699. *Organic Fluoro-compounds. Part VII.** *Some 2-Trihalogenocoumarones.*

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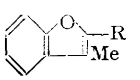
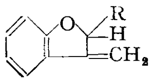
This paper describes the application of the Hoesch reaction with trifluoromethyl and trichloromethyl cyanides to a series of coumarones.

Recent work in these laboratories (Dean, Halewood, Mongolsuk, Whalley, and Robertson, *J.*, 1953, 1250) has conclusively demonstrated that the isomerisation of usnic acid to usnolic acid involves, *inter al.*, the unexpected transformation of the angular methyl group of the coumarone system of usnic acid into the exocyclic methylene residue of usnolic acid. To obtain collateral information concerning this easy change we examined a series of coumarones of type (I) containing substituents in the α-position which might be expected to facilitate the conversion of (I) into the usnolic acid coumarone type (II). In view of our previous experience (cf. Whalley, *J.*, 1951, 3229), the trifluoroacetyl and trichloroacetyl residues seemed suitable for our purpose, and this communication describes the preparation and properties of a number of hydroxy- and methoxy-coumarones containing these moieties.



(I)



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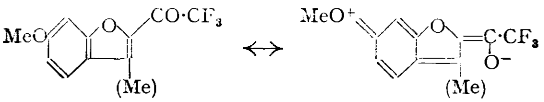

(III)

The application of the Hoesch ketone synthesis with trifluoro- and trichloro-methyl cyanides to 3-methylcoumarone, 6-hydroxy-, 6-methoxy-, 4 : 6-dimethoxy-, 5 : 6-dimethoxy-, 5-hydroxy-, and 5-methoxy-3-methylcoumarone gave the corresponding 2-trihalogenoacetyl derivatives (see table); 7-methoxy-3-methylcoumarone furnished a mixture of 7-methoxy-3-methyl-2-trifluoroacetylcoumarone and an isomeric ketone which is probably either the 4- or 5-trifluoroacetyl compound. This is the first instance in which the application of the Hoesch ketone synthesis to a methoxy-3-methylcoumarone unsubstituted in the 2-position has furnished a derivative in which the entering substituent does not occupy that position.

			Found, %,			Requires, %,		
2-Trifluoroacetylcoumarone	M. p.	Formula	C	H	F	C	H	F
3-Methyl-	54°	$C_{11}H_7O_2F_3$	—	—	24·4	—	—	25·0
6-Hydroxy-	168	$C_{10}H_5O_3F_3$	52·0	2·5	23·8	52·2	2·3	24·8
6-Hydroxy-3-methyl-	154	$C_{11}H_7O_3F_3$	54·7	3·3	—	54·1	2·9	—
4 : 6-Dimethoxy-3-methyl-	112	$C_{13}H_{11}O_4F_3$	53·8	3·5	18·9	54·2	3·8	19·4
5 : 6-Dimethoxy-	147	$C_{12}H_9O_4F_3$	52·7	3·4	21·1	52·6	3·3	20·8
5-Hydroxy-3-methyl-	171	$C_{11}H_7O_3F_3$	53·7	3·4	—	54·1	2·9	—
5-Methoxy-3-methyl-	97	$C_{12}H_9O_3F_3$	55·9	3·8	—	56·0	3·5	—
5-Methoxy-	85	$C_{11}H_7O_3F_3$	53·8	3·3	24·0	54·1	2·9	23·4

			Found, %,			Requires, %,		
2-Trichloroacetylcoumarone	M. p.	Formula	C	H	Cl	C	H	Cl
3-Methyl-	85°	$C_{11}H_7O_2Cl_3$	47·9	2·6	38·2	47·7	2·5	38·4
6-Hydroxy-	150	$C_{10}H_5O_3Cl_3$	43·0	2·1	37·2	43·0	1·8	37·9
6-Methoxy-	130	$C_{11}H_7O_3Cl_3$	45·0	2·6	36·2	45·1	2·4	36·3
4 : 6-Dimethoxy-3-methyl-	134	$C_{13}H_{11}O_4Cl_3$	46·2	3·2	31·4	46·3	3·3	31·6
5 : 6-Dimethoxy-3-methyl-	140	$C_{13}H_{11}O_4Cl_3$	46·6	3·4	31·1	46·3	3·3	31·6
5-Hydroxy-3-methyl-	168	$C_{11}H_7O_3Cl_3$	45·5	2·7	36·2	45·1	2·4	36·4
5-Methoxy-3-methyl-	108	$C_{12}H_9O_3Cl_3$	46·7	3·3	34·5	46·9	2·9	34·5

5-Hydroxy-3-methylcoumarone failed to undergo the Gattermann aldehyde condensation or the Hoesch reaction with trifluoro- and trichloro-methyl cyanides, but the corresponding benzyl ether gave good yields of the respective ketones, debenzylation occurring during the Hoesch condensation. Modification of the usual reaction conditions (see Experimental) enabled the Hoesch reaction with these cyanides to be applied to a

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* Part VI, *J.*, 1951, 3235.

number of αβ-unsubstituted coumarones. Thus, 6-hydroxy-, 6-methoxy-, and 5 : 6-dimethoxy-coumarone furnished the respective 2-trihalogenoacetyl derivatives; 4 : 6-dimethoxycoumarone gave only a low yield of 4 : 6-dimethoxy-2-trichloroacetylcoumarone and with trifluoromethyl cyanide furnished a mixture of 4 : 6-dimethoxy-2-trifluoroacetylcoumarone and larger amounts of an isomeric ketone which is formulated as 4 : 6-dimethoxy-7-trifluoroacetylcoumarone, by analogy with the production of 7-formyl-4 : 6-dimethoxycoumarone from 4 : 6-dimethoxycoumarone under the conditions of the Gattermann aldehyde synthesis (Foster and Robertson, *J.*, 1939, 921).

7-Methoxycoumarone failed to condense with trichloromethyl cyanide but with trifluoromethyl cyanide gave a ketone which is probably either the 4- or the 5-trifluoroacetyl derivative, since hydrolysis gave an acid isomeric but not identical with 7-methoxycoumarone-2-carboxylic acid.

The orientation of the trihalogenoacetylcoumarones was by hydrolysis to the corresponding carboxylic acids. Several of the coumarones used in this work are new; they were prepared by the application of standard methods as described in the Experimental section.

A comparative examination of the ultra-violet absorption spectra of these various ketones shows that a change of type (I) to (II) probably does not occur to an appreciable extent, if at all; however, the intense yellow colour exhibited by the majority of these compounds does indicate that they are probably more correctly represented as resonance structures of type (III) (cf. Whalley, *J.*, 1951, 3229).

EXPERIMENTAL

The Hoesch condensations with 3-methylcoumarones were carried out in the normal manner; the modified conditions necessary for the application of this reaction to αβ-unsubstituted coumarones are exemplified by the following preparation.

6-Methoxy-2-trifluoroacetylcoumarone.—Prepared by the gradual addition of a solution of 6-methoxycoumarone (Pfeiffer and Grimmer, *Ber.*, 1917, **42**, 911) (1 g.) in ether (10 ml.) to a mixture of zinc chloride (1 g.) in ether (50 ml.) and trifluoromethyl cyanide [from the amide (7 g.)] previously saturated with hydrogen chloride at 0°, *6-methoxy-2-trifluoroacetylcoumarone* (1 g.) separated from light petroleum (b. p. 60—80°) in prisms, m. p. 114° (Found : C, 54·1; H, 3·6; F, 24·6. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9; F, 23·4%). Hydrolysis with warm 2N-sodium hydroxide gave 6-methoxycoumarone-2-carboxylic acid, identical with an authentic specimen (Will and Beck, *Ber.*, 1886, **19**, 1783).

The Hoesch Reaction with 4 : 6-Dimethoxycoumarone and Trifluoromethyl Cyanide.—Hydrolysis of the amorphous ketimine complex from 4 : 6-dimethoxycoumarone (Foster and Robertson, *loc. cit.*) furnished a crude product which upon sublimation at 100°/0·01 mm. gave a crystalline mixture (400 mg.). Purification from light petroleum (b. p. 60—80°) gave 4 : *6-dimethoxy-7(?)-trifluoroacetylcoumarone* (200 mg.) in needles, m. p. 115° (Found: C, 52·2; H, 3·4. $C_{12}H_9O_4F_3$ requires C, 52·5; H, 3·3%). Hydrolysis furnished *7(?)-carboxy-4 : 6-dimethoxycoumarone* in needles (from aqueous acetone), m. p. 207° (decomp.) (Found : C, 59·5; H, 5·0. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

Concentration of the petroleum mother liquors gave 4 : 6-dimethoxy-2-trifluoroacetylcoumarone (15 mg.), as yellow prisms [from light petroleum (b. p. 60—80°)], m. p. 122°. Hydrolysis readily furnished 4 : 6-dimethoxycoumarone-2-carboxylic acid, identical with an authentic specimen (Reichstein, Oppenauer, Grüssner, Hirt, Rhyner, and Glatthaar, *Helv. Chim. Acta*, 1935, **18**, 816).

5 : 6-Dimethoxy-3-methyl-2-trifluoroacetylcoumarone.—Prepared from 5 : 6-dimethoxy-3-methylcoumarone (Jones, Mackenzie, Robertson, and Whalley, *J.*, 1949, 562) (0·8 g.), 5 : *6-dimethoxy-3-methyl-2-trifluoroacetylcoumarone* (1 g.) separated from light petroleum (b. p. 60—80°) in lemon-yellow prisms, m. p. 128° (Found : C, 53·9; H, 3·9. $C_{13}H_{11}O_4F_3$ requires C, 54·2; H, 3·8%). The cherry-red solution of this coumarone in concentrated sulphuric acid became deep red when warmed, whilst hydrolysis with warm 2N-sodium hydroxide rapidly gave a quantitative yield of 5 : *6-dimethoxy-3-methylcoumarone-2-carboxylic* acid as prisms, m. p. 228° (decomp.) (from aqueous acetone) (Found : C, 60·9; H, 5·4. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%). The green solution in sulphuric acid became violet when warmed. The same acid was obtained by the cyclisation of ethyl 2-acetyl-4 : 5-dimethoxyphenoxyacetate with sodium ethoxide, in the usual manner, followed by hydrolysis of the crude ester.

5 : 6-*Dimethoxycoumarone.*—When a solution of 2-hydroxy-4 : 5-dimethoxybenzaldehyde (Head and Robertson, *J.*, 1930, 2434) (5 g.) in acetone (75 ml.) containing ethyl bromoacetate (6 g.) and potassium carbonate (15 g.) was heated under reflux for 6 hr. and the product isolated in the usual way, *ethyl* 2-*formyl*-4 : 5-*dimethoxyphenoxyacetate* (6 g.) separated as prisms (from ethanol), m. p. 129°, having a negative ferric reaction in alcohol (Found: C, 58·1; H, 6·3. $C_{13}H_{16}O_6$ requires C, 58·2; H, 6·0%).

Cyclisation of this phenoxy-ester (1 g.) in ethanol (25 ml.) furnished ethyl 5 : 6-dimethoxycoumarone-2-carboxylate (0·2 g.) in needles, m. p. 107° (from ethanol), having a negative ferric reaction in alcohol and hydrolysed by warm 2N-sodium hydroxide to 5 : 6-*dimethoxycoumarone*-2-*carboxylic acid*, which separated from acetone in needles, m. p. 244—246° (decomp.) (Found: C, 59·4; H, 5·0. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%).

2N-Sodium hydroxide (25 ml.) was added to a solution in ethanol (25 ml.) of ethyl 2-formyl-4 : 5-dimethoxyphenoxyacetate (4 g.), and 15 min. later the solution was diluted with water (100 ml.) and acidified; 2-*formyl*-4 : 5-*dimethoxyphenoxyacetic acid* separated in quantitative yield and was purified from aqueous acetone, forming needles, m. p. 196°, having a negative ferric reaction in alcohol (Found: C, 55·1; H, 5·3. $C_{11}H_{12}O_6$ requires C, 55·0; H, 5·0%).

A solution of this acid (3 g.) in acetic anhydride (40 ml.) containing sodium acetate (7 g.) was refluxed for 4 hr. and then diluted with water. 5 : 6-*Dimethoxycoumarone* crystallised from aqueous methanol in needles, m. p. 59° (1·2 g.) (Found: C, 67·6; H, 5·9. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·7%).

5-*Hydroxy*-3-*methylcoumarone.*—A solution of 2 : 5-dihydroxyacetophenone (10 g.) (Morris, *J. Amer. Chem. Soc.*, 1949, **71**, 2056), benzyl bromide (12 g.), and anhydrous potassium carbonate (25 g.) in acetone (125 ml.) was refluxed for 4 hr. After isolation, 5-*benzyloxy*-2-*hydroxyacetophenone* (12 g.) separated from aqueous methanol or light petroleum (b. p. 60—80°) in prisms, m. p. 69°, having a blue ferric reaction in alcohol (Found: C, 74·3; H, 6·1. Calc. for $C_{15}H_{14}O_3$: C, 74·4; H, 5·8%) (Bhalla, Mahal, and Venkataraman, *J.*, 1935, 868, record m. p. 70°).

The benzyl ether gave quantitatively *ethyl* 2-*acetyl*-4-*benzyloxyphenoxyacetate* which separated from light petroleum (b. p. 60—80°), in prisms, m. p. 50° (Found: C, 69·4; H, 6·1. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%). Attempts to cyclise this ester to the corresponding coumarone were unsuccessful.

Hydrolysis of this phenoxyacetate with 5% aqueous alcoholic sodium hydroxide gave a quantitative yield of 2-*acetyl*-4-*benzyloxyphenoxyacetic acid* as prisms, m. p. 139° (from aqueous acetic acid) (Found: C, 67·7; H, 4·61. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·3%).

Cyclisation of this phenoxy-acid (10 g.) in boiling acetic anhydride (100 ml.) containing sodium acetate (25 g.) gave 5-*benzyloxy*-3-*methylcoumarone* (7 g.) as prisms [from light petroleum (b. p. 40—60°)], m. p. 66° (Found: C, 80·5; H, 6·1. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%).

A solution of this coumarone (2 g.) in acetic acid (15 ml.) and concentrated hydrochloric acid (8 ml.) was refluxed during 45 min., and the cooled solution made alkaline with 2N-sodium hydroxide and extracted with ether. The alkaline liquors were then acidified and extracted with ether, and the washed and dried extract evaporated to furnish 5-*hydroxy*-3-*methylcoumarone* (0·6 g.), which was purified by vacuum sublimation (80°/0·01 mm.), forming prisms, m. p. 92° (Found: C, 73·1; H, 5·8. $C_9H_8O_2$ requires C, 73·0; H, 5·4%).

5-*Methoxy*-3-*methylcoumarone.*—Prepared from 2-hydroxy-5-methoxyacetophenone (Robinson and Smith, *J.*, 1926, 392) (3 g.) in boiling acetone (50 ml.) containing ethyl bromoacetate (3·2 g.) and potassium carbonate (7 g.), *ethyl* 2-*acetyl*-4-*methoxyphenoxyacetate* (4·5 g.) separated from light petroleum in prisms, m. p. 69° (Found: C, 61·9; H, 6·3. $C_{13}H_{16}O_5$ requires C, 61·9; H, 6·4%).

Cyclisation of this keto-ester (2 g.) in ethanol (25 ml.) containing sodium ethoxide [from sodium (0·2 g.) and alcohol (10 ml.)] furnished *ethyl* 5-*methoxy*-3-*methylcoumarone*-2-*carboxylate* in prisms, m. p. 105° (Found: C, 66·7; H, 6·1. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The green solution in cold, concentrated sulphuric acid became cherry-red when warmed. Hydrolysis gave the corresponding *acid* as prisms (from aqueous acetone), m. p. 210° (Found: C, 64·0; H, 5·3. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). Methylation with diazomethane furnished methyl 5-methoxy-3-methylcoumarone-2-carboxylate, identical with the previously prepared specimen.

Hydrolysis of ethyl 2-acetyl-4-methoxyphenoxyacetate readily gave a quantitative yield of the corresponding acid as needles, m. p. 140°, from aqueous acetone (Found: C, 59·0; H, 5·4. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%) (Graffenreid and von Kostanecki, *Ber.*, 1910, **43**, 2155, record m. p. 144—145°).

Cyclisation of this phenoxy-acid (2 g.) in boiling acetic anhydride (10 ml.) containing sodium acetate (5 g.) furnished *5-methoxy-3-methylcoumarone* (1·5 g.), b. p. 105°/0·05 mm. (Found: C, 73·9; H, 6·3. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%).

5-Methoxycoumarone.—When a solution of 2-hydroxy-5-methoxybenzaldehyde (6·5 g.) (Rubenstein, *J.*, 1925, 1998) and chloroacetic acid (15 g.) in water (50 ml.) containing potassium hydroxide (15 g.) was warmed on the steam-bath during 70 min., cooled, and acidified, a crystalline precipitate separated. Recrystallisation from aqueous acetone furnished *2-formyl-4-methoxyphenoxyacetic acid* (7 g.) in prisms, m. p. 155—156°, having a negative ferric reaction in alcohol and instantly soluble in 2N-sodium hydrogen carbonate (Found: C, 56·8; H, 5·2. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

This phenoxy-acid (7 g.) furnished 5-methoxycoumarone (2·5 g.), b. p. 160°/14 mm. (Stoermer, *Annalen*, 1900, **312**, 335), which was insoluble in 2N-sodium hydroxide; its reddish-green solution in cold concentrated sulphuric acid became deep red when warmed.

Prepared from 2-hydroxy-5-methoxybenzaldehyde (5 g.), in the usual way, ethyl 2-formyl-4-methoxyphenoxyacetate was obtained in quantitative yield. Cyclisation of this liquid ester (10 g.) with sodium ethoxide [from sodium (1 g.)] in alcohol (25 ml.) furnished *ethyl 5-methoxycoumarone-2-carboxylate* (1·5 g.) as prisms (from aqueous ethanol), m. p. 62° (Found: C, 65·2; H, 5·9. $C_{12}H_{12}O_4$ required C, 65·4; H, 5·5%). Hydrolysis gave *5-methoxycoumarone-2-carboxylic acid*, needles (from aqueous acetone), m. p. 217° (Found: C, 62·5; H, 4·2. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%), identical with the product obtained by the hydrolysis of 5-methoxy-2-trifluoroacetylcoumarone.

7-Methoxycoumarone.—A mixture of *o*-vanillin (10 g.), chloroacetic acid (15 g.), potassium hydroxide (15 g.), and water (75 ml.) was warmed on the steam-bath for 1½ hr., cooled, diluted with water (100 ml.), and acidified, and the crystalline solid which separated was dissolved in ether (200 ml.). Extraction of this ethereal solution with 2N-sodium hydrogen carbonate and acidification of the extract furnished *2-formyl-6-methoxyphenoxyacetic acid* (6 g.) in prisms, m. p. 119° (from aqueous acetone) (Found: C, 57·2; H, 5·1. $C_{10}H_{10}O_5$ requires C, 57·1; H, 4·8%).

A solution of this phenoxy-acid (6·5 g.) in acetic anhydride (50 ml.) containing sodium acetate (10 g.) was refluxed for 5 hr. (shorter periods gave much uncyclised phenoxy-acid), and after isolation and separation from starting material 7-methoxycoumarone (2·2 g.) was obtained, b. p. 140°/16 mm. (Reichstein *et al.*, *loc. cit.*, record b. p. 68°/0·4 mm.).

The Hoesch Reaction with 7-Methoxycoumarone and Trifluoromethyl Cyanide.—7-Methoxycoumarone (1 g.) furnished *7-methoxy-*x*-trifluoromethylcoumarone* (0·8 g.), as prisms, m. p. 110°, from light petroleum (b. p. 60—80°) (Found: C, 53·6; H, 3·3. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%).

Hydrolysis of this ketone furnished *7-methoxycoumarone-*x*-carboxylic acid* as needles (from aqueous acetone), m. p. 227° (Found: C, 62·6; H, 4·5. $C_{10}H_8O_4$ requires C, 62·5; H, 4·2%). The mixed m. p. with an authentic specimen of 7-methoxycoumarone-2-carboxylic acid (Reichstein *et al.*, *loc. cit.*) was *ca.* 200°.

7-Methoxy-3-methylcoumarone.—Prepared from 2-hydroxy-3-methoxyacetophenone, ethyl 2-acetyl-6-methoxyphenoxyacetate was obtained in quantitative yield as a pale yellow oil which was cyclised to give *ethyl 7-methoxy-3-methylcoumarone-2-carboxylate* (0·7 g.) which separated from aqueous acetone in needles, m. p. 70° (Found: C, 67·1; H, 6·3. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%).

Hydrolysis of this ester furnished a quantitative yield of *7-methoxy-3-methylcoumarone-2-carboxylic acid* in needles, m. p. 216° (from aqueous acetone) (Found: C, 64·1; H, 4·9. $C_{11}H_{10}O_4$ requires C, 64·5; H, 5·3%).

Ethyl 2-acetyl-6-methoxyphenoxyacetate was hydrolysed quantitatively with warm dilute aqueous-alcoholic sodium hydroxide to give the *acid* in needles, m. p. 122° (from aqueous acetone) (Found: C, 59·1; H, 5·4. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%). When a solution of this acid (5 g.) in acetic anhydride (25 ml.) containing fused sodium acetate (15 g.) was refluxed for 3 hr. and then poured into water (300 ml.), a dark crystalline solid slowly separated (24 hr.). The dried product was distilled to give *7-methoxy-3-methylcoumarone* (3 g.), b. p. 80°/0·01 mm., m. p. 46°; it was very soluble in the usual organic solvents (Found: C, 73·9; H, 6·3. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%).

7-Methoxy-3-methyl-2-trifluoroacetylcoumarone.—Purification from light petroleum (b. p. 40—60°) of the product from 7-methoxy-3-methylcoumarone gave *7-methoxy-3-methyl-2-trifluoroacetylcoumarone* (0·5 g.) in stout prisms, m. p. 131° (Found: C, 55·8; H, 3·5. $C_{12}H_9O_3F_3$ requires C, 56·0; H, 3·5%). Hydrolysis readily furnished 7-methoxy-3-methylcoumarone-2-carboxylic acid, identical with an authentic specimen.

Concentration of the light petroleum mother-liquors furnished *7-methoxy-3-methyl-*x*-tri-*

fluoroacetylcoumarone (0·4 g.) (Found : C, 55·8; H, 3·6%), which was hydrolysed to 7-*methoxy*-3-*methylcoumarone*-x-*carboxylic acid*, needles, m. p. 216° (from aqueous acetone) (Found : C, 64·5; H, 5·0. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%). The pale yellow solution in sulphuric acid became violet when warmed, and the mixed m. p. with the 2-carboxylic acid was *ca.* 175°.

7-Methoxy-3-methylcoumarone failed to undergo the Gattermann aldehyde condensation and was recovered.

The absorption spectra were determined in 95% ethanol solution on a Carey Self-recording Spectrophotometer, Model 11, by courtesy of Smith, Kline, and French Laboratories, Philadelphia.

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