140. *Studies in Chelation. Part II. The Stabilisation of Kekulé Forms in* o-*Hydroxyacetophenones.*

By Wilson Baker and (Miss) O. M. Lothian.

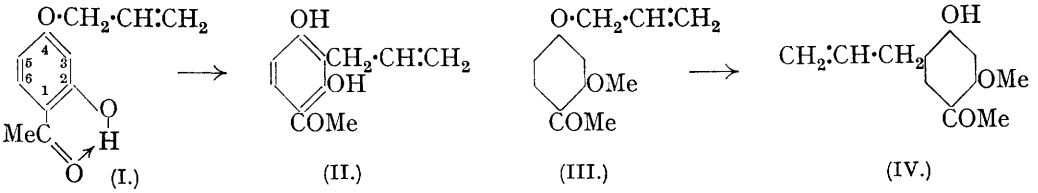
Evidence was brought forward by Baker (J., 1934, 1684 *) that the formation of six-membered chelate rings containing co-ordinately linked hydrogen in *o*-hydroxyacetophenones was dependent upon the presence of a double bond between the carbon atoms bearing the hydroxyl and the acetyl group. It was shown that this accounted for (1) the difference in properties between 2 : 4- and 4 : 6-diacetylresorcinol, only the former of which behaved like a fully chelated compound, (2) the non-chelation of saturated β-hydroxyketones as compared with the known chelation of the unsaturated enolic forms of β-diketones, and (3) the abnormal formation of 2 : 4-diacetylresorcinol from 4-*O*-acetylresacetophenone by heating with aluminium chloride. It is evident that (1) and (3) involve the idea of a "fixed" (or largely fixed) Kekulé form in the aromatic nucleus, and in connexion with the present work it was essential to find a trustworthy means of detecting such a stable form.

In order to detect fixed Kekulé forms Mills and Nixon (J., 1930, 2510) utilised the fact that *o*-diazo-coupling, or *o*-bromination of *p*-substituted phenols, will occur on that side of the hydroxyl group which bears the double bond, and Baker (*loc. cit.*) similarly made use of the migration of an acetyl group from the phenolic oxygen atom to an *o*-carbon atom (Fries reaction). Objections may be raised to each of these methods when applied to *o*-hydroxyacetophenones; in particular, both bromine and aluminium chloride may prevent chelation by combining with the nuclear acetyl group (see Baker, *loc. cit.*, p. 1686).

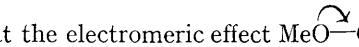
The molecular rearrangement of the phenyl allyl ethers to give *o*-allylphenols appears to afford one of the best methods of establishing the position of the double bonds in the nucleus. It is evident that the allyl group can migrate only to that *o*-carbon atom which is doubly bound to the $C{\cdot}O{\cdot}CH_2{\cdot}CH{:}CH_2$ group, since, if we may assume the symmetrical arrangement of the double bonds in naphthalene, the facts that β-naphthyl allyl ether rearranges to 1-allyl-2-naphthol, and that the allyl ether of 1-allyl-2-naphthol will not rearrange at all (Claisen, *Ber.*, 1912, **45**, 3157), can only be interpreted in this sense (compare also the rearrangements of the *O*-allyl ethers of acetoacetic ester and acetylacetone; Claisen, *loc. cit.*). Again no reasonable mechanism of the reaction can be devised without assuming the participation of a double bond (see Ingold, *Ann. Reports*, 1926, 143). This rearrangement of the phenyl allyl ethers has been the subject of much study (Claisen, *loc. cit.*; Claisen and Eisleb, *Annalen*, 1913, **401**, 21; Claisen, Kremers, Roth, and Tietze, *ibid.*, 1925, **442**, 210; Claisen and Tietze, *ibid.*, 1926, **449**, 81; *Ber.*, 1925, **58**, 275; 1926, **59**, 2344; Hurd, Greengard, and Pilgrim, *J. Amer. Chem. Soc.*, 1930, **52**, 1700) and in connexion with the present work the following points may be noted: (1) the reaction, usually more or less exothermic, takes place when the allyl ethers are heated to about 200°, no catalyst or solvent being necessary, and thus any interference with the chelation between hydroxy and acetyl (or other chelating groups) is avoided; (2) the yields are generally satisfactory; (3) the reaction is free from the ambiguity as to which ortho-position is the most "active" in the ordinary sense of the word, a difficulty which may arise in all cases, except those few where the whole molecule is symmetrical about the phenolic group and the alternative positions are identical (*e.g.*, phenol itself, simple *p*-

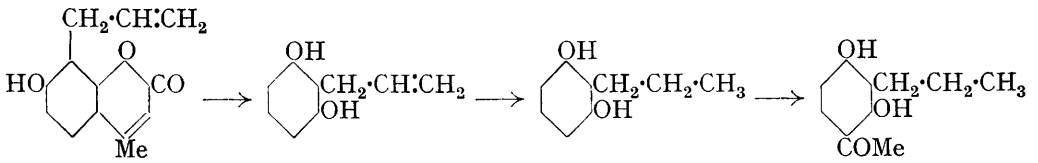
* This paper, entitled "A New Factor controlling Certain Chelations, with Special Reference to Disubstitution in the Resorcinol Nucleus," is to be regarded as Part I.

substituted phenols, etc.), where reactions such as bromination or diazo-coupling are employed; (4) the somewhat high temperatures involved, as compared with those employed in the other reactions cited, do not appear to be a disadvantage, since chelation is not affected, at least to any great extent, by considerable rise of temperature; indeed the abnormal boiling points of certain *o*-compounds as compared with the *m*- and *p*-isomerides—many well above 200°—afford, perhaps, the most important indication of chelation, and, further, the chelation of, for example, *o*-nitrophenol shows no sign of breaking down in presence of water at 200° (Sidgwick, Spurrell, and Davies, J., 1915, **107**, 1202).



(I.) (II.) (III.) (IV.)

The present paper deals with the molecular rearrangement of 4-O-*allylresacetophenone* (I), and of 2-O-*methyl*-4-O-*allylresacetophenone* (III). Owing to chelation between the hydroxyl and the acetyl group in (I), the double bonds in the benzene nucleus should be stabilised as shown, and the allyl group should migrate to position 3, giving 3-*allylresacetophenone* (II). This expectation was realised, since the rearrangement of (I) gave (II) in not less than 85% yield, and no other definite product could be isolated. In 2-*O*-methyl-4-*O*-allylresacetophenone (III) chelation between the methoxyl and the acetyl group is impossible, no fixation of a Kekulé form will occur, and molecular rearrangement should give the usual symmetrical type of product, namely, 2-O-*methyl*-5-*allylresacetophenone* (IV). This prediction was again verified, since (IV) was produced from (III) in a yield of 60%, and no other individual product could be isolated. These results are entirely in harmony with the deductions drawn in Part I concerning the chelation between hydroxyl and acetyl. It may be noted that the electromeric effect  possible in (III) is apparently too weak to prevent the migration of the allyl group into the normal position 5.

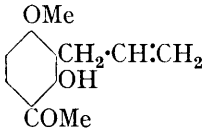


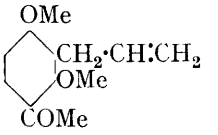
(V.) (VI.) (VII.) (VIII.)

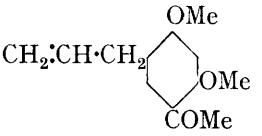
Compound (I) was prepared by direct allylation of resacetophenone, and methylation of (I) with methyl sulphate in acetone solution gave (III). These compounds were shown to be 4-*O*-allyl derivatives by the fact that (III) could also be obtained by the allylation of *iso*paeanol. The orientation of the allyl group in (II) was established in the following way. Catalytic reduction of (II) with hydrogen and palladium gave 3-n-*propylresacetophenone* (VIII), a compound which was then synthesised by an unambiguous method. 7-Hydroxy-4-methylcoumarin was converted into 7-*allyloxy*-4-*methylcoumarin*, and thence by the action of heat into 7-*hydroxy*-4-*methyl*-8-*allylcoumarin* (V), which when hydrolysed by boiling with aqueous sodium hydroxide yielded 2-*allylresorcinol* (VI) (compare Limaye, *Ber.*, 1932, **65**, 375; Baker, J., 1934, 1954). Catalytic reduction of (VI) gave 2-n-*propylresorcinol* (VII), which reacted with acetonitrile under the conditions of the Hoesch synthesis to give 3-*n*-propylresacetophenone (VIII), identical with that prepared by the catalytic reduction of (II). Owing to the reactivity of the allyl group it was found impossible to convert (VI) directly into (II) by the method either of Hoesch or of Nencki. The structures assigned to (V), (VI), and (VII) are established by the facts that both (VI) and (VII) differ widely in their properties from the known 4-allyl- and 4-*n*-propyl-resorcinols.

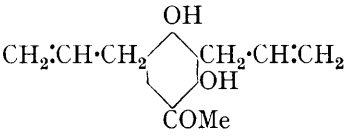
Methylation of (II) with methyl sulphate under ordinary conditions gives mainly

4-O-*methyl*-3-*allylresacetophenone* (IX), but in acetone solution the product is 3-*allylresacetophenone dimethyl ether* (X) (liquid, b. p. 169—170°/15 mm.). Methylation of (IV) gave the isomeric 5-*allylresacetophenone dimethyl ether* (XI) (m. p. 88—89°); the non-identity of these two compounds establishes the position of the allyl group in (IV).

(IX.) 

(X.) 

(XI.) 

(XII.) 

Allylation of (II) gave a monoallyl ether, 4-O-*allyl*-3-*allylresacetophenone*. If the fixation of the double bonds in this compound is complete, the normal rearrangement should not occur; the reaction was found to take place slowly (4 hours), and was not exothermic, an approximately 20% yield of crude 3 : 5-*diallylresacetophenone* (XII) being isolated. Allylation of (IV) gave 2-O-*methyl*-4-O-*allyl*-5-*allylresacetophenone*, which underwent rearrangement (slightly exothermic) to give 2-*O*-methyl-3 : 5-diallylresacetophenone (uncharacterised) (30% yield), which was directly methylated, yielding 3 : 5-*diallylresacetophenone dimethyl ether*. This same dimethyl ether was obtained by the methylation of (XII), the identity of the two specimens being established by a direct comparison of their crystalline *semicarbazones*, thus proving the constitutions assigned to (XII), 2-*O*-methyl-4-*O*-allyl-5-allylresacetophenone, and 3 : 5-diallylresacetophenone. These facts indicate that the fixation by chelation of the Kekulé forms in *o*-hydroxyacetophenones is not rigidly complete, although the rearrangement of (I) shows that the fixation must occur to a considerable extent.

Experimental.

4-O-*Allylresacetophenone* (I).—A mixture of resacetophenone (76 g.; 1 mol.), freshly ignited potassium carbonate (90 g.), and allyl bromide (61 g.; 1 mol.) in anhydrous acetone (180 c.c.) was refluxed and continuously stirred on the water-bath for 6 hours. Most of the acetone was now removed by distillation, and the remaining solution was acidified with dilute hydrochloric acid and extracted with ether. The pure product is best obtained by isolation as its very sparingly soluble sodium salt. The ethereal layer was shaken with excess of 2*N*-sodium hydroxide, and the precipitated sodium salt collected on a sintered glass funnel. Decomposition with dilute acid and extraction with ether yielded 4-O-*allylresacetophenone* (67 g.) as a faintly yellow liquid, b. p. 156—157°/9 mm. (Found: C, 68·9; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·2%). It gives an intense brownish coloration with alcoholic ferric chloride.

2-O-*Methyl*-4-O-*allylresacetophenone* (III).—(A) The methylation of 4-*O*-allylresacetophenone could be satisfactorily accomplished only in acetone solution, owing to the feeble phenolic function of the hydroxyl group (compare Baker and Robinson, J., 1928, 3115). 4-*O*-Allylresacetophenone (5 g.) in acetone (150 c.c.) was methylated by the alternate addition of methyl sulphate (45 c.c.) and an excess of 20% aqueous potassium hydroxide in small quantities, the mixture being allowed to boil, and then shaken at frequent intervals during ½ hour. The alkaline liquor was diluted and extracted with ether and the extracts were shaken with 20% potassium hydroxide solution, dried, and distilled, leaving a faintly coloured oil, which solidified at 0°. 2-O-*Methyl*-4-O-*allylresacetophenone* distils unchanged at 171°/9 mm., and separates from light petroleum (b. p. 40—60°) at 0° in flaky irregular crystals, m. p. 31° (Found: C, 69·8; H, 6·8. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). (B) *iso*Paeanol (1·5 g.) (Baker, J., 1934, 1691; compare Mauthner, *J. pr. Chem.*, 1933, **136**, 208), allyl bromide (3 c.c.), acetone (25 c.c.), and potassium carbonate (5 g.) were heated on the steam-bath for 6 hours with continual stirring. After addition of dilute sodium hydroxide solution, ether extracted a colourless oil, which solidified at 0° and then melted at 28—29°. After crystallisation it melted at 31°, either alone or mixed with the specimen prepared as under (A).

3-*Allylresacetophenone* (II).—Pure 4-*O*-allylresacetophenone (2 g.) was heated cautiously

in an oil-bath, the temperatures both of the bath and of the substance being recorded. Rearrangement began at about 180° with evolution of heat and the tube was raised from the bath for a few minutes so that the temperature of the melt did not rise above 200°. Unless this precaution was taken, the highly exothermic rearrangement caused considerable rise of temperature, and profound decomposition of the product ensued. The temperature was then kept at 200—210° for 2½ hours, and, on cooling, faintly coloured crystalline 3-allylresacetophenone (2 g.), m. p. 113—130°, was obtained. The powdered product, washed twice with cold light petroleum (b. p. 40—60°), lost 6% in weight and the melting point rose to 119—130°; the washings contained about 50% of 3-allylresacetophenone.

A similar rearrangement of 4-*O*-allylresacetophenone (5·9 g.) at 210—215° for 1½ hours gave a product, which was fractionally crystallised from light petroleum (b. p. 80—100°). After several crystallisations there was isolated a total of 4·79 g. of pure 3-allylresacetophenone, m. p. 132—133° (80% yield). The mother-liquors contained a further small quantity of crude 3-allylresacetophenone, but no other crystalline substance could be obtained.

The results of these two experiments indicate that the molecular rearrangement of 4-*O*-allylresacetophenone gives certainly not less than an 85% yield of 3-allylresacetophenone. 3-*Allylresacetophenone* separates from benzene, dilute alcohol, or acetic acid in flat prisms, m. p. 133° (Found: C, 68·9; H, 6·3. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·2%). Addition of ferric chloride to its alcoholic solution gives an intense dull purplish-red colour.

4-O-*Methyl*-3-*allylresacetophenone* (IX).—3-Allylresacetophenone was methylated in 10% aqueous potassium hydroxide with methyl sulphate at about 30°, the mixture being finally heated on the steam-bath for ½ hour. An ethereal extract yielded a solid, which separated from dilute acetic acid in colourless, compact, rhombic plates, m. p. 61° (Found: C, 69·9; H, 6·9. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). The substance gives an intense reddish-violet colour with alcoholic ferric chloride, and dissolves to a pale yellow solution in hot dilute aqueous sodium hydroxide.

3-*Allylresacetophenone Dimethyl Ether* (X).—3 Allylresacetophenone (1 g.) was treated in acetone (40 c.c.) with methyl sulphate (15 c.c.) and excess of 20% aqueous potassium hydroxide, as in the methylation of (I) (above). There was finally obtained a colourless oil, which was twice distilled in a vacuum; b. p. 169—170°/15 mm. (Found: C, 70·9; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

7-*Allyloxy*-4-*methylcoumarin*.—A mixture of 7-hydroxy-4-methylcoumarin (88 g.; 1 mol.), allyl bromide (61 g.; 1 mol.), anhydrous potassium carbonate (100 g.), and acetone (300 c.c.) was stirred under reflux on the steam-bath for 6 hours. After removal of the acetone by distillation and addition of water, the colourless solid was collected, washed with dilute sodium hydroxide solution, then water, and dried (yield, 87 g.). The compound had m. p. 101°, unaltered by crystallisation from dilute acetic acid, from which it separated in prismatic needles (Found: C, 72·1; H, 5·6. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·5%).

7-*Hydroxy*-4-*methyl*-8-*allylcoumarin* (V).—The preceding compound was heated in an oil-bath in quantities of 5 g., the precaution described in the molecular rearrangement of (I) being taken. After the exothermic reaction, which took place at about 240°, the product was kept at 210° for 1½ hours; the crude product thus obtained melted at 165—175°. 7-*Hydroxy*-4-*methyl*-8-*allylcoumarin* separated from alcohol in small compact bi-pyramids, m. p. 193—194° (Found: C, 72·1; H, 5·7. $C_{13}H_{12}O_3$ requires C, 72·2; H, 5·5%). Its alcoholic solution shows a weak blue fluorescence, and gives no coloration with ferric chloride. The solution in concentrated sulphuric acid is pale yellow and possesses a strong blue fluorescence.

2-*Allylresorcinol* (VI).—7-Hydroxy-4-methyl-8-allylcoumarin (5 g.) was heated on the steam-bath for 4 hours with 20% aqueous sodium hydroxide (35 c.c.) in an atmosphere of coal gas. The liquid was acidified, and yielded to ether a light brown oil, which solidified on cooling. This was distilled, and the fraction, b. p. 155—160°/11 mm., recrystallised from light petroleum (b. p. 40—60°). It formed colourless prismatic needles, m. p. 53° (Found: C, 71·5; H, 6·6. $C_9H_{10}O_2$ requires C, 72·0; H, 6·7%). It was easily soluble in water, and the cold aqueous solution gave an indigo-blue colour with a trace of ferric chloride; if the mixture was kept or gently warmed, the blue colour faded and an insoluble reddish oxidation product separated. 2-*Allylresorcinol* gives no coloration with alcoholic ferric chloride (the isomeric 4-allylresorcinol is a liquid, b. p. 144—146°/5 mm.; Hurd, Greengard, and Pilgrim, *loc. cit.*).

2-*Propylresorcinol* (VII).—2-Allylresorcinol (3·5 g.) was reduced in alcohol (20 c.c.) with hydrogen in presence of palladium chloride (0·2 g.) at room temperature; the theoretical absorption of hydrogen took place in 2 hours. After filtration, the alcohol on evaporation left a colourless solid (m. p. 90—95°), which separated from benzene in flat lustrous prisms, m. p.

106° (Found: C, 70·9; H, 7·9. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%). 2-*Propylresorcinol* is easily soluble in water, and its behaviour towards aqueous or alcoholic ferric chloride is identical with that of 2-allylresorcinol. The fluorescein reaction leads to a cherry-red solution exhibiting a weak green fluorescence (compare Crabtree and Robinson, J., 1918, **113**, 869) (the isomeric 4-*n*-propylresorcinol has m. p. 81—82°, and its aqueous solution gives a red-violet coloration with ferric chloride).

3-n-*Propylresacetophenone* (VIII).—(A) A mixture of 2-propylresorcinol (1 g.), acetonitrile (2 c.c.; distilled over phosphoric oxide), dry ether (20 c.c.), and powdered anhydrous zinc chloride (1 g.) was saturated with hydrogen chloride at 0°. After 24 hours, fresh dry ether was added; after shaking, it was decanted from the ketimine hydrochloride, which was hydrolysed by heating on the water-bath for ½ hour. The ketone (1·1 g.; m. p. 124—126°) which separated was crystallised from 50% alcohol and then from light petroleum (b. p. 80—100°) and obtained as small prismatic needles, m. p. 127—128° (Found: C, 67·9; H, 7·2. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%). 3-n-*Propylresacetophenone* gives a dull reddish-brown colour with ferric chloride, and sublimes slowly at 100°. (B) 3-Allylresacetophenone (5 g.) was reduced in alcohol (25 c.c.) with hydrogen in presence of palladium chloride (0·4 g.). Theoretical absorption of hydrogen took place in 1 hour, and evaporation of the filtered solution left a colourless solid; crystallisation from 50% alcohol gave lustrous hexagonal plates, m. p. 127—128°, which was not depressed on admixture with the substance prepared by method (A) (Found in material dried at 100° in a vacuum over phosphoric oxide: C, 67·9; H, 7·2%).*

2-O-*Methyl*-5-*allylresacetophenone* (IV).—Pure 2-*O*-methyl-4-*O*-allylresacetophenone (III) (5 g.) was heated (oil-bath at 215°) for ¾ hour, the maximum temperature reached by the melt being 218°. On cooling, a semi-solid, light reddish-violet mass was obtained, which was shaken with excess of 10% aqueous sodium hydroxide and ether. The ethereal layer yielded unchanged material (III) (1 g.), and the alkaline layer on acidification gave crude 2-O-*methyl*-5-*allylresacetophenone* (4·0 g.). Recrystallisation from a small volume of benzene gave a slightly coloured product (2·4 g.), m. p. 135° with slight previous softening; yield, 60%. It separated from benzene in minute prisms, or from very dilute acetic acid in branching fern-like aggregates, m. p. 136° (Found in material dried over sodium hydroxide in a vacuum at 100°: C, 69·7, 69·8; H, 6·9, 6·6. $C_{12}H_{14}O_3$ requires C, 69·9; H, 6·8%). The benzene mother-liquors left a dark oil, which yielded a further very small quantity of 2-*O*-methyl-5-allylresacetophenone, but no other crystalline material could be isolated. The substance gives no coloration with alcoholic ferric chloride, but is freely soluble in cold aqueous sodium hydroxide.

5-*Allylresacetophenone Dimethyl Ether* (XI).—The foregoing compound, after treatment with aqueous potassium hydroxide and methyl sulphate in the usual way, yielded to ether a colourless solid, which separated from light petroleum (b. p. 60—80°) in irregular prisms, m. p. 88—89° (Found: C, 70·9; H, 7·5. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

4-O-*Allyl*-3-*allylresacetophenone*.—3-Allylresacetophenone (II) (4 g.) in acetone (100 c.c.) was stirred under reflux at the boiling point for 6 hours with allyl bromide (2·5 g.) and potassium carbonate (12 g.). After removal of the acetone and addition of dilute hydrochloric acid the product was extracted with ether and the extracts were shaken with 8% sodium hydroxide solution, dried, and distilled, leaving an oil, which solidified on cooling (3 g.). It separated at 0° from light petroleum, in which it was rather easily soluble, in needles, m. p. 34·5° (Found: C, 72·2; H, 6·9. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%). The compound is weakly phenolic, being extracted from dilute alkaline solutions by ether, but its alcoholic solution gives a deep purplish colour with ferric chloride.

3 : 5-*Diallylresacetophenone* (XII).—4-*O*-Allyl-3-allylresacetophenone (1·5 g.) was heated for 6 hours at 210°, and the resulting dark pasty product was crystallised successively from light petroleum (b. p. 60—80°), dilute alcohol, and light petroleum, yielding 0·3 g. of colourless prisms, m. p. 89—90° (Found: C, 72·7; H, 7·3. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

2-O-*Methyl*-4-O-*allyl*-5-*allylresacetophenone*.—This substance was prepared by allylation of 2-*O*-methyl-5-allylresacetophenone (IV) (3·4 g.) in the usual way with allyl bromide (3·4 g.), potassium carbonate, and acetone (20 c.c.) for 5 hours, and subsequent dilution (yield, 3·8 g.). It separated from alcohol in long needles, m. p. 79° (Found: C, 73·2; H, 7·4. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·4%).

3 : 5-*Diallylresacetophenone Dimethyl Ether*.—(A) The preceding compound (2 g.) was heated

* The orientation of 3-*n*-propylresacetophenone establishes the correctness of the formula assigned to a product, m. p. 108—109°, obtained by Rosenmund, Buchwald, and Deligiannis (*Arch. Pharm.*, 1933, **271**, 344) and regarded as 5-*n*-propylresacetophenone.

for ¾ hour at 210° (maximum temperature of the melt, 213°), and then shaken with ether and 8% sodium hydroxide solution. The ethereal layer yielded unchanged material (1 g.), and the alkaline layer was treated with excess of methyl sulphate and alkali, yielding an oil (0·3 g.), which distilled at 178—179°/13 mm. (Found: C, 73·9; H, 7·6. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). (B) **3** : 5-Diallylresacetophenone (XII), when treated with excess of methyl sulphate and alkali in acetone, gave the dimethyl ether, b. p. 178—179°/13 mm. (Found: C, 73·7; H, 7·6%). These products were separately treated with semicarbazide hydrochloride and sodium acetate in dilute alcoholic solution at 60° for 20 minutes; after crystallisation from benzene the two specimens of the *semicarbazone*, minute needles, melted at 135—136°, either alone or mixed (Found: N, 13·4. $C_{17}H_{23}O_3N_3$ requires N, 13·3%).

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