Synthetic Studies on the Benzofuran Derivatives. Part IV. A New Synthesis of Benzyl 2-Methoxyphenyl Ketones and a Synthesis of Benzyl 4-Methoxy-5-benzofuranyl Ketone (Benzyl O-Methyl-karanjyl Ketone)

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(Received April 16, 1958)

In the preceding paper[1] of this series, the preparation of furano (2′, 3′ : 7, 8)-2-methylisoflavone (I), m.p. 187~188°C, was described, but as mentioned already, the melting points of it and the related compounds were quite different from those of the compounds reported by Row et al.[2]

Now, to further confirm the structure of the expected benzyl 4-hydroxy-5-benzofuranyl ketone (benzyl karanjyl ketone) (II) which was obtained by alkaline hydrolysis[1] of I, a synthesis of II or its methyl ether III by a different method from that of Row et al. 's[2] was attempted; III was prepared by the interaction of 4-methoxy-5-benzofuranoyl chloride (*O*-methyl-karanjic acid chloride) (IV) and dibenzylcadmium.

The usual preparative methods of benzyl 2-hydroxyphenyl ketones are: a) the interaction of phenols with phenylacetonitriles or phenylacetic acids or phenylacetyl chlorides, according to the Hoesch, Nencki, and Friedel-Crafts reaction, respectively; b) the rearrangement of phenyl phenylacetates according to the Fries reaction. In these reactions, however, the position of the phenylacetyl group which enters into the phenol nucleus is restricted, and thus the preparation of the hydroxyketone II from 4-hydroxybenzofuran (karanjol) by these methods is unsuccessful[3].

A new synthetic route to benzyl 2-hydroxyphenyl ketones was recently reported by one of the authors[4], which involves the ester condensation of methyl 2-methoxybenzoates with phenylacetonitriles followed by hydrolysis. But an attempted synthesis, by this method, of II from methyl 4-methoxy-5-benzofuranoate (methyl *O*-methyl-karanjate) and phenylacetonitrile resulted in failure because of the abortive ester condensation.

The preparation of benzyl 2-methoxyphenyl ketones has been described by Tiffeneau et al.[5], but this method which involves the Grignard reaction and the Tiffeneau rearrangement is unfavorable in the present case.

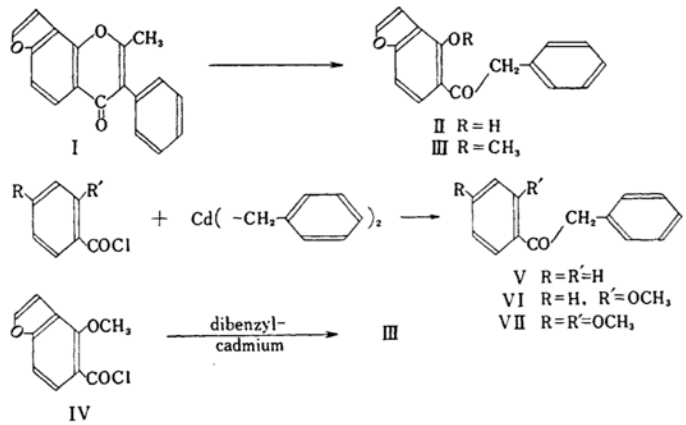
Therefore, another method of synthesis for benzyl 2-methoxyphenyl ketones was explored. By this means it was found that a reaction of 2-methoxybenzoyl chlorides with dibenzylcadmium in anhydrous benzene was feasible. A reaction of benzoyl chloride or 2-methoxybenzoyl chloride or 2,4-dimethoxybenzoyl chloride with dibenzylcadmium gave phenyl benzyl ketone (deoxybenzoin) (V), benzyl 2-methoxyphenyl ketone (VI), and benzyl 2,4-dimethoxyphenyl ketone (VII), respectively. A small amount of 1,2-diphenyl ethane was obtained as a by-product from the forerun of the distillates.

By the interaction of IV and dibenzylcadmium in anhydrous benzene, the desired methoxy-ketone (III) was obtained in colorless crystals, m.p. 63~63.5°C, which was identical with the sample reported in the preceding paper.

Experimental[6]

Phenyl Benzyl Ketone (Deoxybenzoin) (V). —The following reaction was carried out under a stream of dry nitrogen gas with stirring. To a solution of Grignard reagent prepared from 4.2 g. of freshly distilled benzyl bromide and 0.6 g. of magnesium in 100 cc. of anhydrous ether was carefully added 2.4 g. of powdered anhydrous cadmium chloride at room temperature, and the mixture was refluxed for 1 hr. Most of the ether was distilled off, 100 cc. of anhydrous benzene

1) Part III by T. Matsumoto, Y. Kawase, M. Nanbu and K. Fukui, This Bulletin, **31**, 688 (1958).
2) L. R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **34A**, 187 (1951); *Chem. Abstr.*, **47**, 12374 (1953).
3) B. L. Manjunath, A. Seetharamiah and S. Siddappa, *Ber.*, **72**, 93 (1939); S. H. Harper, *J. Chem. Soc.*, **1942**, 593; A. Seetharamiah, ibid., **1948**, 894.
4) Y. Kawase, This Bulletin, **31**, 390 (1958).
5) J. Lévy and R. Pernot, *Bull. soc. chim.*, **49**, 1730 (1931); M. Tiffeneau, A. Oryékhov and M. Roger, ibid., **49**, 1757 (1931).
6) Melting and boiling points are uncorrected.



was added, and the remaining ether was distilled off. Then a solution of 5 g. of benzoyl chloride in 50 cc. of anhydrous benzene was added slowly at room temperature, and the mixture was refluxed for ca. 4 hr. The cooled reaction mixture was shaken with 200 cc. of dilute sulfuric acid, the organic portion separated, washed with water, and then warmed with 5% aqueous sodium hydroxide with shaking for a while to decompose the excess of chloride. The benzene solution which had separated was washed with water, dried, and the solvent was distilled off. The residual oily product was distilled, b.p. 120~180°C/4 mm. (bath temperature); yield 2.3 g. A sample of V for analysis was obtained from a higher-boiling fraction by crystallization from ethanol in colorless needles, m.p. 52~53°C, which was identical with an authentic sample[7]. V which was contained in the distillate was confirmed through its 2,4-dinitrophenylhydrazone, m.p. 197~197.5°C, identical with an authentic sample, m.p. 197~198°C; reported b.p. 160°C/5 mm., m.p. 55~56°C[7] and m. p. of 2, 4-dinitrophenylhydrazone 202~204°C[8].

Anal. of V. Found: C, 85.41; H, 6.35. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16%.

From the mother liquor of 2,4-dinitrophenylhydrazone, 1,2-diphenylethane was obtained by distillation. Crystallization from ethanol gave colorless crystals, m.p. 51~52°C, which was identical with an authentic sample[9]; yield 0.4 g.; reported b.p. 158°C/10 mm. and m.p. 51°C[9].

Benzyl 2-Methoxyphenyl Ketone (VI).— By the procedure described before, dibenzylcadmium was prepared from 2.3 g. of cadmium chloride and benzylmagnesium bromide (from 3.5 g. of benzyl bromide and 0.5 g. of magnesium) in 100 cc. of anhydrous benzene. The reagent was allowed to react with a solution of 5 g. of 2-methoxybenzoyl chloride in 50 cc. of benzene; the chloride was prepared from 2-methoxybenzoic acid and excessive thionyl chloride, b.p. 145~146°C/25 mm. After the same treatment as described before, two fractions were obtained by distillation: (a) b.p. 90~150°C/4 mm., yield 0.5 g.; (b) b.p. 163~164°C/4 mm., yield 1.5 g. The lower boiling fraction became solid on standing, which on recrystallization from ethanol yielded a compound, m.p. 50~51°C, identical with an authentic sample of 1,2-diphenylethane. The higher boiling fraction which remained unsolidified consisted of VI, which was ascertained from its 2,4-dinitrophenylhydrazone, m.p. 162~163°C (from ethanol), identical with the other sample[4]. Reported boiling points of VI are 202~204°C/14 mm.[5], 198~202°C/14 mm.[5] and 130~131°C/0.001 mm.[4], and the melting point of the 2,4-dinitrophenylhydrazone 163~164°C[4].

Benzyl 2,4-Dimethoxyphenyl Ketone (VII).—The preparation followed the same method as in the above case. 2,4-Dimethoxybenzoyl chloride was employed in place of 2-methoxybenzoyl chloride; the chloride was prepared by heating an excess of thionyl chloride with 7 g. of 2,4-dimethoxybenzoic acid at 50° for twenty minutes, the excess of thionyl chloride removed in vacuo, and the crude chloride was used. The product was distilled at 160~180°C/4 mm. (bath temperature) to give colorless oil, yield 2 g., which was crystallized from ethanol in colorless needles, m.p. 46.5~47°C, identical with an authentic sample prepared by methylation of benzyl 2,4-dihydroxyphenyl ketone. The 2,4-dinitrophenylhydrazone, m.p. 194~195°C (from ethanol-ethyl acetate), was identical with an authentic sample; reported m.p. of VII 47~48°C[5].

Anal. of VII. Found: C, 74.90; H, 6.40. Calcd. for $C_{16}H_{16}O_3$: C, 74.96; H, 6.30%.

From the forerun in the case of the distillation (0.5 g.), 1,2-diphenylethane was obtained, m.p. 52~53°C.

Benzyl 4-Methoxy-5-benzofuranyl Ketone (III).— *O*-Methyl-karanjic acid (4-methoxy-5-benzofuranoic acid)[10] was prepared from karanjic

7) C. F. H. Allen and W. E. Barker, *Org. Synth.*, **Coll. Vol. II,** 156 (1943).
8) M. S. Newman and W. M. Edwards, *J. Am. Chem. Soc.*, **76**, 1840 (1954).
9) T. Reichstein and R. Oppenauer, *Helv. Chim. Acta*, **16**, 1377 (1933).
10) T. R. Seshadri and V. Venkateswalu, *Proc. Indian Acad. Sci.*, **13A**, 404 (1941), *Chem. Abstr.*, **35**, 7961 (1941); B. L. Manjunath and A. Seetharamiah, *J. Mysore Univ.*, **Sec. B. 2**, 3, 19 (1941), *Chem. Abstr.*, **36**, 1935 (1942).

acid[11] by refluxing it with dimethyl sulfate and potassium carbonate in acetone for 15 hr. The product was subjected to alkaline hydrolysis, and the acid obtained (3 g.) was warmed with excessive thionyl chloride at 50°C for 20 min., and the excessive thionyl chloride was removed in vacuo. Benzene (50 cc.) was added to the residue, and the traces of thionyl chloride, together with benzene, were removed by warming to dryness in vacuo. A solution of the crude chloride IV[10] in 50 cc. of anhydrous benzene was added to a suspension of dibenzylcadmium (prepared from 2 g. of cadmium chloride and benzylmagnesium bromide (from 2.7 g. of benzyl bromide and 0.4 g. of magnesium)) in 100 cc. of anhydrous benzene. After the same treatment as described before, the product was distilled at 150~180°C/0.003 mm. (bath temperature) to give colorless oil, yield 1.1 g., which was crystallized from ethanol in colorless crystals, m.p. 63~63.5°C, and identical with the sample reported in the preceding paper. It gave 2,4-dinitrophenylhydrazone of m.p. 227~228°C (from ethanol-ethyl acetate).

Anal. of III. Found: C, 76.23; H, 5.41. Calcd. for $C_{17}H_{14}O_3$: C, 76.66; H, 5.30%.

From the forerun in the case of the distillation (0.3 g.), 1,2-diphenylethane was obtained, m.p. 51~52°C.

We are grateful to the Institute of Agricultural Chemistry, Faculty of Agriculture, Kyoto University for microanalyses.

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11) R. T. Foster and A. Robertson, *J. Chem. Soc.*, **1948**, 115.