5·0; OMe, 21·9%] (Berstein, Fraschina, and Kostanecki, *Ber.*, 1905, **38**, 2180). When 3′ : 4′-dimethoxyflavanone (5 g.) was oxidised with lead tetra-acetate (2 mols.), and the product separated by fractional crystallisation, unchanged flavanone (0·5 g.) and 3′ : 4′-dimethoxyflavone (1·5 g.) were obtained.

Oxidation of 7 : 3′ : 4′-*Trimethoxyflavanone*.—The product formed by the standard method was crystallised from ethyl acetate, and the mixed pale yellow needles, mainly 7 : 3′ : 4′-*trimethoxyflavone*, and coloured plates, mainly 7 : 3′ : 4′-trimethoxy*iso*flavone, were separated manually. Resolution of the product (6·2 g.) from 7 : 3′ : 4′-trimethoxyflavanone (7·2 g.) by the chromatographic method gave the *iso*flavone (from the chloroform eluate), forming colourless plates (0·8 g.), m. p. and mixed m. p. 161°, from benzene, and the flavone (from the benzene mother-liquors and methanolic eluate) which separated from light petroleum and then methanol in almost colourless needles (1·3 g.), m. p. and mixed m. p. 176° (Found : C, 69·5; H, 5·5. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·1%).

7 : 3′ : 4′-*Trimethoxyflavone*.—Prepared from 4-*O*-methylresacetophenone (4 g.) and veratroyl chloride (5 g.) in pyridine (30 ml.), 4-*methoxy*-2-*veratroyloxyacetophenone* separated from alcohol in plates (4·9 g.), m. p. 157°, with a negative ferric reaction [Found : C, 64·8; H, 5·4; OMe, 27·1. $C_{15}H_9O_3(OMe)_3$ requires C, 65·5; H, 5·5; OMe, 28·2%]. A solution of this compound (4·5 g.) in benzene (100 ml.), containing sodamide (20 g.), was heated under reflux for 4 hr., filtered (salts being washed with benzene), and poured into water at 0°. After the acidification of the mixture the benzene liquor was separated with the aid of ether and the residue left on evaporation of the solvents was crystallised from methanol, giving a compound in pale yellow needles (0·3 g.), m. p. 150° (a weak red-brown ferric reaction), which appeared to be 2-*hydroxy*-4-*methoxy*-ωω-*diveratroylacetophenones* [Found : C, 65·7; H, 5·5; OMe, 30·4. $C_{22}H_{11}O_4(OMe)_5$ requires C, 65·6; H, 5·3; OMe, 31·4%]. On concentration the methanolic liquors deposited a mixture of colourless prisms and bright yellow needles from which the latter were separated manually. Recrystallised from benzene–light petroleum this product gave 2-*hydroxy*-4-*methoxy*-ω-*veratroylacetophenone* in yellow needles (0·4 g.), m. p. 129°, with a deep reddish-maroon ferric reaction [Found : C, 65·6; H, 5·8; OMe, 30·8. $C_{15}H_9O_3(OMe)_3$ requires C, 65·5; H, 5·5; OMe, 28·2%].

Cyclisation with 80% sulphuric acid (20 ml.) at room temperature for 2 hr., followed by hydrolysis of the sulphate precipitated with water (200 ml.), of 2-hydroxy-4-methoxy-ω-veratroylacetophenone yielded 7 : 3′ : 4′-trimethoxyflavone which separated from methanol in colourless needles (0·25 g.), m. p. 176° [Found : C, 69·6; H, 5·4; OMe, 30·1. $C_{15}H_7O_2(OMe)_3$ requires C, 69·2; H, 5·1; OMe, 29·8%].

7 : 3′ : 4′-*Trimethoxy*iso*flavone*.—Pulverised sodium (1 g.) was added to a mixture of 3′ : 4′-dimethoxybenzyl 2-hydroxy-4-methoxyphenyl ketone (Bentley and Robinson, *J.*, 1950, 1353) (1·5 g.) and methyl formate (50 ml.) at 0°, and 24 hr. later the mixture was treated with water. Isolated with ether, the product was crystallised from ethyl acetate and then methanol, giving the iso*flavone* in colourless needles (0·5 g.), m. p. 161° (Found : C, 69·2; H, 5·1; OMe, 29·8%).

7-*Methoxy*-3′-*nitroflavanone*.—Interaction of 4-*O*-methylresacetophenone (20 g.), *m*-nitrobenzaldehyde (18·2 g.), and 60% aqueous sodium hydroxide (30 ml.) in alcohol (50 ml.) at 55° for 5 min. and then at room temperature for 24 hr. furnished 2′-*hydroxy*-4′-*methoxy*-3-*nitrochalkone*, forming yellow needles (15·8 g.), m. p. 182°, from ethyl acetate, with a pale brown ferric reaction (Found : C, 64·4; H, 4·5; N, 4·8. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·4; N, 4·7%). A mixture of this chalkone (34 g.), alcohol (4 l.), and 3% hydrochloric acid was heated under reflux for 30 hr., the greater part of the alcohol was distilled, and the chalkone–flavanone mixture was precipitated with water. Repeated crystallisation of the solid from benzene and then ethyl acetate gave 7-*methoxy*-3′-*nitroflavanone* in colourless plates (14 g.), m. p. 211° (Found : C, 64·0; H, 4·6; N, 4·6%).

The crude product (5·7 g.) from the oxidation of this flavanone (8 g.) with lead tetra-acetate (1 mol.) under the usual conditions could not be conveniently chromatographed. Fractional crystallisation from alcohol gave 7-*methoxy*-3′-*nitroflavone* in colourless needles (1·2 g.), m. p. 212°, identical with a synthetical specimen (Found : C, 64·8; H, 3·6; N, 4·4. OMe, 11·5. $C_{15}H_8O_4N{\cdot}OMe$ requires C, 64·7; H, 3·7; N, 4·7; OMe, 10·4%). The residue left on evaporation of the alcoholic liquors was crystallised from benzene, ethyl acetate, and finally chloroform and, by repeated chromatography from benzene on aluminium oxide, was then resolved into unchanged 7-methoxy-3′-nitroflavanone (0·7 g.), m. p. and mixed m. p. 211°, and fractions of m. p. *ca.* 150—165° from which a pure compound could not be isolated.

7-*Methoxy*-3′-*nitroflavone*.—The m-*nitrobenzoate* of 4-*O*-methylresacetophenone (8 g.) separated from ethyl acetate in colourless prisms (10·5 g.), m. p. 109° (Found : C, 60·6; H, 4·1; N, 4·5; OMe, 8·7. $C_{15}H_{10}O_5N{\cdot}OMe$ requires C, 61·0; H, 4·1; N, 4·4; OMe, 9·8%). A mixture of this ester (5 g.), benzene (50 ml.), and sodamide (25 g.) was heated under reflux for 4 hr., and a solution of the resulting orange precipitate in water at 0° was acidified with acetic

acid. The dark solid was repeatedly extracted with chloroform, the solvent evaporated, and the residue extracted with light petroleum (b. p. 60—80°), giving *ω-benzoyl-2-hydroxy-4-methoxy-3′-nitroacetophenone* which separated from ethyl acetate–light petroleum in yellow needles (0·5 g.), m. p. 160° (Found: C, 60·7; H, 4·0; N, 4·1. $C_{16}H_{13}O_6N$ requires C, 61·0; H, 4·1; N, 4·4%). Cyclised with 80% sulphuric acid at room temperature, this diketone (0·4 g.) furnished 7-methoxy-3′-nitroflavone, which separated from benzene in needles (0·3 g.), m. p. 212°, identical with the specimen obtained from 7-methoxy-3′-nitroflavanone.

Bromination of 7-Methoxyflavanone.—(*A*) In an attempt to prepare 3-acetoxy-7-methoxyflavanone by way of the 3-bromoflavanone, a route which Zemplen and Bognar (*Ber.*, 1943, **76**, 452) used for preparation of 3 : 5 : 7 : 3′-tetrahydroxy-4′-methoxyflavanone, the dropwise addition of bromine (0·32 g.) in carbon disulphide (5 ml.) to 7-methoxyflavanone (0·5 g.) in the same solvent (10 ml.) gave *3-bromo-7-methoxyflavanone*, forming colourless rectangular prisms (0·2 g.), m. p. 163—164°, from methanol (Found: C, 58·0; H, 4·2; Br, 23·4. $C_{16}H_{13}O_3Br$ requires C, 57·7; H, 3·9; Br, 24·0%). The same product was formed with carbon tetrachloride as the solvent but the use of chloroform gave unsatisfactory results. With silver acetate (0·1 g.) in boiling acetic anhydride (5 ml.) and acetic acid (5 ml.) this compound furnished 7-methoxyflavone (0·1 g.), m. p. and mixed m. p. 110°, which was also formed by heating the bromo-compound (0·4 g.) with potassium acetate (0·2 g.) in boiling alcohol (30 ml.) for 1½ hr.

(*B*) A mixture of 7-methoxyflavanone (2 g.), *N*-bromosuccinimide (1·4 g.), and carbon tetrachloride (30 ml.) was heated under reflux for 1 hr.; the solution became brown and then colourless. On isolation the product was repeatedly crystallised from methanol, giving 6-bromo-7-methoxyflavanone in colourless plates (0·5 g.), m. p. 134° (Found: C, 57·8; H, 4·1; Br, 24·1. $C_{16}H_{13}O_3Br$ requires C, 57·7; H, 3·9; Br, 24·0%). From the methanolic liquors a small amount of *dibromo-7-methoxyflavanone* was obtained which formed colourless needles (0·2 g.), m. p. 173—174°, from methanol (Found: C, 46·4; H, 3·2; Br, 38·6. $C_{16}H_{12}O_3Br_2$ requires C, 46·6; H, 2·9; Br, 38·8%). Bromination with *N*-bromosuccinimide (1·2 g.) in carbon tetrachloride (20 ml.) for 1½ hr. gave only the 6-bromo-derivative, m. p. 134°. Similarly, 7-methoxyflavanone (5 g.) and *N*-bromosuccinimide (3·6 g.) in boiling chloroform (70 ml.) containing benzoyl peroxide (0·2 g.) for ½ hr. gave 6-bromo-7-methoxyflavanone (2·2 g.), m. p. 134° (cf. Lorette, Gage, and Wender, *J. Org. Chem.*, 1951, **16**, 930, who converted flavanones into flavones by this method).

A mixture of 6-bromo-7-methoxyflavanone (4·7 g.), potassium hydroxide or potassium acetate (3 g.), and alcohol (30 ml.) was heated under reflux for ½ hr., diluted with water (200 ml.), and acidified with hydrochloric acid. Crystallised from ethyl acetate–light petroleum, the precipitate gave *5′-bromo-2′-hydroxy-4′-methoxychalkone* in yellow needles (4·2 g.), m. p. 171°, with an orange-brown ferric reaction (Found: C, 58·2; H, 4·3; Br, 24·0. $C_{16}H_{13}O_3Br$ requires C, 75·7; H, 3·9; Br, 24·0%). On methylation by the methyl iodide–potassium carbonate method this compound (2 g.) yielded *5′-bromo-2′ : 4′-dimethoxychalkone* which separated from alcohol in pale yellow leaflets (1·6 g.), m. p. 133°, with a negative ferric reaction (Found: C, 58·8; H, 4·3; Br, 23·3. $C_{17}H_{15}O_3Br$ requires C, 58·8; H, 4·3; Br, 23·1%). Oxidation of this ether (1 g.) with potassium permanganate (3·2 g.) in acetone (1·2 l.) at room temperature for 24 hr. gave benzoic, m. p. 121°, and 5-bromo-2 : 4-dimethoxybenzoic acid, needles (0·25 g.), m. p. 197° (from ethyl acetate) (Found: C, 41·6; H, 3·2; Br, 30·3. Calc. for $C_9H_9O_4Br$: C, 41·4; H, 3·5; Br, 30·7%) (Reichert and Koch, *Ber.*, 1935, **68**, 445). The methyl ester separated from methanol in plates, m. p. 117° [Found: C, 43·9; H, 4·0; Br, 28·9; OMe, 32·6. Calc. for $C_7H_2OBr(OMe)_3$: C, 43·6; H, 4·0; Br, 29·1; OMe, 33·8%].

3-Acetoxychroman-4-one appeared to be the sole oxidation product formed when chroman-4-one (Powell, *J. Amer. Chem. Soc.*, 1923, **45**, 2711) (3·5 g.) was treated with lead tetra-acetate (12 g.) in acetic acid (60 ml.) at 80—90° for 2 hr. (test for quadrivalent lead then negative). Precipitated with water (600 ml.), and crystallised from light petroleum containing a trace of ethyl acetate, the product formed needles (1·8 g.), m. p. 74°, with a negative ferric reaction (Found: C, 63·9; H, 4·9. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). Attempts to deacetylate this compound with warm methanolic hydrochloric acid or with cold 80% sulphuric acid gave small amounts of intractable mixtures; in one experiment a solid, m. p. *ca.* 140—150°, was obtained which had a red-brown ferric reaction.

2-Methylchroman-4-one.—Esterification of phenol (18·8 g.) with crotonyl chloride (23 g.) and magnesium (2·8 g.) in boiling benzene (50 ml.) by Spassow's method (*Ber.*, 1942, **75**, 779) yielded *phenyl crotonate* (31·9 g.), b. p. 96°/5 mm. (Found: C, 74·0; H, 6·2. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%). On being heated with aluminium chloride (20 g.) at 140—150° for 2 hr. this ester (20 g.) furnished a mixture of 2-hydroxycrotonylbenzene and the chromanone as an

oil (6·4 g.), b. p. 134—136°/1 mm., which gave a purple ferric reaction and a red 2 : 4-dinitrophenylhydrazone. This product (7·5 g.) was refluxed in alcohol (100 ml.) and 3% hydrochloric acid (100 ml.) for 24 hr., the alcohol was evaporated, and the residue was diluted with saturated aqueous ammonium sulphate. Isolated with ether, the resulting pale yellow oil (6·9 g.), b. p. 132—134°/25 mm., was purified by chromatography from benzene–light petroleum (1 : 2) on aluminium oxide (50 × 2·5 cm.), giving *2-methylchroman-4-one* in white plates (5·2 g.), m. p. 32°, with a negative ferric reaction (Found : C, 73·9; H, 6·1. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%) (cf. Müller and Wieseman, *Annalen*, 1938, **537**, 86, who isolated this compound as the *p*-nitrophenylhydrazone). The 2 : 4-*dinitrophenylhydrazone* formed orange-red plates, m. p. 236°, from ethyl acetate (Found : C, 55·7; H, 4·2; N, 16·4. $C_{16}H_{14}O_5N_4$ requires C, 56·1; H, 4·1; N, 16·4%).

3-*Hydroxy-2-methylchroman-4-one*.—3-*Acetoxy-2-methylchroman-4-one* (3·1 g.) was obtained from 2-methylchroman-4-one (10 g.) with lead tetra-acetate (27 g.) by the standard method and, on repeated crystallisation from methanol, formed needles (2·6 g.), m. p. 97°, with a negative ferric reaction (Found : C, 65·5; H, 5·6. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). In addition an indefinite oily product was isolated which on acetylation gave more 3-acetoxy-2-methylchroman-4-one (0·8 g.), m. p. 97°, after purification from ethyl acetate–light petroleum and then methanol.

Deacetylation of the acetate (0·2 g.) with a boiling mixture of concentrated hydrochloric acid (1 ml.) and methanol (20 ml.) yielded *3-hydroxy-2-methylchroman-4-one*, forming needles (0·1 g.), m. p. 103°, from methanol with a negative ferric reaction (Found : C, 67·7; H, 8·9. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%). With methanolic *o*-phenylenediamine (0·15 g.) this hydroxy-ketone (0·22 g.) gave the *dihydroquinoxaline* which separated from alcohol in pale orange needles (0·15 g.), m. p. 155°, having a red-brown sulphuric acid reaction which became intense purple on the addition of water, and forming a yellow solution in hydrochloric acid which rapidly became green and then deep violet (Found : C, 76·9; H, 5·4; N, 1·1. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

7-*Methoxy-2-methylchroman-4-one*.—Prepared by the Spassow method (*loc. cit.*), *3-methoxyphenyl crotonate* was a colourless oil, b. p. 125°/3 mm. (Found : C, 69·3; H, 6·5. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·3%). With aluminium chloride (20 g.) at 140—150° for 2 hr. it (20 g.) gave a mixture (6·4 g.), b. p. 134—136°/1 mm., which was heated with boiling alcohol (100 ml.) and 3% hydrochloric acid (100 ml.) for 24 hr. On isolation the resulting 7-methoxy-2-methylchroman-4-one was distilled in a vacuum and then purified by chromatography and obtained in plates [from light petroleum–benzene (2 : 1; 100 ml.)] (4·2 g.), m. p. and mixed m. p. 77° (Found : C, 68·8; H, 6·1. Calc. for $C_{11}H_{12}O_3$: C, 68·8; H, 6·3%); the 2 : 4-dinitrophenylhydrazone had m. p. 252° (cf. Richards, Robertson, and Ward, *J.*, 1948, 1610).

3-*Hydroxy-7-methoxy-2-methylchroman-4-one*.—Oxidation of the foregoing 7-methoxy-2-methylchromanone (5 g.) by the standard method gave an oil which on trituration with alcohol, furnished a mixture (2·9 g.), m. p. 80—100°. Fractional crystallisation of this from ethyl acetate gave two very similar isomeric compounds; the less soluble *3-acetoxy-7-methoxy-2-methylchroman-4-one* (A) separated from methanol in colourless needles (1·1 g.), m. p. 120° (Found : C, 62·4; H, 5·5; OMe, 11·6. $C_{12}H_{11}O_4$·OMe requires C, 62·4; H, 5·6; OMe, 12·4%), and the more soluble *3-acetoxy-7-methoxy-2-methylchroman-4-one* (B) from methanol in colourless plates (6·8 g.), m. p. 118° (Found : C, 62·9; H, 5·6; OMe, 11·6%). A mixture of (A) and (B) had m. p. *ca.* 100°.

Deacetylation of (A) (0·4 g.) with hot methanol (20 ml.) containing concentrated hydrochloric acid (2 ml.), or with 80% sulphuric acid (10 ml.) at room temperature for ½ hr., gave *3-hydroxy-7-methoxy-2-methylchroman-4-one*, forming needles (0·3 g.), m. p. 152°, from methanol, with a negative ferric acid reaction (Found : C, 63·7; H, 6·2; OMe, 14·5. $C_{10}H_9O_3$·OMe requires C, 63·5; H, 5·8; OMe, 14·9%). With *o*-phenylenediamine this hydroxychromanone furnished the *dihydroquinoxaline* which separated from alcohol in pale yellow needles, m. p. 122° (Found : C, 72·4; H, 5·5; N, 9·4. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·7; N, 10·0%).

Deacetylation of acetate (B) with warm methanol–hydrochloric acid yielded 3-hydroxy-7-methoxy-2-methylchroman-4-one, m. p. and mixed m. p. 152° (Found : C, 63·9; H, 6·1; OMe, 14·6%). With 80% sulphuric acid (10 ml.) at room temperature for ½ hr., acetate (B) (0·3 g.) gave 7-methoxy-2-methylchromone in colourless needles, m. p. and mixed m. p. 113°.

Acetylation of 3-hydroxy-7-methoxy-2-methylchroman-4-one (0·3 g.), from either acetate (A) or (B), with acetic anhydride (8 ml.) and sodium acetate (0·2 g.) on the steam-bath for 1 hr. gave only acetate (A), m. p. and mixed m. p. 120°.

3-*Hydroxy-7-methoxy-2* : 2-*dimethylchroman-4-one*.—Oxidation of 7-methoxy-2 : 2-dimethyl-

chroman-4-one (Bridge, Crocker, Cubin, and Robertson, *J.*, 1937, 1530) (4 g.) by the standard method yielded a solid (3·5 g.) which on crystallisation from ethyl acetate and then methanol gave 3-*acetoxy*-7-*methoxy*-2 : 2-*dimethylchroman*-4-*one* in rectangular prisms (2·8 g.), m. p. 129° (Found : C, 63·4; H, 6·3; OMe, 12·6. $C_{13}H_{13}O_4$·OMe requires C, 63·6; H, 6·1; OMe, 11·7%). Deacetylation of this acetate (0·5 g.) with methanol–hydrochloric acid furnished 3-*hydroxy*-7-*methoxy*-2 : 2-*dimethylchroman*-4-*one*, forming plates (0·3 g.), m. p. 110°, from methanol [Found : C, 64·7; H, 6·2; OMe, 14·6. $C_{11}H_{11}O_3$(OMe) requires C, 64·9; H, 6·3; OMe, 14·0%], and giving a *dihydroquinoxaline* which separated from methanol in yellow needles, m. p. 154°, with an intense purple sulphuric acid reaction (Found : C, 73·7; H, 5·5; N, 9·3. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1; N, 9·5%).

Oxidation of Benzyl Phenyl Ethers.—Benzyl phenyl ether (3·7 g.) in glacial acetic acid (20 ml.) was treated with lead tetra-acetate (9·4 g.) at 100° for 3 hr.; tests for quadrivalent lead were then negative. The mixture was diluted with water (250 ml.). The oily product, which was isolated with ether, was insoluble in 2N-aqueous sodium hydroxide. It was hydrolysed with this reagent at 100° for ½ hr., giving benzaldehyde, identified as the 2 : 4-dinitrophenylhydrazone (0·6 g.), m. p. 234°, and phenol, characterised as 2 : 4 : 6-tribromophenol, m. p. 93—94° (0·7 g.).

A mixture of phenol (4·7 g.), *m*-nitrobenzyl bromide (10·8 g.), and potassium carbonate (7·0 g.) was heated in boiling ethyl methyl ketone (200 ml.) for 4 hr. On isolation, the resulting m-*nitrobenzyl phenyl ether* was a yellow oil, b. p. 182°/3 mm. (6·9 g.) (Found : C, 67·7; H, 4·7. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·8%).

This ether (2·3 g.) did not react with lead tetra-acetate (4·4 g.) in acetic acid (20 ml.) at room temperature, but at 108° for 1½ hr. it gave a yellow oil which, when purified by disillation, had b. p. 149°/0·1 mm. (yield, 1·8 g.) and an acetyl value indicating that the mixture contained *ca.* 43% of (XI; R = NO_2) (Found : OAc, 6·7. Calc. for $C_{15}H_{13}O_5N$: OAc, 15·0%). This product (1·0 g.) was heated at 80° in alcohol (20 ml.) and 2N-hydrochloric acid (5 ml.) for 20 min., and the resulting *m*-nitrobenzaldehyde isolated as the 2 : 4-dinitrophenylhydrazone, forming dark red prisms, m. p. 286° (decomp.) (0·4 g.), from Carbitol (diethylene glycol monoethyl ether) (Found : N, 20·8. Calc. for $C_{13}H_9O_6N_5$: N, 21·1%). Attempts to improve the yield of (XI; R = NO_2) were unsuccessful.

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