118. *Investigations on Natural Tannins. Part I. Acidic Condensation Reactions between Phenols and αβ-Unsaturated Carbonyl Compounds.*

By David W. Clayton, William E. Elstow, Ranajit Ghosh, and Bertie C. Platt.

In the presence of acid, phenols condense with αβ-unsaturated carbonyl compounds to give six-membered heterocyclic compounds. Contrary to Adler and Tingstam (*Arkiv Kemi, Min., Geol.*, 1943, **16**, *B*, No. 18), 2 : 4-dimethylphenol and acraldehyde give 2-(2 : 4-dimethylphenoxy)-6 : 8-dimethylchroman (II). Whereas resorcinol and benzylideneacetone in methanolic hydrogen chloride at 65° yield 7-hydroxy-2-methyl-4-phenylchrom-2-en (VI; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph), in methanolic hydrogen chloride at 40° or in ethanolic hydrogen chloride at 45° the products are 4-phenylchromans (III; R^1 = 7-OH, R^2 = Me, R^3 = OMe or OEt, R^4 = H, R^5 = Ph) (cf. G.P. 357,755). Acidic condensation of resorcinol with acraldehyde or crotonaldehyde gives chroman derivatives of type (III).

The recorded acidic condensation reactions between phenols and αβ-unsaturated carbonyl compounds are discussed with reference to two modes of interaction (A and B).

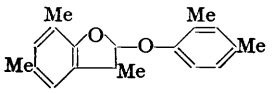
Substituted flavans are required for an investigation of the catechin–tannin transformation. One possible synthesis appeared to be acidic condensation of phenols with αβ-unsaturated carbonyl compounds. It is generally assumed that such reactions lead to six-membered heterocyclic compounds, but Adler and Tingstam (*Arkiv Kemi, Min., Geol.*, 1943, **16**, *B*, No. 18) reported condensation of 2 : 4-dimethylphenol (2 mols.) with acraldehyde (1 mol.) in the cold under weakly acid conditions to give a five-membered ring compound, 2-(2 : 4-dimethylphenoxy)-3 : 5 : 7-trimethylcoumaran (I). The degradative evidence given in support of this structure is not flawless and the following further examination has shown that the product is 2-(2 : 4-dimethylphenoxy)-6 : 8-dimethylchroman (II).

If reaction of a dimethylphenol with acraldehyde gave a 3-methylcoumaran as

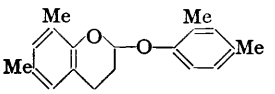
postulated by Adler and Tingstam, then that with crotonaldehyde would give a 3-ethylcoumaran; both products would possess the same terminal methyl content (Kuhn–Roth). If the products are chromans, that from acraldehyde would have no substituent at position 4, and that from crotonaldehyde a 4-methyl substituent. The terminal methyl contents of the products obtained from 2 : 4- and 3 : 4-dimethylphenol and acraldehyde under Adler and Tingstam's conditions were 14·7 and 15·3% respectively, whilst that of the product from 3 : 4-dimethylphenol and crotonaldehyde was 19·3%. This increase corresponds to one methyl group, so that the products are chromans.

Resorcinol and benzylideneacetone have been reported (Chem. Fabrik. Weiler-ter Meer, G.P. 357,755/1922) to yield 7-hydroxy-4-methyl-2-phenylchrom-3-en (VII; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph). However, we have shown that the product is a 4-phenylchroman derivative.

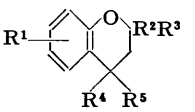
A substituted phenol and an αβ-unsaturated ketone might react according to scheme A



(I)

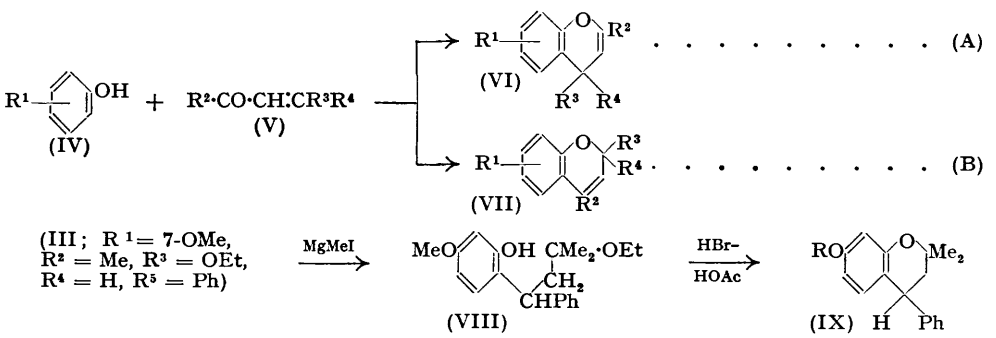


(II)



(III)

or B, of which the latter is favoured by the German workers for reaction in presence of hydrogen chloride in acetic acid. We find that resorcinol and benzylideneacetone in methanolic hydrogen chloride at 65° give a 4-phenylchrom-2-en (VI; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph), but at 40—45° in methanolic or ethanolic hydrogen chloride give a methoxy- or ethoxy-4-phenylchroman (III; R^1 = 7-OH, R^2 = Me, R^3 = OMe or OEt, R^4 = H, R^5 = Ph), *i.e.*, in both cases according to (A). The structure of the ethoxy-



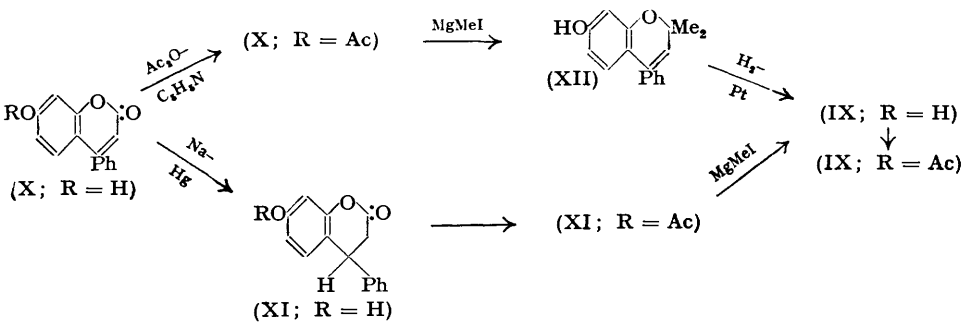
compound follows from its conversion into crystalline 7-acetoxy-2 : 2-dimethyl-4-phenylchroman (IX; R = Ac) identical (mixed m. p.) with two specimens synthesised by different, unambiguous methods. The methyl ether of the ethoxy-compound with methylmagnesium iodide gave the open-chain derivative (VIII) (formation of an acetate confirmed the opening of the pyran ring), and by demethylation and ring closure this gave (IX; R = H). Acetylation then gave the acetate (IX; R = Ac).

In our first synthesis, β-phenylumbelliferone (X; R = H) was reduced to 7-hydroxy-3 : 4-dihydro-4-phenylcoumarin (XI; R = H) (cf. Liebermann and Hartmann, *Ber.*, 1892, **25**, 2130). Acetylation and treatment with methylmagnesium iodide gave 7-hydroxy-2 : 2-dimethyl-4-phenylchroman (IX; R = H), and thence its crystalline acetate. In the second synthesis, (X; R = H) was first acetylated and then treated with methylmagnesium iodide to give 7-hydroxy-2 : 2-dimethyl-4-phenylchromen (XII), hydrogenation of which gave (IX; R = H) and thence (IX; R = Ac), m. p. 127—128°.

Resorcinol with acraldehyde or crotonaldehyde in ethanolic hydrogen chloride at 35—40° gave products which are formulated by analogy as (III; R^1 = 7-OH, R^2 = R^5 = H, R^3 = OEt, R^4 = H or Me respectively). This interpretation is supported by elementary and *C*-Me analyses of both the products and of a derivative.

Known acidic condensation reactions of phenols and αβ-unsaturated carbonyl compounds can be classified as occurring according to either scheme A or scheme B.

Phenol (4 or 2 mols.) and mesityl oxide (1 mol.) give 4'-hydroxy-2 : 4 : 4-trimethylflavan (III; $R^1 = H$, $R^2 = p$-HO·C_6H_4, $R^3 = R^4 = R^5 = Me$) with dry hydrogen chloride at room temperature (Dianin, *J. Russ. Phys.-chem. Soc.*, 1914, **46**, 1310; *Chem.*

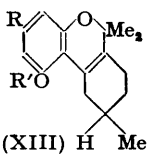


Zentr., 1915, I, 1063) or with zinc chloride under reflux (Niederl, Niederl, and Reznek, *J. Amer. Chem. Soc.*, 1936, **58**, 657); equimolecular proportions in the presence of cold concentrated sulphuric acid give 2-hydroxy-2 : 4 : 4-trimethylchroman (III; $R^1 = H$, $R^3 = R^4 = R^5 = Me$, $R^2 = OH$) which reacts further to give the dichromanyl ether (Niederl, *J. Amer. Chem. Soc.*, 1929, **51**, 2426). These reactions are based on scheme A.

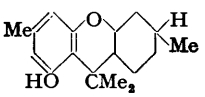
The following are examples of reactions according to scheme B. 2-(2 : 4-Dihydroxyphenyl)-4-methylpent-3-en-2-ol is reported to result from equimolecular proportions of resorcinol and mesityl oxide in the presence of hot dilute hydrochloric acid (Sen and Quadrat-i-Khuda, *J. Indian Chem. Soc.*, 1930, **7**, 167). The acid condensation of pulegone with orcinol and olivetol has been studied by Todd and his co-workers (*J.*, 1941, 137; 1942, 185) and by Adams *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 1973). The orcinol–pulegone condensation gave a crystalline acetate, the structure of which was established as (XIII; R = Me, R' = Ac); this product was formed by scheme B. However, the possibility of reaction according to A, to give a substituted tetrahydroxanthen (XIV or XV), is not entirely precluded, since a large part of the product remained as an unidentified oil.

Whether the reaction follows route A or route B probably depends on the nature and positions of the substituents in both of the reactants. No general rule can yet be laid down, but it has been established that six-membered and not five-membered heterocyclic compounds are formed.

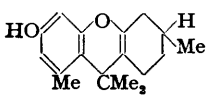
After these failures to synthesise flavans, phenol and resorcinol were treated with



(XIII)



(XIV)



(XV)

cinnamaldehyde in methanolic hydrogen chloride, but no crystalline products were isolated.

Experimental

Microanalyses are by Drs. Weiler and Strauss, Oxford.

2-(2 : 4-*Dimethylphenoxy*)-6 : 8-*dimethylchroman* (II).—2 : 4-Dimethylphenol (10·0 g.) was treated with acraldehyde (2·7 ml.) according to Adler and Tingstam (*loc. cit.*) except that the aldehyde solution was added in one portion and the resultant mixture shaken for 2 hours before the addition of concentrated hydrochloric acid. The *chroman* (3·9 g., 34%; Adler and Tingstam give 17%) had m. p. 88° (Adler and Tingstam, 89°) (Found: C, 80·5; H, 7·8; *C*-Me, 14·7. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·8; 4*C*-Me, 21·3%).

2-(3 : 4-*Dimethylphenoxy*)-6 : 5(or 7)-*dimethylchroman*.—Acraldehyde (1 mol., 2·7 ml.) in acetic acid (3 ml.) was run into 3 : 4-dimethylphenol (2 mols., 10 g.) containing an acetic acid solution (3·2 ml.) of hydrogen chloride (0·5%), with shaking, at <5°. After 1 hour concentrated hydrochloric acid (0·3 ml.) was added and the mixture left overnight. Distillation gave a fraction, b. p. 92—120°/1 mm.; this crystallised from alcohol to give the *chroman*, m. p. 116° (Found: C, 80·5; H, 8·0; *C*-Me, 15·3%).

2-(3 : 4-*Dimethylphenoxy*)-4 : 6 : 5(or 7)-*trimethylchroman*.—Crotonaldehyde (1 mol., 3·5 ml.) in acetic acid (3·5 ml.) was caused to react with 3 : 4-dimethylphenol (2 mols., 7·1 g.) and 0·5% dry hydrogen chloride–acetic acid solution (3·5 ml.) as above (90 minutes' storage before acidification). After evaporation the residue was shaken in ether with 2N-sodium hydroxide. Removal of the ether, distillation at 154° (bath)/0·01 mm., chromatography (in benzene on alumina), and redistillation gave the *chroman*, b. p. 140° (bath)/0·003 mm., m. p. 155° (Found: C, 81·0; H, 8·3; *C*-Me, 19·3. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1; 5*C*-Me, 25·3%).

2-*Ethoxy*-7-*hydroxy*-2-*methyl*-4-*phenylchroman* (III; R^1 = 7-OH, R^2 = Me, R^3 = OEt, R^4 = H, R^5 = Ph).—Ethanolic hydrogen chloride (3 g.; 22% w/w) was added to benzylideneacetone (4 g., 1 mol.) and resorcinol (3·2 g., 1 mol.) in dry ethyl alcohol (25 g.). After 3·5 hours' heating at 45° the solution was concentrated at 40°/20 mm. to a red syrup, which was dissolved in 2N-sodium hydroxide (150 ml.) and extracted with ether (100 ml.). This extract was extracted with 2N-sodium hydroxide (100 ml.) and the combined alkaline solutions were extracted with ether (9 × 100 ml.). The combined ethereal extracts were washed with water until neutral and dried (Na_2SO_4). After removal of the solvent, the residue (5·5 g.) was extracted with boiling light petroleum (b. p. 100—120°; 2 × 50 ml.). The colourless insoluble residue was recrystallised from aqueous alcohol, to give the *chroman*, needles, m. p. 167° (3·7 g., 45%) (Found: C, 75·8; H, 7·1. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·0%).

The *acetate*, obtained (70% yield) by use of boiling acetic anhydride (3 hours), formed needles, m. p. 101—102°, from alcohol (Found: C, 73·9; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

The *methyl ether*, obtained (95% yield) by means of methyl sulphate and sodium hydroxide in acetone (2 hours on the water-bath), crystallised from ether as needles, m. p. 82° (Found: C, 76·4; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

2-*Ethoxy*-4-(2-*hydroxy*-4-*methoxyphenyl*)-2-*methyl*-4-*phenylbutane* (VIII).—A solution of 2-ethoxy-7-methoxy-2-methyl-4-phenylchroman (7·5 g., 1 mol.) in dry ether (500 ml.) was slowly added to a rapidly stirred solution of methylmagnesium iodide [4·3 mol.; from magnesium (2·4 g.) and methyl iodide (8·5 ml.)] in dry ether (300 ml.). The stirred mixture was heated under reflux for 10 hours. The ice-cooled mixture was cautiously acidified with ice-cold hydrochloric acid (400 ml. of 10%) and the ethereal layer separated. The aqueous layer was twice extracted with ether and the combined ethereal extracts were washed with 2N-sodium hydroxide (100 ml.), then with water, and dried (Na_2SO_4). Removal of the ether gave an oil (8·6 g.) which distilled at 146° (bath)/0·035 mm., to give the *phenylbutane* as a pale yellow oil (7·0 g., 88%) (Found: C, 76·6; H, 8·3. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%).

The *acetate*, obtained by means of acetic anhydride in hot pyridine (3½ hours), was a pale yellow oil, b. p. 144° (bath)/0·04 mm. (Found: C, 74·1; H, 7·7. $C_{22}H_{28}O_4$ requires C, 74·2; H, 7·9%).

7-*Acetoxy*-2 : 2-*dimethyl*-4-*phenylchroman* (IX; R = Ac).—2-Ethoxy-4-(2-hydroxy-4-methoxyphenyl)-2-methyl-4-phenylbutane (VIII) (1·1 g.) in acetic acid (15 ml.) was boiled for 1 hour with 46—48% hydrobromic acid (15 ml.). Most of the solvent was removed under reduced pressure and the residue extracted in ether with 10% sodium hydroxide solution. The alkaline solution was re-extracted once with ether and the combined ethereal extracts were washed with water until neutral and dried (Na_2SO_4). After removal of the solvent, the dark green oil (1·0 g.) was distilled. The fraction (0·35 g.) of b. p. 138—140° (bath)/0·003—0·006 mm. was treated with acetic anhydride (8 ml.) in boiling dry pyridine (8 ml.) for 3½ hours, freed from reagents by distillation under reduced pressure, dissolved in ether, and washed successively with dilute hydrochloric acid, sodium hydroxide solution (1%), and water, and dried (Na_2SO_4). Removal of the ether gave a yellow oil (0·3 g.); crystallised from alcohol this gave the *acetoxychroman* as cubes, m. p. 127—128°, alone or mixed with either of the samples synthesised as described below (Found: C, 77·2; H, 6·6. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

3 : 4-*Dihydro*-7-*hydroxy*-4-*phenylcoumarin* (XI; R = H).—7-Hydroxy-4-phenylcoumarin (X; R = H) (prepared in good yield by von Pechmann and Hanke's method, *Ber.*, 1901, **34**, 356) was reduced to the dihydrocoumarin (XI; R = H) (99%; m. p. 140°) with 2% sodium amalgam at room temperature. (Liebermann and Hartmann, *Ber.*, 1892, **25**, 2130, used a temperature of 50—60° and record m. p. 137°.)

This (1·3 g.) with acetic anhydride (5 ml.) in boiling pyridine (5 ml.) (3 hours) gave the *acetate*, rhombs, m. p. 89—91° (from methyl alcohol) (0·9 g.) (Found: C, 72·0; H, 5·0. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

7-Hydroxy-2 : 2-dimethyl-4-phenylchroman (IX; R = H).—The foregoing acetate (5 g., 1 mol.) in dry ether (150 ml.) was slowly added to a solution of methylmagnesium iodide [12 mols.; from magnesium (5·3 g.) and methyl iodide (13·3 ml.)] in dry ether (400 ml.). The mixture was heated under reflux for 7 hours, cooled, and cautiously acidified with 15% hydrochloric acid (500 ml.) containing ice (approx. 100 g.). The ethereal layer was separated and the aqueous layer twice extracted with ether; the combined ethereal extracts were washed with 2N-sodium hydroxide (50 ml.), then with water until neutral, and dried (Na_2SO_4). After removal of the ether the residual *chroman* (5 g.) distilled at 160° (bath)/0·03 mm. as a pale amber oil.

Its *acetate*, obtained in pyridine, crystallised from alcohol as cubes, m. p. 127—128° (Found: C, 76·8; H, 6·9%).

7-Hydroxy-2 : 2-dimethyl-4-phenylchromen (XII).—7-Acetoxy-4-phenylcoumarin (X; R = Ac) (5 g.; von Pechmann and Hanke, *Ber.*, 1901, **34**, 356) with excess of methylmagnesium iodide, as in the preparation of 7-hydroxy-2 : 2-dimethyl-4-phenylchroman, gave a product, b. p. 130° (bath)/0·04 mm., which, when crystallised from ether–light petroleum (b. p. 40—60°), gave the *chromen* as plates, m. p. 122·5° (2·6 g., 58%) (Found: C, 80·7; H, 6·1. $C_{17}H_{16}O_2$ requires C, 81·0; H, 6·3%). Its *acetate*, prepared in pyridine, formed plates, m. p. 91°, from alcohol (Found: C, 77·8; H, 6·1. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1%).

7-Hydroxy-2 : 2-dimethyl-4-phenylchroman (IX; R = H).—The chromen (XII) (1·2 g.) in acetic acid was hydrogenated at atmospheric pressure and room temperature in the presence of Adams's platinum catalyst (0·04 g.). After 5 hours, hydrogen (absorption, 115 ml.; theor. 113 ml.) ceased to be absorbed; after filtration and evaporation under reduced pressure, the residue was shaken in ether with sodium hydrogen carbonate solution, then water, dried (Na_2SO_4), and distilled, giving a pale yellow oil, b. p. 130° (bath)/0·002 mm. (0·5 g., 41%).

Acetic anhydride in pyridine afforded the acetate as cubes, m. p. 127—128° (from methyl alcohol).

7-Acetoxy-2-methoxy-2-methyl-4-phenylchroman (III; R^1 = 7-OAc, R^2 = Me, R^3 = OMe, R^4 = H, R^5 = Ph).—Methanolic hydrogen chloride (3 g., 10% w/w) was added to a solution of resorcinol (3·9 g., 1 mol.) and benzylideneacetone (5 g., 1 mol.) in dry methyl alcohol (25 g.), and the solution kept at 40° for 4½ hours. The solvent was then removed at 40° under reduced pressure and an ethereal solution of the red residue was extracted with 2N-sodium hydroxide (8 × 50 ml.). The combined alkaline extracts were then shaken with ether (8 × 50 ml.) and the combined ethereal solutions were washed with water and dried (Na_2SO_4). Removal of the ether gave a product (1·2 g.) which distilled at 140—145° (bath)/0·09 mm. as a pale yellow oil.

Treatment with acetic anhydride in boiling pyridine (2 hours) and recrystallisation from aqueous methyl alcohol gave the *acetate* (0·6 g.), needles, m. p. 115—116° (Found: C, 73·2; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%).

7-Hydroxy-2-methyl-4-phenylchrom-2-en (VI; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph).—The same amounts of reactants were used as in the previous experiment, but the solution was kept at 65° for 5 hours. The product, purified as described previously, gave the unsaturated *compound* as an almost colourless oil, b. p. 140—142° (bath)/0·02 mm. (Found: C, 80·5; H, 5·9. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%).

2-Ethoxy-7-hydroxychroman (III; R^1 = 7-OH, R^2 = R^4 = R^5 = H, R^3 = OEt).—Resorcinol (4 g., 1 mol.), acraldehyde (2 ml., 1 mol.), and ethanolic hydrogen chloride (2 ml.; 20% w/w) in dry ethyl alcohol (40 ml.) were kept at 35—40° for 4 hours. After removal of the solvent at 40° under reduced pressure, the dark oily residue was dissolved in 2N-sodium hydroxide (150 ml.) and extracted with ether (9 × 100 ml.). The combined ethereal extracts were washed with water and dried (Na_2SO_4). Removal of the solvent left an almost colourless oil (2 g.) which on distillation gave the *chroman*, b. p. 98° (bath)/0·002 mm. (Found: C, 68·0; H, 7·3; *C*-Me, 7·2. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·2; 1*C*-Me, 7·7%).

The *7-acetate*, prepared by acetic anhydride and pyridine, was an oil, b. p. 93° (bath)/0·004 mm. (Found: C, 66·2; H, 7·1; *C*-Me, 13·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8; 2*C*-Me, 12·7%).

2-Ethoxy-7-hydroxychroman (0·59 g.) with 3 : 5-dinitrobenzoyl chloride (1·17 g.) in dry pyridine (2 ml.) at 100° (½ hour) gave the *3 : 5-dinitrobenzoate* as pale yellow needles, m. p. 113·5°, from alcohol (Found: C, 55·7; H, 4·1; N, 7·3. $C_{18}H_{16}O_8N_2$ requires C, 56·0; H, 4·2; N, 7·2%).

2-*Ethoxy*-7-*hydroxy*-4-*methylchroman* (III; R^1 = 7-OH, R^2 = R^5 = H, R^3 = OEt, R^4 = Me) —Ethanolic hydrogen chloride (2 ml.; 20% w/w) was added to resorcinol (4 g., 1 mol.) and crotonaldehyde (3 ml., 1 mol.) in dry ethyl alcohol (40 ml.). The solution was heated at 35—40° for 2½ hours. The *chroman*, isolated as described for 2-ethoxy-7-hydroxychroman, was an oil (2 g., 27%), b. p. 102° (bath)/0·003 mm. (Found : C, 69·5; H, 7·8; *C*-Me, 13·9. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7; 2*C*-Me, 14·4%).

The 3 : 5-*dinitrobenzoate* crystallised as pale yellow needles, m. p. 108°, from alcohol (Found : C, 56·8; H, 4·6. $C_{19}H_{18}O_8N_2$ requires C, 56·7; H, 4·5%).

The authors thank the Director and Council of the British Leather Manufacturers' Research Association for permission to publish this work.

BRITISH LEATHER MANUFACTURERS' RESEARCH ASSOCIATION,
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[*Received, July 31st*, 1952.]