713. *Organic Fluoro-compounds. Part VI.* Some Trifluoromethyl-chromones and -coumarins.*

By W. B. Whalley.

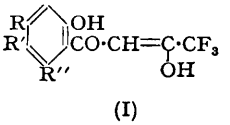
The condensation of ethyl trifluoroacetate with *o*-hydroxyacetophenones proceeds normally, to furnish *o*-hydroxy-diketones of type (I), which are cyclised by mineral acid to the corresponding 2-trifluoromethylchromones (II). Condensation of the appropriate phenols with ethyl trifluoroacetoacetate readily gives the isomeric 4-trifluoromethylcoumarins (III), except in the case of phloroglucinol, which furnishes the α-pyrono-coumarin (VI), whilst 3 : 5-dihydroxybenzotrifluoride and ethyl acetoacetate yield a mixture of 5-hydroxy-4-methyl-7-trifluoromethyl- (X; R = H) and 7-hydroxy-4-methyl-5-trifluoromethyl-coumarin (IX; R = H). The preparation of 3-trifluoroacetylcoumarins of type (IV) from *o*-hydroxy-aldehydes and ethyl trifluoroacetate does not proceed easily.

With the object of exploring the potentialities of suitable substances containing the trifluoromethyl and trifluoroacetyl groups as intermediates for the preparation of difficultly accessible fluorine-free oxygen-heterocylic compounds, the preparation and properties of several ω-trifluoroacetylacetones and trifluoromethyl-chromones and -coumarins have been investigated.

Condensation of 2-aceto-*p*-cresol (OH = 1), 2-hydroxy-4 : 6-dimethylacetophenone, and 2-hydroxy-4-methoxyacetophenone with ethyl trifluoroacetate proceeded normally under the influence of powdered sodium with the production of the corresponding diketones (I), which very easily suffer fission by alkali with the regeneration of the parent acetophenones. The diketones cyclised readily in boiling alcohol containing hydrochloric acid to furnish the corresponding chromones (II), and gave rise to monoximes; these oximes are presumably represented by structures of type (V) because by analogy with the ω-trifluoroacetophenones (Part IV, *J.*, 1951, 665) the carbonyl group adjacent to the trifluoromethyl group will be comparatively unreactive towards carbonyl reagents, owing to enolisation. In contrast with the ω-trifluorohydroxy- and ω-trichlorohydroxy-acetophenones (Part IV, *loc. cit.*, and Part V, preceding paper), these hydroxy-diketones are colourless; this is in accord with general considerations which indicate that the electrophilic properties of the ω-fluoro atoms can be

* Part V, preceding paper.

exerted by the production of the enol (I), and thus the quinonoid structure which causes colour in the acetophenones is not invoked (cf. preceding paper).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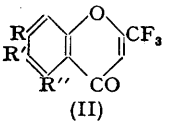
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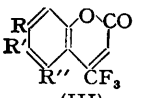
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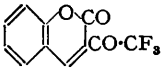
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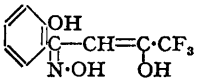
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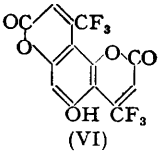
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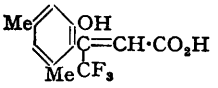
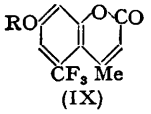

(VII)

By the Pechmann condensation (*Ber.*, 1883, **16**, 2119) with ethyl trifluoroacetoacetate, *p*-cresol, 3 : 5 : 1-xylenol, resorcinol, and resorcinol monomethyl ether gave the corresponding 4-trifluoromethylcoumarins (III) in excellent yield, the structure of which is clearly indicated by the products' not being identical with the chromones obtained by the unequivocal method recorded above. However, condensation of phloroglucinol with ethyl trifluoroacetoacetate gave a compound which appeared to consist entirely of one of the possible isomeric forms of the α-pyrono-coumarin type (VI) : it is of interest that phloroglucinol and ethyl acetoacetate furnish the expected 5 : 7-dihydroxy-4-methylcoumarin (Pechmann and Cohen, *Ber.*, 1884, **17**, 2189). Theoretical considerations indicate that the 4-trifluoromethyl group in these coumarins should be of great stability, and this has been confirmed by the failure to produce the corresponding coumarin-4-carboxylic acid by a variety of hydrolytic methods.

When solutions of 6-methyl-4-trifluoromethylcoumarin (III; R′ = R″ = H, R′ = Me) and 7-methoxy-4-trifluoromethylcoumarin (III; R = R″ = H, R = OMe) in 2N-sodium hydroxide were acidified, the parent coumarin was isolated. However, 5 : 7-dimethyl-4-trifluoromethylcoumarin (III; R′ = H, R = R″ = Me) gave under these conditions the corresponding cinnamic acid (VII), which exhibited considerable stability and was converted into the parent coumarin only by evaporation above the melting point. This behaviour of *cis-o*-hydroxycinnamic acids has been noted in very few cases and only where negative substituents are present (*e.g.*, Miller and Kinkelin, *Ber.*, 1889, **22**, 1706; Jordan and Thorpe, *J.*, 1915, 387); it is presumably to be ascribed in this instance to the influence of the strongly electrophilic trifluoromethyl group.

Application of the Pechmann condensation with ethyl acetoacetate to 3 : 5-dihydroxybenzotrifluoride (VIII; R = H) (Part I, *J.*, 1949, 3016) gave, as might be expected, a mixture of the isomeric coumarins (IX and X; R = H). The structures of these two substances were not rigorously established but are based on the production of a yellow solution by one coumarin in 2N-sodium hydroxide, and the absence of such a coloration in the case of the second; production of this colour is a well-known characteristic reaction of 5-hydroxycoumarins (Collie


(VIII)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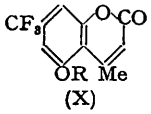
(X)

and Chrystall, *J.*, 1907, **91**, 1804; Dey, *J.*, 1915, **107**, 1614, 1621) and hence the coumarin which responds positively to this test is allotted the structure (X; R = H). Methylation by potassium carbonate–methyl iodide readily furnished the corresponding methyl ethers (IX and X; R = Me). Condensation of 3-hydroxy-5-methoxybenzotrifluoride (VIII; R = Me) (Part I, *loc. cit.*) yielded a small quantity of a mixture from which only 7-methoxy-4-methyl-5-trifluoromethylcoumarin could be isolated in a state of purity.

Demethylation of 3-hydroxy-5-methoxybenzotrifluoride (VIII; R = Me), which is now readily available (Robertson, Whalley, and Yates, *J.*, 1951, 2013), provides a much improved route to 3 : 5-dihydroxybenzotrifluoride.

3-Trifluoroacetylcoumarins of type (IV) could not be obtained from ethyl trifluoroacetoacetate and the appropriate *o*-hydroxy-aldehydes; condensation did not proceed easily at room temperature under normal conditions, and application of heat gave rise to dark red resins.

Experimental.

6-Methyl-2-trifluoromethylchromone (II; R = R'' = H, R' = Me).—A mixture of 2-hydroxy-5-methylacetophenone (5 g.), ethyl trifluoroacetate (17 ml.), and powdered sodium (2 g.) was heated on the steam-bath during 1 hour. The semi-solid yellow mixture was decomposed by the careful addition of ice-water (100 ml.), well shaken to homogenise the product, and acidified with acetic acid, and the semi-crystalline precipitate collected and purified from aqueous methanol, giving *2-hydroxy-5-methyl-ω-trifluoroacetoacetophenone* (3 g.) as colourless, slender prisms or, from benzene–light petroleum as rosettes of glistening, colourless needles, m. p. 157° (Found: C, 53·6; H, 3·4; F, 22·1. $C_{11}H_9O_3F_3$ requires C, 53·7; H, 3·7; F, 23·2%). The product is readily soluble in methyl alcohol, ethyl alcohol, acetone, and ether, moderately soluble in benzene, and sparingly soluble in light petroleum, and exhibits a weak green-brown ferric reaction in alcohol. The *oxime* prepared by the sodium acetate method separated from aqueous methanol in colourless needles, m. p. 140° (Found: C, 49·9; H, 3·9; N, 4·9. $C_{11}H_{10}O_3NF_3$ requires C, 50·5; H, 4·0; N, 5·4%).

When a solution of the diketone in 2N-sodium hydroxide was kept at room temperature for 6 hours and acidified, 2-hydroxy-5-methylacetophenone was precipitated in quantitative yield.

A solution of the foregoing diketone (0·5 g.) in ethanol (5 ml.) containing concentrated hydrochloric acid (3 drops) was heated under reflux during 3 minutes, cooled, and diluted with water. The oil initially precipitated rapidly crystallised, and was purified from aqueous methanol, giving *6-methyl-2-trifluoromethylchromone*, m. p. 53°, in quantitative yield (Found: C, 57·2; H, 3·4. $C_{11}H_7O_2F_3$ requires C, 57·9; H, 3·1%). The chromone was easily soluble in alcohol, ether, acetone, benzene, and light petroleum, and gave no ferric reaction in alcohol.

7-Methoxy-2-trifluoromethylchromone (II; R = OMe, R' = R'' = H).—When a solution of 2-hydroxy-4-methoxyacetophenone (5 g.) in ethyl trifluoroacetate (20 ml.) containing powdered sodium (2 g.) was heated on the steam-bath during 1½ hours, and the product isolated as previously described, *2-hydroxy-4-methoxy-ω-trifluoroacetoacetophenone* (3·5 g.) separated from benzene in rosettes of colourless, long, slender needles, m. p. 136°, which changed to colourless, massive prisms, m. p. 136°, on prolonged contact with the solution (Found: C, 50·8; H, 3·4; F, 22·0. $C_{11}H_9O_4F_3$ requires C, 50·4; H, 3·4; F, 21·7%). The solution in alcohol gave a weak red-brown ferric reaction.

A solution of the diketone (0·2 g.) in 2N-sodium hydroxide (5 ml.) was kept at room temperature during 6 hours and then acidified; pæonol (0·15 g.) was precipitated. Prepared by the sodium acetate method, the *oxime* separated from aqueous methanol in colourless plates, m. p. 125° (Found: C, 45·2; H, 4·1; N, 4·8. $C_{11}H_{10}O_4NF_3,H_2O$ requires C, 45·4; H, 4·1; N, 4·8%).

Cyclisation of the diketone in boiling alcohol containing 3 drops of concentrated hydrochloric acid during 5 minutes gave *7-methoxy-2-trifluoromethylchromone* in quantitative yield. From aqueous methyl alcohol it formed colourless, long, slender prisms, m. p. 110°, insoluble in cold 2N-sodium hydroxide and giving a negative ferric reaction in alcohol (Found: C, 53·7; H, 3·0; F, 23·6. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9; F, 23·3%).

5: 7-Dimethyl-2-trifluoromethylchromone (II; R = R'' = Me, R' = H).—Prepared from 2-hydroxy-4: 6-dimethylacetophenone (5 g.), ethyl trifluoroacetate (20 ml.), and powdered sodium (2 g.) in the usual way, *2-hydroxy-4: 6-dimethyl-ω-trifluoroacetoacetophenone* separated from aqueous methanol or benzene in colourless prisms (3 g.), m. p. 137°, readily soluble in 2N-sodium hydroxide and exhibiting a weak green-brown ferric reaction in alcohol (Found: C, 55·4; H, 4·4; F, 21·9. $C_{12}H_{11}O_3F_3$ requires C, 55·4; H, 4·2; F, 21·9%). The diketone was hydrolysed quantitatively to 2-hydroxy-4: 6-dimethylacetophenone during 6 hours when dissolved in 2N-sodium hydroxide. The *oxime*, prepared by the sodium acetate method, separated from aqueous methanol in clusters of colourless prisms, m. p. 138° (Found: C, 52·2; H, 4·5; N, 4·2. $C_{12}H_{12}O_3NF_3$ requires C, 52·4; H, 4·4; N, 5·1%).

Prepared in almost quantitative yield by the cyclisation of the foregoing diketone in boiling alcohol containing 3 drops of concentrated hydrochloric acid *5: 7-dimethyl-2-trifluoromethylchromone* separated from aqueous methanol in colourless shimmering, long, flat prisms, m. p. 105° (Found: C, 59·4; H, 3·8; F, 23·4. $C_{12}H_9O_2F_3$ requires C, 59·5; H, 3·7; F, 23·5%). The chromone was insoluble in cold 2N-sodium hydroxide and gave a negative ferric reaction in alcohol.

6-Methyl-4-trifluoromethylcoumarin (III; R = R'' = H, R' = Me).—*p*-Cresol (3 g.) and ethyl trifluoroacetoacetate (6 g.) were dissolved in concentrated sulphuric acid (10 ml.) and 2 days later the solution was poured on crushed ice. The colourless precipitate crystallised from methanol, to furnish *6-methyl-4-trifluoromethylcoumarin* in long, slender, glistening, colourless prisms (2 g.), m. p. 111° (Found: C, 57·9; H, 3·1; F, 25·4. $C_{11}H_7O_2F_3$ requires C, 57·9; H, 3·1; F, 25·0%). When a suspension of this coumarin was warmed on the steam-bath with 2N-sodium hydroxide, dissolution occurred during 20 minutes; careful acidification (Congo-red) with 2N-hydrochloric acid then precipitated the coumarin, identified by m. p. and mixed m. p.

7-Methoxy-4-trifluoromethylcoumarin (III; R = OMe, R' = R'' = H).—(*a*) Prepared from resorcinol (2 g.), ethyl trifluoroacetoacetate (5 g.), and concentrated sulphuric acid (5 ml.) during 2 days in the usual way, *7-hydroxy-4-trifluoromethylcoumarin* separated from methanol in colourless, glistening plates (1·6 g.), m. p. 178°, easily soluble in cold 2N-sodium hydroxide and exhibiting a negative ferric reaction in alcohol (Found: C, 52·3; H, 2·1; F, 24·3. $C_{10}H_5O_3F_3$ requires C, 52·2; H, 2·2; F, 24·8%). Methylation of the foregoing coumarin in boiling acetone by potassium carbonate–methyl iodide during 3 hours gave *7-methoxy-4-trifluoromethylcoumarin* which separated from aqueous methanol in clusters of colourless needles, m. p. 112°, unchanged by sublimation at 120°/0·1 mm. (Found: C, 53·7; H, 3·2. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%).

(*b*) Resorcinol monomethyl ether (0·5 g.) and ethyl trifluoroacetoacetate (1 g.) were dissolved in concentrated sulphuric acid (5 ml.) and 2 days later the solution was poured on ice. The product

(0·5 g.) which separated from aqueous methanol in clusters of colourless needles was identical with that prepared by method (*a*).

A suspension of this coumarin in 2N-sodium hydroxide was warmed on the steam-bath during 30 minutes, and the clear solution cooled and acidified, giving rise to the parent coumarin.

5 : 7-*Dimethyl-4-trifluoromethylcoumarin* (III; R = R'' = Me, R' = H).—Prepared from 3 : 5 : 1-xylenol (3 g.), ethyl trifluoroacetoacetate (6 g.), and concentrated sulphuric acid (10 ml.) during 2 days, 5 : 7-*dimethyl-4-trifluoromethylcoumarin* separated from methanol in massive, colourless, glistening prisms (4 g.), m. p. 99° (Found: C, 59·6; H, 3·7; F, 23·9. $C_{12}H_9O_2F_3$ requires C, 59·5; H, 3·7; F, 23·5%). The mixed m. p. with 5 : 7-dimethyl-2-trifluoromethylchromone was about 75°. The coumarin dissolved during 30 minutes on the steam-bath in 2N-sodium hydroxide, and after acidification the precipitated *cinnamic acid* was crystallised from benzene–light petroleum as colourless, rectangular plates, m. p. 149°, easily soluble in 2N-sodium hydrogen carbonate solution (Found: C, 55·2; H, 4·4. $C_{12}H_{11}O_3F_3$ requires C, 55·4; H, 4·2%). Sublimation at 160°/0·1 mm. regenerated the parent coumarin (m. p. and mixed m. p.).

Condensation of Phloroglucinol with Ethyl Trifluoroacetoacetate.—Prepared from phloroglucinol (2 g.) and ethyl trifluoroacetoacetate (4 g.) in concentrated sulphuric acid (10 ml.) during 2 days, 5-*hydroxy*-4 : 4'-*bistrifluoromethyl*-2'-*pyrono*(6' : 5'-7 : 8)*coumarin*(?) (VI) separated from methanol in very pale yellow, stout prisms (1·2 g.), m. p. 299—300° (Found: C, 45·1; H, 1·4; F, 30·2. $C_{14}H_4O_5F_6$ requires C, 45·9; H, 1·1; F, 31·2%).

3 : 5-*Dihydroxybenzotrifluoride.*—A mixture of 3-hydroxy-5-methoxybenzotrifluoride (15 g.) and hydriodic acid (100 ml.; *d* 1·7) was refluxed for 20 hours, diluted with water (125 ml.), and steam-distilled to remove a trace of starting material. The cooled reaction mixture was extracted with ether (5 × 100 ml.), and the extract washed with 2N-sodium hydrogen carbonate, dilute sodium bisulphite solution, and water, dried, and distilled, to give 3 : 5-dihydroxybenzotrifluoride (12·5 g.), b. p. 104°/3 mm., identical with a specimen prepared by an alternative method (Part I, *loc. cit.*).

7-*Methoxy*-4-*methyl*-5-*trifluoromethylcoumarin.*—(*a*) A solution of 3 : 5-dihydroxybenzotrifluoride (5 g.) and ethyl acetoacetate (5 g.) in concentrated sulphuric acid (10 ml.) was kept at room temperature for 5 days, and the resultant golden-yellow solution poured on crushed ice (50 g.). The dried colourless, crystalline precipitate (3·5 g.) was fractionally crystallised from ethyl acetate. The first, sparingly soluble fraction (*ca.* 1 g.) separated from ethyl acetate in stout colourless needles of 7-*hydroxy*-4-*methyl*-5-*trifluoromethylcoumarin*, m. p. 273° (Found: C, 54·3; H, 3·2. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%). The substance was very readily soluble in methanol and ethanol with a blue fluorescence, gave no ferric reaction in alcohol, and dissolved in cold 2N-sodium hydroxide to furnish a colourless solution. Methylation of this coumarin in boiling acetone during 1 hour by methyl iodide–potassium carbonate gave a quantitative yield of 7-*methoxy*-4-*methyl*-5-*trifluoromethylcoumarin* which separated from methanol in long, slender, colourless prisms, m. p. 192° (Found: C, 55·4; H, 3·3; F, 21·7. $C_{12}H_9O_3F_3$ requires C, 55·8; H, 3·5; F, 22·1%).

The mother-liquors from the fractional crystallisation were evaporated to dryness and repeatedly extracted with hot benzene. Concentration of this benzene extract gave rise to 5-*hydroxy*-4-*methyl*-7-*trifluoromethylcoumarin* (*ca.* 1 g.) which separated from benzene or aqueous methanol in colourless plates, m. p. 251° (Found: C, 54·3; H, 3·4. $C_{11}H_7O_3F_3$ requires C, 54·1; H, 2·9%). The substance gives no ferric reaction in alcohol, is readily soluble in hot benzene, and dissolves in cold 2N-sodium hydroxide to give a bright yellow solution. The alcoholic solution exhibits a faint blue fluorescence. Methylation by the methyl iodide–potassium carbonate method during 1 hour gave a quantitative yield of 5-methoxy-4-methyl-7-trifluoromethylcoumarin which separated from aqueous methanol in colourless needles, m. p. 147° (mixed m. p. with the isomeric coumarin was about 135°) (Found: C, 55·4; H, 3·3; F, 21·7. $C_{12}H_9O_3F_3$ requires C, 55·8; H, 3·5; F, 22·1%).

(*b*) A solution of 3-hydroxy-5-methoxybenzotrifluoride (5 g.) and ethyl acetoacetate (5 g.) in concentrated sulphuric acid was kept at room temperature for 3 days and after isolation the colourless precipitate (1 g.) was fractionally crystallised from aqueous methanol to give a small quantity (*ca.* 0·2 g.) of 7-*methoxy*-4-*methyl*-5-*trifluoromethylcoumarin*, m. p. 192°, identical with a specimen prepared by method (*a*).

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