Reactions of Active Methylene Compounds. VII. Synthesis of Benzofuro[3', 2' : 3, 4]coumarins and 2-Phenylbenzo[b]-furans

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In previous papers[1] was reported the action of hydrohalogenic acids, of aluminum chloride and of pyridine hydrochloride on 2-methoxybenzoyl-phenylacetonitriles and related esters. The present paper describes the action of the same reagents on 2-methoxybenzoyl-2-methoxyphenylacetonitriles (Ia, b) and related esters (IIa, b) to give 2-hydroxyphenyl 2-methoxybenzyl ketones (IIIa, b), benzofuro[3', 2' 3, 4]-coumarins (IVa, b, b') and 2-phenylbenzo[*b*]-furans (Va, b', IX).

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[1] Y. Kawase, This Bulletin, 31, 390, 440 (1958); 32, 9, 11 (1959); *Experientia*, 14, 435 (1958).

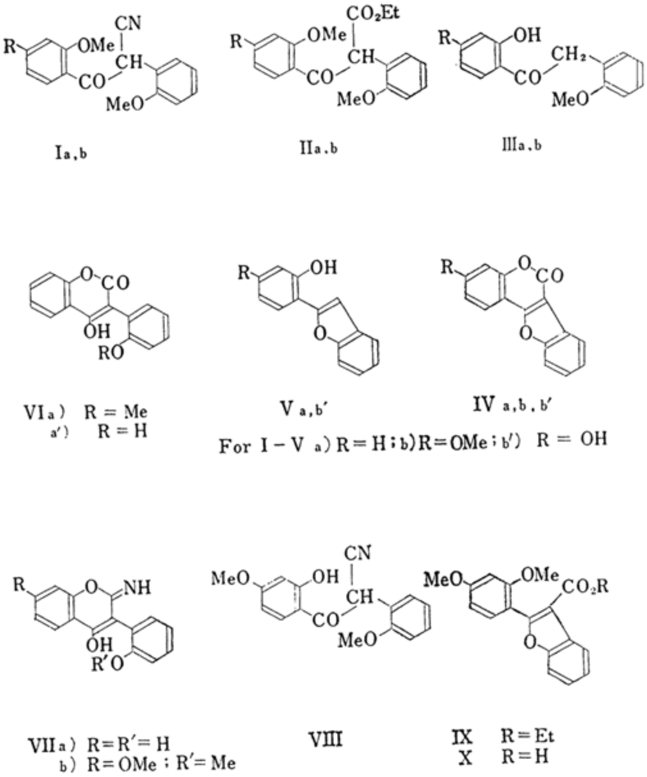

Chart 1

Recently, four derivatives of benzofurocoumarin (wedelolactone[2], coumestrol[3], erosnin[4] and psoralidin[5]) have been isolated from natural sources, and the synthesis of benzofurocoumarins has already been carried out by the action of hydrohalogenic acid, of pyridine hydrochloride, or of aniline hydrochloride on 3-(2-methoxyphenyl)-4-hydroxycoumarins[6] and on 2-methoxybenzoyl-2-methoxyphenylacetonitriles[7]. Also, the formation of 2-phenylbenzofurans has been achieved by the ring closure of 2'-methoxydeoxybenzoins[8] or ω-phenoxyacetophenones[9] and by the interaction of 2-hydroxybenzaldehyde with ethyl α-bromophenylacetates[10].

In the present experiments, benzofurocoumarins (IVa, b, b') were obtained from nitriles Ia, b by the action of hydrobromic or hydroiodic acid in acetic acid or of pyridine hydrochloride, and from esters IIa, b by the action of hydroiodic acid as the main product. It seems that in these cases the reagents cause first a cleavage of the methoxy group ortho to the carbonyl before that cleavage of the nitrile or ester group which forms the coumarin-ring. On the other hand, the action of hydrochloric acid on nitriles Ia, b or esters IIa, b gave deoxybenzoin derivatives, (IIIa, b), while that of hydrobromic acid or pyridine hydrochloride on esters IIa, b gave 2-phenylbenzofurans (Va, b'). In these cases the reagents cause first a cleavage of the nitrile or ester group, followed by that of the methoxy group, furnishing IIIa, b and Va, b' respectively. The action of aluminum chloride on nitrile Ia or ester IIa gave benzofurocoumarin (IVa) through each intermediate, 4-hydroxycoumarin-2-imide derivative (VIIa) or 4-hydroxycoumarin derivative (VIa), but that on nitrile Ib or ester IIb gave only partialy demethylated products,

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[2] T. R. Govindachari et al., *J. Chem. Soc.*, **1956**, 629; **1957**, 545.

[3] E. M. Bickoff et al., *J. Am. Chem. Soc.*, **80**, 3969 (1958).

[4] J. Eisenbeiss and H. Schmid, *Helv. Chim. Acta*, **42**, 61 (1959).

[5] P. C. Duttagupta et al., *Chem. and Ind.*, **1960**, 937.

[6] W. J. Bowyer et al., *J. Chem. Soc.*, **1957**, 542; T. R. Govindachari et al., ibid., **1957**, 548; O. H. Emerson and E. M. Bicoff, *J. Am. Chem. Soc.*, **80**, 4381 (1958); C. Deschamps-Vallet and C. Mentzer, *Compt. rend.*, **251**, 736 (1960).

[7] J. N. Chatterjea and S. K. Roy, *J. Indian Chem. Soc.*, **34**, 98 (1957); J. N. Chatterjea, ibid., **36**, 256 (1959); Y. Kawase, This Bulletin, **32**, 690 (1959).

[8] F. B. LaForge, *J. Am. Chem. Soc.*, **55**, 3040 (1933); W. B. Whalley and G. L. Lhoyd, *J. Chem. Soc.*, **1956**, 3213; M. Miyano and M. Matsui, *Chem. Ber.*, **91**, 2052 (1958); O. Dann et al., *Ann.*, **631**, 116 (1960).

[9] W. Davies and S. Middleton, *J. Chem. Soc.*, **1958**, 822.

[10] S. Kawai et al., *Ber.*, **72**, 1146 (1939).

TABLE I THE REACTION PRODUCTS

Reagent	Starting			
	Ia	Ib	IIa	IIb
HCl-AcOH	IIIa	IIIb	IIIa	IIIb
HBr-AcOH	IVa+IIIa	IVb+Vb'	Va	Vb'
HI-AcOH	IVa+VIa'	IVb'	IVa	IVb'
Pyridine-HCl	IVa+VIa'	IVb'	Va	Vb'
$AlCl_3$-$PhNO_2$	VIIa	VIII+VIIb	IVa+VIa	IX

2-hydroxy analog (VIII) of Ib and its ring-closed isomer 4-hydroxycoumarin-2-imide derivative (VIIb) or benzofuran-carboxylic ester derivative (IX) respectively, as is shown in Table I. The structures of VIa, a' and VIIa, b seem to be chromone derivatives, namely 2-hydroxy- and 2-amino-isoflavones respectively; the wave number of the carbonyl band is smaller than that of 4-hydroxycoumarins1), e. g., IVa.

Experimental*

Preparation of the Starting Materials.—*2-Methoxybenzoyl-2-methoxyphenylacetonitrile (Ia).*—To a solution of methyl 2-methoxybenzoate (4 g.) and 2-methoxyphenylacetonitrile (3.5 g.) in anhydrous benzene (50 ml.) was added sodium hydride (1 g. or 1.7 mol.), and the mixture was refluxed for 4 hr. on an oil-bath (95~100°C), most of the benzene having been distilled off in the meantime. The well-cooled mixture was treated with a little ethanol and then with water, and was extracted with ether. The aqueous layer was acidified, and the solid product formed was collected, washed with aqueous sodium bicarbonate and recrystallized from ethanol as colorless prisms, m. p. 107~108°C; yield 2.8 g. or 42%, IR 2247 (CN), 1681 cm^{-1} (CO). Reported m. p. is 112°C7).

Found: C, 72.92; H, 5.71; N, 5.11. Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98%.

Ethyl 2-Methoxybenzoyl-2-methoxyphenylacetate (IIa).—A solution of Ia (3.3 g.) in ethanol (50 ml.) containing one mole of water was saturated with dry hydrogen chloride, and was left at room temperature for 3 days. Water was added to the solution, and ethanol was removed in vacuo. The gummy product separated was dissolved in ethyl acetate, washed with aqueous sodium hydroxide, and then crystallized from dilute ethanol; m. p. 76~77°C, yield 2.2 g. or 57%, IR 1739 (ester), 1695 cm^{-1} (CO).

Found: C, 69.59; H, 6.42. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14%.

The prerparation of nitrile Ib and ester IIb has been described in a previous paper1).

Reaction with Hydrochloric Acid.—*Nitrile Ia to Give 2-Hydroxyphenyl 2-Methoxybenzyl Ketone (IIIa).* —A solution of Ia (0.5 g.) in acetic acid (10 ml.) containing concentrated hydrochloric acid (5 ml.) was heated on a steam-bath for 15 hr. The cooled solution was made alkaline with aqueous sodium hydroxide and was then extracted with ether. The residual product from the ether solution was distilled to give IIIa as colorless oil, b. p. 140~150°C/0.004 mmHg; yield 0.2 g. 2,4-Dinitrophenylhydrazone, m. p. 188~189°C (from ethanol).

Found (for 2,4-dinitrophenylhydrazone): C, 59.82; H, 4.26; N, 13.18. Calcd. for $C_{21}H_{18}O_6N_4$: C, 59.71; H, 4.30; N, 13.27%.

Ester IIa to Give IIIa.—A similar treatment of IIa (0.5 g.) in acetic acid (10 ml.) with hydrochloric acid (5 ml.) gave 0.2 g. of IIIa; 2,4-dinitrophenylhydrazone, m. p. 187~188°C.

Reaction with Hydrobromic Acid.—*Nitrile Ia to Give Benzofuro[3',2':3,4]coumarin (IVa) and IIIa.* —A solution of Ia (0.5 g.) in acetic acid (5 ml.) containing 48% hydrobromic acid (5 ml.) was refluxed on an oil-bath (140°C) for 3 hr. The cooled solution was diluted with water, made alkaline with aqueous sodium hydroxide, and then extracted with ether. The residual product from the ether solution was crystallized from methanol to give IVa as colorless needles, m. p. 180~180.5°C; yield 0.05 g., IR 1730 cm^{-1} (α-pyrone). Reported m. p. is 180~181°C7) or 181~182°C6).

Found: C, 76.29; H, 3.32. Calcd. for $C_{15}H_8O_3$: C, 76.27; H, 3.41%.

From the mother solution in the above-mentioned crystallization, 2,4-dinitrophenylhydrazone of IIIa was obtained by the action of dinitrophenylhydrazine sulfate; m. p. 190~191°C.

Nitrile Ib to Give 3-Methoxybenzofuro[3',2':3,4]-coumarin (IVb) and 2-(2,4-Dihydroxyphenyl)-benzo-[b]furan (Vb').—A similar treatment of Ib (0.5 g.) in acetic acid (5 ml.) with hydrobromic acid (5 ml.) gave IVb as slightly brown-colored needles, m. p. 192~193°C, 0.05g., from an alkali insoluble part through crystallization from ethanol.

Found: C, 72.32; H, 4.23. Calcd. for $C_{16}H_{10}O_4$: C, 72.18; H, 3.79%.

From a sodium hydroxide soluble part a small amount of Vb', m. p. 133~135°C (from benzene), was obtained through distillation; b. p. 180~200°C/ 0.004 mmHg, identical with the other sample.

Ester IIa to Give 2-(2-Hydroxyphenyl)-benzo[b]furan (Va).—A similar treatment of IIa (0.4 g.) in acetic acid (5 ml.) with hydrobromic acid (5 ml.) furnished Va, m. p. 93~94°C (form benzene), from an alkali insoluble part; yield 0.1 g. Reported m. p. is 95°C7), 95~98°C8) or 96~99°C8).

Found: C, 79.96; H, 4.87. Calcd. for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79%.

Ester IIb to Give Vb'.—A similar treatment of IIb (0.4 g.) in acetic acid (5 ml.) with hydrobromic acid (5 ml.) furnished Vb' as colorless needles,

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* Melting and boiling points are uncorrected, and infrared spectra are measured in Nujol.

m. p. 136~138°C (from benzene), from a sodium hydroxyde soluble part through distillation in vacuo, b. p. 180~210°C/0.004 mmHg, identical with the other sample; yield 0.1 g.

Reaction with Hydroiodic Acid.—*Nitrile Ia to Give IVa and 3-(2-Hydroxyphenyl)-4-hydroxycoumarin (VIa′).*—A mixture of Ia (0.5 g.), acetic acid (5 ml.), hydroiodic acid (d=1.7, 10 ml.) and acetic anhydride (5 ml.) was refluxed for 30 min. on an oil-bath (160°C) in a carbon dioxide atmosphere. The cooled solution was diluted with aqueous sodium bisulfite, made alkaline with aqueous sodium hydroxide, and then extracted with ether. From the ether extract, IVa (0.05 g.) was obtained; m. p. 176~177°C (from ethanol).

By acidifying the aqueous alkaline solution of the above-mentioned extraction, a small amount of VIa′ was obtained; m. p. 250°C (from dilute ethanol), identical with the other sample.

Nitrile Ib to Give 3-Hydroxybenzofuro[3′, 2′, : 3, 4]-coumarin (IVb′).—A similar treatment of Ib (1 g.) with hydroiodic acid (15 ml.) in acetic acid (7.5 ml.) and acetic anhydride (7.5 ml.) furnished IVb′ as slightly brown-colored microcrystals (from ethanol) from a sodium hydroxide soluble part; m. p. 273~274°C, identical with the other sample. Acetate, colorless needles (from ethyl acetate), m. p. 210~211°C, identical with the other sample.

Ester IIa to Give IVa.—A similar treatment of IIa (0.5 g.) with hydroiodic acid (10 ml.) in acetic acid (5 ml.) and acetic anhydride (5 ml.) furnished IVa, m. p. 177~178°C (from ethanol), from an alkali insoluble part; yield 0.1 g.

Ester IIb to Give IVb′.—A similar treatment of IIb (0.5 g.) furnished IVb′ as slightly brown-colored microcrystals, m. p. 274~275°C (from ethanol), identical with the other sample; yield 0.1 g.

Reaction with Pyridine Hydrochloride.—*Nitrile Ia to give IVa and VIa′.*—A mixture of Ia (0.5 g.) and anhydrous pyridine hydrochloride (2.5 g.) was refluxed for 40 min. on an oil-bath (220~230°C). Dilute hydrochloric acid was added to the cooled mixture, and the solution was warmed for several minutes on a steam-bath. The crystalline product formed on cooling was collected, washed with aqueous sodium hydroxide, and recrystallized from ethanol to give IVa, m. p. 176~177°C; yield 0.2 g.

By acidifying the alkaline solution in the above-mentioned washing, 0.1 g. of VIa′ was obtained as colorless microcrystals, m. p. 261~262°C (decomp.) (from ethanol), IR 3390, 3205 (OH), 1664 cm^{-1} (γ-pyrone). The reported m. p. is 253°C[6]

Found: C, 70.63; H, 4.17. Calcd. for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96%.

This VIa′ was converted into IVa, m. p. 179~180°C, by heating at 280°C for 2 hr. following the method of Govindachari's report[6].

Nitrile Ib to Give IVb′.—A similar treatment of Ib (0.5 g.) furnished IVb′ as slightly brown-colored microcrystals, m. p. 276~277°C (from ethanol); yield 0.2 g.

Found: C, 71.22; H, 3.34. Calcd. for $C_{15}H_8O_4$: C, 71.43; H, 3.20%.

Acetate was prepared by the pyridine-acetic anhydride method; colorless needles, m. p. 211~212°C (from ethyl acetate).

Found: C, 69.04; H, 3.17. Calcd. for $C_{17}H_{10}O_5$: C, 69.39; H, 3.43%.

Ester IIa to Give Va.—A similar treatment of IIa (0.4 g.) with pyridine hydrochloride (2 g.) furnished Va, m. p. 94~95°C (from benzene), from an alkali soluble part; yield 0.1 g.

Ester IIb to Give Vb′.—A similar treatment of IIb (0.4 g.) furnished Vb′ as colorless needles, m. p. 137~139°C (from benzene); yield 0.1 g.

Found: C, 73.95; H, 4.51. Calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46%.

Reaction with Aluminum Chloride.—*Nitrile Ia to Give 3-(2-Hydroyxphenyl)-4-hydroxycoumarin-2-imide (VIIa).*—A mixture of Ia (0.5 g.) and anhydrous aluminum chloride (0.5 g. or 2.1 mol.) in anhydrous nitrobenzene (5 ml.) was heated for 1 hr. on a steam-bath. The cooled solution was treated with water, and the nitrobenzene was removed by steam-distillation. The residual semi-solid product was taken up in ethyl acetate and washed with aqueous sodium carbonate and with aqueous sodium hydroxide. The product obtained from the ethyl acetate solution was crystallized from ethanol to give VIIa as colorless microcrystals, m. p. 230°C (decomp.), soluble in dilute hydrochloric acid; yield 0.1 g., IR 3571, 3333, 3077 (NH_2, OH), 1613 cm^{-1} (γ-pyrone).

Found: C, 70.92; H, 4.67; N, 5.43. Calcd. for $C_{15}H_{11}O_3N$: C, 71.15; H, 4.34; N, 5.53%.

This VIIa was converted into IVa, m. p. 178~179°C, by hydrolysis with dilute hydrochloric acid.

Nitrile Ib to Give 2-Hydroxy-4-methoxybenzoyl-2-methoxyphenylacetonitrile (VIII) and 3-(2-Methoxyphenyl)-7-methoxy-4-hydroxycoumarin-2-imide (VIIb).—A similar treatment of Ib (0.4 g.) with aluminum chloride (0.7 g. or 4 mol.) furnished VIII, m. p. 168~169°C (from ethanol), from a sodium hydroxide soluble part; yield 0.05 g., with a red ferric chloride reaction, IR 2247 (CN), 1608 cm^{-1} (CO).

Found: C, 68.50; H, 5.17. Calcd. for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.08%.

From an alkali insoluble part was obtained VIIb, m. p. 180~182°C (from dilute ethanol), soluble in dilute hydrochloric acid, with a negative ferric chloride reaction; IR 3450, 3250, 3120 (NH_2), 1655 cm^{-1} (γ-pyrone).

Found: C, 68.53; H, 4.82; N, 4.51. Calcd. for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.08; N, 4.71%.

This VIIb was also obtained from VIII by warming it with dilute aqueous sodium hydroxide for a while.

Ester IIa to Give IVa and 3-(2-Methoxyphenyl)-4-hydroxycoumarin (VIa).—A similar treatment of IIa (0.4 g.) with aluminum chloride (0.7 g. or 4 mol.) in nitrobenzene (5 ml.) furnished 0.1 g. of IVa, m. p. 175~176°C, from an alkali insoluble part, and 0.05 g. of VIa, m. p. 171~172°C (from ethanol), from a sodium carbonate soluble part. The reported melting point of VIa is 176°C[6].

Found (for VIa): C, 71.77; H, 4.91. Calcd. for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51%.

Ester IIb to Give Ethyl 2-(2, 4-Dimethoxyphenyl)-benzo[b]furan-3-carboxylate (IX).—A similar treatment of IIb (0.4 g.) with aluminum chloride (0.6 g. or 4 mol.) in nitrobenzene (5 ml.) furnished 0.1 g. of IX, m. p. 80~81°C (from ethanol), from an alkali insoluble part; IR 1718 cm^{-1} (ester).

Found: C, 70.01; H, 5.89. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56%.

This IX was converted into 2-(2, 4-dimethoxyphenyl)-benzofuran-3-carboxylic acid (X) by hydrolysis with aqueous sodium hydroxide; m. p. 214~216°C (decomp.) (from dilute ethanol), IR 1669 cm^{-1} (CO_2H).

Found: C, 68.05; H, 5.05. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73%.

This acid X was identical with the sample, m. p. 213~214°C (decomp.), prepared from IVb′ by methylation with dimethylsulfate and sodium hydroxide, followed by hydrolysis.

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