Reactions of Active Methylene Compounds. VIII. A New Route to 3-Alkyl-4-hydroxycoumarins

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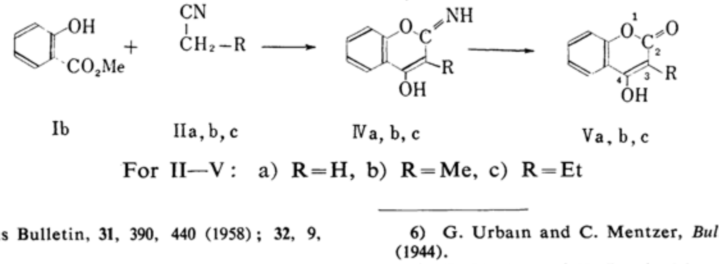
(Received July 16, 1962)

In previous papers[1], one of the present authors has reported the synthesis of 3-aryl-4-hydroxycoumarins by the ester condensation of methyl *o*-methoxy- or *o*-hydroxy-benzoate and phenylacetonitriles, followed by the ring closure of the condensation products. Now the method has been applied, with some modifications, to the synthesis of 3-alkyl-4-hydroxycoumarins (V).

For the preparation of 3-alkyl-4-hydroxycoumarins, several methods have hitherto been reported: (a) by the reaction of *o*-acetoxybenzoyl chlorides with ethyl alkylmalonates, alkylacetoacetates or alkylcyanoacetates, followed by hydrolysis[2], (b) by the ring closure of *o*-acyloxybenzoates[3], (c) by the reaction of alkyl *o*-hydroxyphenyl ketones with ethyl carbonate[4] or with carbon dioxide and potassium carbonate[5], and (d) by the reaction of phenols with ethyl alkylmalonates[6] or by the ring closure of phenyl alkylmalonates[7].

For the present paper the authors synthesized 3-alkyl-4-hydroxycoumarins (Va, b, c) by two similar routes. In one route, the ester condensation of methyl *o*-methoxybenzoate (Ia) and nitriles (IIa, b, c) gave α-(*o*-methoxybenzoyl)-nitriles (IIIa, b, c) in a good yield by a method analogous to that reported by Hauser et al.[8] for ester condensation; one mole of ester Ia was made to react with the sodio compound prepared from 2.5 mol. of sodium amide and 2 mol. of nitrile II in liquid ammonia. In this procedure, care was taken to prevent the formation of *o*-methoxybenzamide and the



For II—V: a) R=H, b) R=Me, c) R=Et

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[1] Y. Kawase, This Bulletin, **31**, 390, 440 (1958); **32**, 9, 11, (1959).

[2] R. Anschütz, *Ber.*, **36**, 465 (1903).

[3] H. Pauli and K. Lockemann, ibid., **48**, 32 (1915); M. A. Stahmann et al., *J. Am. Chem. Soc.*, **65**, 2285 (1943).

[4] J. Boyd and A. Robertson, *J. Chem. Soc.*, **1948**, 174.

[5] P. Da Re and E. Sandri, *Chem. Ber.*, **93**, 1085 (1960).

[6] G. Urbain and C. Mentzer, *Bull. Soc. Chim.*, **11**, 171 (1944).

[7] E. Ziegler and H. Junek, *Montatsh.*, **86**, 29 (1955).

[8] R. Levine and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 760 (1946); C. J. Eby and C. R. Hauser, ibid., **79**, 723 (1957).

self-condensation of the nitrile. On the other hand, only poorer yields were obtained by the method reported previously for phenylacetonitriles[1] in which sodium hydride was used in benzene. The nitriles III were then demethylated by anhydrous aluminum chloride in nitrobenzene to give 3-alkyl-4-hydroxycoumarin-2-imides (IVa, b, c), which were readily hydrolyzed by dilute hydrochloric acid to 3-alkyl-4-hydroxycoumarins (Va, b, c). The intermediate *o*-hydroxybenzoyl-acetonitrile (VI) was isolated in the case of *o*-methoxybenzoylacetonitrile (IIa).

By another route, the ester condensation of methyl salicylate (Ib) and nitriles IIa, b, c directly gave the imides IVa, b, c in a fairly good yield by means of sodium amide in liquid ammonia.

Attempted condensations of Ia or Ib and dinitriles (e. g., malono-, succino-, glutaro- and adipo-nitriles) failed, furnishing only the self-condensed products of nitriles.

Experimental*

o-Methoxybenzoylacetonitrile (IIIa). — *a) By Sodium Amide in Liquid Ammonia.*—A solution of acetonitrile IIa (3 g., 0.072 mol.) in an equal volume of anhydrous ether was stirred over a period of 5 min. into a solution of sodium amide in liquid ammonia (prepared from 2.1 g. (0.09 mol.) of sodium and 50 ml. of ammonia) and then cooled in dry ice-acetone. After 5 min., a solution of *o*-methoxybenzoate (Ia) (6 g., 0.036 mol.) in an equal volume of ether was added rapidly, and the stirring and cooling were continued for one hour The ammonia was then removed, and the residue was treated with ice water. The aqueous solution obtained was washed with ether, filtered and acidified with dilute hydrochloric acid. The crystalline product obtained was washed with aqueous sodium bicarbonate and then recrystallized from ethanol to give IIIa in the form of colorless needles; m. p., 86~87°C; yield, 5.3 g. (84%). The reported m. p. is 87°C[9].

Found: N, 8.28. Calcd. for $C_{10}H_9O_2N$: N, 8.00%.

b) By Sodium Hydride in Benzene.—A mixture of Ia (8.4 g., 0.05 mol.), sodium hydride (1.8 g., 0.075 mol.) and anhydrous benzene (100 ml.) was refluxed for 2 hr., and for a further 5 hr. after the addition of IIa (3.1 g., 0.075 mol.). The cooled mixture was treated with water, and the aqueous layer obtained was acidified with hydrochloric acid. The crystalline product formed was washed with aqueous sodium bicarbonate and recrystallized from ethanol; m. p., 84.5~85.5°C; yield, 2.4 g. (27.4%).

α-(o-Methoxybenzoyl)propionitrile (IIIb). —*a) By Sodium Amide.* — Ia (7.5 g., 0.045 mol.) was made to react in a manner similar to that described for IIIa, with the sodio compound prepared from 2.6 g. (0.11 mol.) of sodium and 5 g. (0.09 mol.) of propionitrile (IIb) in liquid ammonia; the oily product formed by acidifying the aqueous alkaline solution was taken up in ether. The ether solution was washed with aqueous sodium bicarbonate, the solvent was removed, and the residual product was distilled in a high vacuum to give IIIb as colorless oil; b. p., 100~150°C/0.003 mmHg; yield, 6.8 g. (80%). 2,4-Dinitrophenylhydrazone: yellow microcrystals; m. p., 167~168°C (from ethanol).

Found: C, 55.48; H, 4.20; N, 19.08. Calcd. for $C_{17}H_{15}O_5N_5$: C, 55.28; H, 4.09; N, 18.96%.

b) By Sodium Hydride.—By the same procedure, 4.5 g. (36.8%) of IIIb (b. p., 100~124°C/0.001 mmHg) were obtained from Ia (10.7 g., 0.065 mol.), sodium hydride (3.3 g., 0.13 mol.) and IIb (3.5 g., 0.065 mol.).

α-(o-Methoxybenzoyl)butyronitrile (IIIc). — *a) By Sodium Amide.*—By the same procedure, 1.4 g. (57%) of IIIc (a colorless oil; b. p., 150~160°C/0.0035 mmHg) were obtaind from sodium (0.7 g., 0.03 mol.), IIc (1.7 g., 0.024 mol.) and Ia (2 g., 0.012 mol.). 2,4-Dinitrophenylhydrazone: yellow microcrystals; m. p., 128~129°C (from ethanol).

Found: C, 56.41; H, 4.55; N, 18.56. Calcd. for $C_{18}H_{17}O_5N_5$: C, 56.39; H, 4.47; N, 18.27%.

b) By Sodium Hydride.—By the same procedure, 0.9 g. (35%) of IIIc was obtained from Ia (2.1 g., 0.0125 mol.), sodium hydride (0.6 g., 0.025 mol.) and IIc (0.9 g., 0.0125 mol.).

4-Hydroxycoumarin-2-imide (IVa). — *a) From Methyl Salicylate (Ib) and IIa.*—Ib (2.5 g., 0.0165 mol.) was made to react in a manner similar to that described for IIIa with the sodio compound prepared from 1.3 g. (0.058 mol.) of sodium and 1.4 g. (0.033 mol.) of IIa in liquid ammonia. The ammonia was removed, and the residue was treated with water; the aqueous solution was filtered, washed with ether, and warmed for a while. The crystalline product separated was collected and recrystallized from ethanol to give IVa as colorless needles (m. p. 275°C (decomp.)), which were soluble in dilute hydrochloric acid; yield, 1 g. (38%).

Found: C, 66.81; H, 4.43; N, 8.97. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38; N, 8.69%.

b) From IIIa.—Powdered anhydrous aluminum chloride (3 g.) was added to a solution of IIIa (1 g.) in nitrobenzene (10 ml.), and the mixture was heated on a steam-bath for 1.5 hr. The cooled solution was then treated with ice water, the nitrobenzene was removed by steam-distillation, and the residual product was dissolved in ethyl acetate. The ethyl acetate solution was washed with aqueous sodium bicarbonate and then extracted with aqueous sodium hydroxide. From the ethyl acetate solution, 0.2 g. (23%) of IVa was obtained (m. p., 272~273°C (decomp.), identical with the other sample). The crystals obtained by acidifying the sodium hydroxide solution were recrystallized from ethanol to give 0.1 g. of *o*-hydroxybenzoylacetonitrile (VI) as colorless microcrystals (m. p., 108~109°C), which gave a red ferric chloride reaction in ethanol.

Found: C, 66.90; H, 4.75; N, 8.32. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.38; N, 8.69%.

This VI was readily converted into IVa by warming its sodium hydroxide solution for a while.

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* Melting and boiling points are uncorrected.

[9] R. S. Long, *Chem. Abstr.*, **40**, 2634 (1946).

3-Methyl-4-hydroxycoumarin-2-imide (IVb). —*a) From Ib and IIb.*—By the same procedure, 5.9 g. (74.4%) of IVb were obtained from Ib (7 g., 0.046 mol.) and the sodio compound prepared from 3.7 g. (0.161 mol.) of sodium and 5.1 g. (0.092 mol.) of IIb in liquid ammonia (colorless microcrystals; m. p., 238~241°C (from dilute ethanol)).

Found: C, 68.47; H, 5.37; N, 7.93. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.00%.

b) From IIIb. — By the same procedure, 0.3 g. (37.7%) of IVb (m. p., 235~239°C) was obtained from 1 g. of IIIb.

3-Ethyl-4-hydroxycoumarin-2-imide (IVc). — *a) From Ib and IIc.*—By the same procedure, 0.6 g. (16.5%) of IVc was obtained from Ib (2.9 g., 0.019 mol.) and the sodio compound prepared from 1.5 g. (0.065 mol.) of sodium and 2.6 g. (0.038 mol.) of IIc in liquid ammonia (colorless microcrystals; m. p., 192~193.5°C (from dilute ethanol)).

Found: C, 69.39; H, 5.77; N, 7.80. Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40%.

b) From IIIc. — By the same procedure, 0.1 g. (21.5%) of IVc (m. p., 185~186°C) was obtained from IIIc (0.5 g.) and aluminum chloride (1.5 g.).

4-Hydroxycoumarin (Va). — *a) From IVa.* — A solution of IVa (0.5 g.) in 2 N hydrochloric acid (20 ml.) was heated on a steam-bath for 2 hr. The crystalline product separated from the cooled solution was recrystallized from dilute ethanol to give Va in the form of colorless needles; m. p., 208.5~209.5°C, identical with the authentic sample; yield, 0.3 g. (60%). The reported m. p. is 204~206°C[2] or 214~216°C[3].

Found: C, 66.61; H, 3.84. Calcd. for $C_9H_6O_3$: C, 66.67; H, 3.73%.

b) From IIIa.—Powdered anhydrous aluminum chloride (3 g.) was added to a solution of IIIa (1 g.) in nitrobenzene (10 ml.), and the mixture was heated on a steam-bath for 1.5 hr. The cooled solution was treated with ice water and hydrochloric acid, and the nitrobenzene was removed by steam-distillation. The crystalline product obtained from the cooled residue was recrystallized from ethanol; m. p., 205~207°C; yield, 0.5 g. (54.3%).

3-Methyl-4-hydroxycoumarin (Vb). — *a) From IVb.*—By the same procedure, 0.35 g. (70%) of Vb was obtained from IVb (0.5 g.); colorless crystals; m. p., 225~227°C (from dilute ethanol). The reported m. p. is 227~228°C[3] or 230°C[6].

Found: C, 68.10; H, 4.53. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.58%.

b) From IIIb.—By the same procedure, 0.4 g. (43%) of Vb was obtained from 1 g. of IIIb.

3-Ethyl-4-hydroxycoumarin (Vc).—*a) From IVc.*—By the same procedure, 0.2 g. (66.7%) of Vc was obtained from IVc (0.3 g.); colorless crystals; m. p., 157~158°C (from benzene). The reported m. p. is 155~156°C[3].

Found: C, 69.52; H, 5.25. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30%.

b) From IIIc. — By the same procedure, 0.2 g. (43%) of Vc (m. p., 156~157°C) was obtained from 0.5 g. of IIIc and 1.5 g. of aluminum chloride.

The authors are grateful to the members of the Faculty of Pharmacology of this University and to the members of the Faculty of Science of Osaka University for their microanalyses.

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