Reactions of Active Methylene Compounds. II. Ester Condensation of Methyl 2-Methoxybenzoate with Phenylacetonitrile, and of each Methoxy Substitute; a New Synthetic Route to 2-Hydroxyphenyl Benzyl Ketones

By Yoshiyuki KAWASE

(Received October 14, 1957)

In the synthesis of isoflavones, 2-hydroxyphenyl benzyl ketones (2-hydroxydeoxybenzoins) have often been used for the starting materials. The preparation of these ketones is usually carried out by the condensation of phenols with phenylacetonitriles (Hoesch reaction), or with phenylacetic acids (Nencki reaction), or with phenylacetyl chlorides (Friedel-Crafts reaction), and further by the rearrangement of phenyl phenylacetates (Fries reaction). The position of the acyl group entering in the phenol nucleus is restricted by the effects of substitutes, and in some cases another preparative method is desirable for this reason and others.

Here, a different route to make the ketones is studied, and the preparation of 2-hydroxyphenyl benzyl ketone and its methoxy substitutes (VII) is described, which involves ester condensation of methyl 2-methoxybenzoate with phenylacetonitrile and of each methoxy substitutes (I, II) followed by hydrolysis.

The ester condensation of unsubstituted methyl benzoate with unsubstituted phenylacetonitrile to produce benzoylphenylacetonitrile was reported long ago[1,2]. Concerning the condensation between substituted ones, however, only benzoyl-2-methoxyphenylacetonitrile was reported[3]. This reaction seems to be reversible, so it was carried out in benzene by distilling off, with the latter, the ethanol produced in the course of the reaction. 2-Methoxybenzoyl-phenylacetonitrile and its methoxy substitutes (IIIa, b, c, d) were obtained in good yield by means of sodium ethoxide or hydride. Ethyl 2-methoxybenzoyl-phenylacetate and its methoxy substitutes (IVa, b, c, d) were prepared from these nitriles by the action of hydrogen chloride in ethanol following the method similar to that reported for unsubstituted nitrile[2-4]. In the case of nitrile IIIa, 2-methoxybenzoyl-phenylacetamide (V) was obtained as by-product in poor yield. The nitriles III and the esters IV were hydrolized to the desired ketones VII by heating them with hydrochloric acid in acetic acid. In the case of hydrolysis of nitrile IIIa, the product was 2-methoxyphenyl benzyl ketone (VI), and 2-hydroxyphenyl benzyl ketone (VIIa) could be obtained under much more drastic conditions. On the other hand, hydrolysis of nitriles III by 10% aqueous sodium carbonate, and of esters IV by 10% aqueous sodium hydroxide, gave 2-methoxy- or 2,4-dimethoxybenzoic acid.

Experimental[5]

Preparation of the Nitriles III.—Sodium ethoxide prepared from $0.4\sim2.3$ g. of sodium and 20 cc. of absolute ethanol was dried up in vacuo at 150°. To a suspension of this dried sodium ethoxide in 100 cc. of absolute benzene, a mixture of methyl methoxybenzoate and phenylacetonitrile was added and heated at $95\sim100°$ on an oil-bath for four hours, during which most of benzene was driven off together with the ethanol produced. Water was added to the well-cooled residue and the mixture was extracted with ether. The gummy product separated by acidification of the aqueous layer was washed with aqueous sodium bicarbonate and then crystallized from ethanol. In some cases, sodium hydride was employed instead of dry sodium ethoxide. The following nitriles were prepared in this way unless otherwise noted.

2-Methoxybenzoyl-phenylacetonitrile (*IIIa*).—Colorless needles from dilute ethanol, m.p. $108\sim9°$;

---

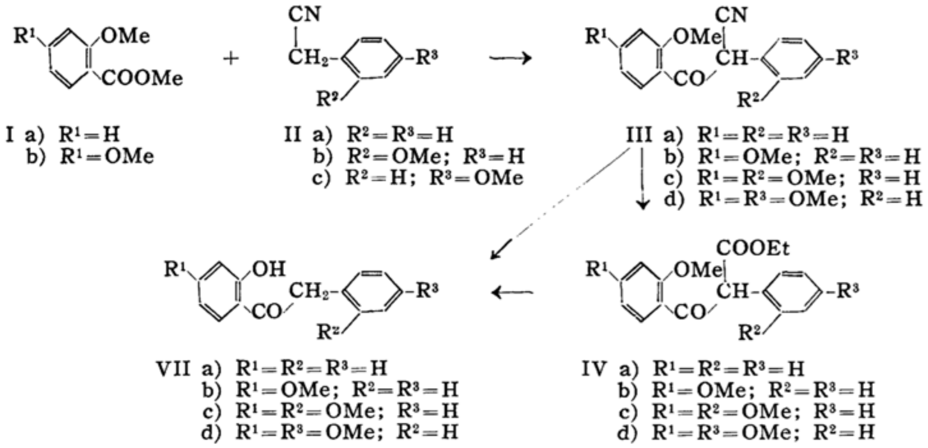
[1] R. Walther and P. G. Schickler, *J. prakt. Chem.*, (2) **55**, 308 (1897); F. Bodroux, *Bull. soc. chim.*, (4). **9**, 651 (1911); B. N. Ghosh, *J. Am. Chem. Soc.*, **109**, 117 (1916).

[2] W. Wislicenus, H. Eichert and M. Marquart, *Ann.*, **436**, 92 (1925); B. W. Howk and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 286 (1932).

[3] J. N. Chatterjea, *J. Indian Chem. Soc.*, **33**, 447 (1956).

[4] E. P. Kohler, *J. Am. Chem. Soc.*, **46**, 1743 (1924).

[5] Melting and boiling points are uncorrected.

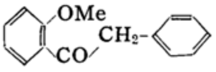

I a) $R^1=H$
b) $R^1=OMe$

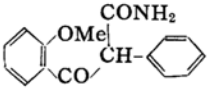
II a) $R^2=R^3=H$
b) $R^2=OMe$; $R^3=H$
c) $R^2=H$; $R^3=OMe$

III a) $R^1=R^2=R^3=H$
b) $R^1=OMe$; $R^2=R^3=H$
c) $R^1=R^2=OMe$; $R^3=H$
d) $R^1=R^3=OMe$; $R^2=H$

VII a) $R^1=R^2=R^3=H$
b) $R^1=OMe$; $R^2=R^3=H$
c) $R^1=R^2=OMe$; $R^3=H$
d) $R^1=R^3=OMe$; $R^2=H$

IV a) $R^1=R^2=R^3=H$
b) $R^1=OMe$; $R^2=R^3=H$
c) $R^1=R^2=OMe$; $R^3=H$
d) $R^1=R^3=OMe$; $R^2=H$


VI


V

TABLE

Product	from	reagent	reac. temp. and hr.	m.p. °C	yield %
IIIa	Ia+IIa	1 m. NaOEt	in EtOH, reflux, 4	108~9	8.
〃	〃	〃	in C_6H_6, distill., 4	〃	40.
〃	〃	2 m. NaOEt	〃	〃	70.
IIIb	Ib+IIa	1 m. NaOEt	〃	108~9	67.
〃	〃	2 m. NaH	〃	105~7	61.
IIIc	Ib+IIb	1.2 m. NaOEt	〃	114~5	42.5
〃	〃	1.7 m. NaH	〃	114~5.5	69.
IIId	Ib+IIc	1 m. NaOEt	〃	105~6	59.
IVa	IIIa	HCl—EtOH	room temp., 3 days	63~5	24.
IVa+V	〃	+1 m. H_2O	〃	67~8	56.2
IVb	IIIb	HCl—EtOH	〃	69~72	16.
〃	〃	+1 m. H_2O	〃	76~7	69.
IVc	IIIc	〃	〃	94~6	69.
IVd	IIId	〃	〃	48~50	43.5
VI	IIIa	AcOH—HCl	steam-bath, 15	oil	56.
VIIa	VI	AcOH—HBr	steam-bath, 10	56~7	61.
〃	〃	$AlCl_3$	steam-bath, 1	51~3	35.5
〃	IIIa	AcOH—HCl	steam-bath, 20	oil	47.5
〃	〃	AcOH—HBr	steam-bath, 10	53~5	34.
〃	IVa	AcOH—HCl	steam-bath, 15	oil	35.
VIIb	IIIb	〃	〃	86~7	46.5
〃	IVb	〃	〃	88~9	68.
VIIc	IIIc	〃	〃	90~1	43.
〃	IVc	〃	〃	88~9	39.5
VIId	IIId	〃	〃	100~0.5	38.
〃	IVd	〃	〃	99~100.5	33.

8.5 g. of the substance (70% yield) was obtained from 8 g. of methyl 2-methoxybenzoate (1 mole) and 5.7 g. of phenylacetonitrile (1 mole) by means of sodium ethoxide (prepared from 2.3 g. of sodium (2 moles)).

When one mole of sodium ethoxide was employed, the yield was lower (40%), and when the reaction was carried out in ethanol under reflux, the yield was poor (8%).

Anal. Found: C, 76.64; H, 5.02; N, 5.34. Calcd. for $C_{16}H_{13}O_2N$: C, 76.47; H, 5.22; N, 5.57%.

2,4-Dimethoxybenzoyl-phenylacetonitrile (IIIb).—Colorless needles, m.p. 108—9°; 8 g. of the compound (67% yield) was obtained from 8.4 g. of methyl 2,4-dimethoxybenzoate and 5 g. of phenylacetonitrile by means of sodium ethoxide (prepared from 1 g. of sodium (1 mole)).

Anal. Found: C, 72.29; H, 5.58; N, 4.74. Calcd. for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98%.

By the use of 0.5 g. of sodium hydride (2 moles), the yield was 1.75 g. (61%) from 2 g. of the ester and 1.2 g. of the nitrile, m.p. 105~7°.

2, 4 - Dimethoxybenzoyl - 2 - methoxyphenylacetonitrile (IIIc).—Colorless needles, m.p. 114~5°; 1.8 g. of the compound (42.5% yield) was obtained from 2.7 g. of methyl 2,4-dimethoxybenzoate and 2 g of 2-methoxyphenylacetonitrile by acting sodium. ethoxide (prepared from 0.4 g. of sodium (1.2 mole)).

Anal. Found: C, 70.11; H, 6.10; N, 5.09. Calcd. for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50%.

By the use of 0.8 g. of sodium hydride (1.7 mole), the yield was 4.2 g. (69%) from 3.8 g. of the ester and 3 g. of the nitrile, m.p. 114~5.5°.

2, 4 - Dimethoxybenzoyl - 4 - methoxyphenylacetonitrile (IIId).—Colorless needles, m.p. 105~6°; 7.8 g. of the compound (59% yield) was obtained from 8.5 g. of methyl 2,4-dimethoxybenzoate and 6.4 g. of 4-methoxyphenylacetonitrile by the use of sodium ethoxide (prepared from 1 g. of sodium (1 mole)).

Anal. Found: C, 69.54; H, 5.49; N, 4.52. Calcd. for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50%.

Preparation of the Esters IV.—A solution of 1.5~3 g. of nitrile III in 50 cc. of absolute ethanol containing one mole of water was saturated with dry hydrogen chloride, and the resulting solution was allowed to stand at room temperature for three days. Water was added to the solution and ethanol was driven off in vacuo. The gummy product separated was crystallized from dilute ethanol. When the ethanolysis of the nitrile was carried out without addition of water, the yield was lower. The following esters were prepared in this way.

Ethyl 2-Methoxybenzoyl-phenylacetate (IVa).—Colorless needles, m.p. 67~8°; 1 g. of the compound (56.2% yield) was obtained from 1.5 g. of nitrile IIIa. A small amount (0.1 g.) of insoluble material was obtained, which on crystallization from a large volume of methanol gave 2-methoxybenzoyl-phenylacetamide (V), colorless microcrystals, m.p. 186~7°.

Anal. of ester IVa. Found: C, 72.69; H, 6.20. Calcd. for $C_{18}H_{18}O_4$: C, 72,46; H, 6.08%.

Anal. of amide V. Found: C, 71.64; H, 5.53; N, 5.45. Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20%.

Ethyl 2, 4 - Dimethoxybenzoyl - phenylacetate (IVb).—Colorless needles, m.p. 76~7°; 1.6 g. of the compound (69% yield) was obtained from 2 g. of nitrile IIIb.

Anal. Found: C, 69.38; H, 6.16. Calcd. for $C_{19}H_{20}O_5$: C, 69.56; H, 6.14%.

Ethyl 2,4-Dimethoxybenzoyl - 2 - methoxyphenylacetate (IVc).—Colorless needles, m.p. 94~6°; 1.6 g. of the compound (69% yield) was obtained from 2 g. of nitrile IIIc.

Anal. Found: C, 67.57; H, 6.50. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19%.

Ethyl 2,4-Dimethoxybenzoyl - 4 - methoxyphenylacetate (IVd).—Colorless needles, m.p. 48~50°; 1.5 g. of the compound (43.5% yield) was obtained from 3 g. of nitrile IIId.

Anal. Found: C, 66.83; H, 6.48. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19%.

Preparation of the Hydroxyphenyl Benzyl Ketones VII.—A solution of 0.4~2 g. of nitrile III or ester IV in 10 cc. of acetic acid containing 5 cc. of concentrated hydrochloric acid was heated on a steam-bath for fifteen hours. After being cooled, the resulting solution was made alkaline with aqueous sodium hydroxide, and the oily product separated was extracted with ether. Ether was evaporated, and the residue was recrystallized from methanol or ethanol (in some cases after distillation in high vacuum). The following ketones were prepared in this way except the case of nitrile IIIa.

2-Hydroxyphenyl Benzyl Ketone (VIIa). — a) From nitrile IIIa.—(i) Via 2-methoxyphenyl benzyl ketone (VI).—The general procedure described before gave 2-methoxyphenyl benzyl ketone (VI) in faintly yellow colored oil, b.p. 130~140°/0.001 mm., yield 0.5 g. (56%) from 1 g. of nitrile IIIa; 2,4-dinitrophenylhydrazone, m.p. 163~4°. Reported b.p. of this ketone is 198~202°/14 mm.6).

Anal. of the hydrazone. Found: C, 61.83; H, 4.39; N, 11.25. Calcd. for $C_{21}H_{18}O_5N_4$: C, 62.06; H, 4.46; N, 13.79%.

A solution of 0.7 g. of this ketone in 8 cc. of acetic acid containing 2 cc. of 47% hydrobromic acid was heated on a steam-bath for ten hours. The resulting solution was treated as before to give ketone VIIa, colorless needles from ethanol, m.p. 56~7°, yield 0.4 g. (61%); 2,4-dinitrophenylhydrazone, m.p. 215~6° (from ethyl acetate). Reported m.p. of ketone VIIa and of its 2,4-dinitrophenylhydrazone are 60° and 219° respectively7).

Anal. of the ketone VIIa. Found: C, 78.99; H, 5.99. Calcd. for $C_{14}H_{12}O_2$: C, 79.22; H, 5.70%.

Anal. of the hydrazone. Found: C, 61.09; H, 4.41; N, 12.23. Calcd. for $C_{20}H_{16}O_5N_4$: C, 61.22; H, 4.11; N, 14.28%.

The demethylation of ketone VI was also carried out by heating 0.6 g. of the ketone with 1 g.

---

6) M. Tiffeneau et al., *Bull. soc. chim.*, **49**, 1757 (1931).

7) S. Skraup and O. Binder, *Ber.*, **62**, 1127 (1929); T. C. Chadha, H. S. Mahal and K. Venkataraman, *J. Chem. Soc.*, **1933**, 1459.

of anhydrous aluminum chloride in 5 cc. of nitrobenzene on steam-bath for one hour. M.p. 51~3°, yield 0.2 g. (35.5%).

(ii) By hydrochloric acid.—A solution of 1.5 g. of nitrile IIIa in 15 cc. of acetic acid containing 10 cc. of concentrated hydrochloric acid was heated for twenty hours with addition of 5 cc. of concentrated hydrochloric acid at the intermediate time. Faintly yellow colored oil, b.p. 150~5°/0.004 mm., yield 0.6 g. (47.5%); 2,4-dinitrophenylhydrazone, m.p. 214~5°.

(iii) By hydrobromic acid.—A solution of 0.7 g. of nitrile IIIa in 8 cc. acetic acid containing 2 cc. of 47% hydrobromic acid was heated for ten hours. Colorless needles, m.p. 53~5°, yield 0.2 g. (34%).

(*b*) *From ester IVa.*—Faintly yellow colored oil, b.p. 145~150°/0.001 mm.; 0.1 g. of the compound (35% yield) was obtained from 0.4 g. of ester IVa by general method, 2,4-dinitrophenylhydrazone, m.p. 217~8°.

2-Hydroxy-4-methoxyphenyl Benzyl Ketone (VIIb).—(*a*) *From nitrile IIIb.*—Colorless needles from methanol, m.p. 86~7°, b.p. 155~165°/0.001 mm. (one distillation); 0.8 g. of the compound (46.5% yield) was obtained from 2 g. of nitrile IIIb; identical with the authentic sample (reported m.p. 90°[8]).

Anal. Found: C, 74.09; H, 5.77. Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%.

(*b*) *From ester IVb.*—Colorless needles, m.p. 88~9°; 0.5 g. of the compound (68% yield) was obtained from 1 g. of ester IVb.

2-Hydroxy-4-methoxyphenyl 2-Methoxybenzyl Ketone (VIIc).—(*a*) *From nitrile IIIc.*—Colorless needles from ethanol, m.p. 90~1°, b.p. 180°/0.001 mm. (one distillation); 0.3 g. of the compound (43% yield) was obtained from 0.8 g. of nitrile IIIc. Reported m.p. of this ketone is 93~4°[9].

Anal. Found: C, 71.15; H, 6.40. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92%.

(*b*) *From ester IVc.*—Colorless needles, m.p. 88~9°, 0.15 g. of the compound (39.5% yield) was obtained from 0.5 g. of ester IVc.

2-Hydroxy-4-methoxyphenyl 4-Methoxybenzyl Ketone (VIId).—(*a*) *From nitrile IIId.*—Recrystallization from ethanol and then from benzene yielded colorless needles, m.p. 100~100.5°, b.p. 190°/0.001 mm. (one distillation); 0.5 g. of the compound (38% yield) was obtained from 1.5 g. of nitrile IIId. Reported m.p. of this ketone is 104°[10].

Anal. Found: C, 70.84; H, 6.48. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92%.

(*b*) *From ester IVd.*—Colorless needles, m.p. 99~100.5°; 0.2 g. of the compound (33% yield) was obtained from 0.8 g. of ester IVd.

The author wishes to express his hearty thanks to Professor K. Fukui for his helpful advice and encouragement, and to Professor Y. Yukawa of Osaka University for his valuable discussion during the course of this work, and to the members of the Agricultural Department of Kyoto University for microanalyses.

Faculty of Literature and Science
Toyama University
Toyama

---

[8] W. Baker and R. Robinson, ibid., **1929**, 160.

[9] P. K. Grover and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **38A**, 122 (1953); W. B. Whalley, *J. Chem. Soc.*, **1953**, 3366.

[10] F. Wessely and F. Lechner, *Monatsh.*, **57**, 395 (1931).