[Contribution from the Department of Organic Chemistry, Radium Institute, University of Paris]

5-(p-Chlorobenzyl)-2-hydroxybenzaldehyde and Some of Its Derivatives

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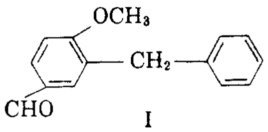
Received July 3, 1956

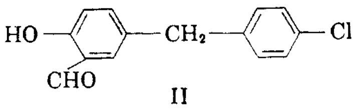
Salicylaldehyde is shown to undergo a zinc chloride-catalyzed reaction with p-chlorobenzyl chloride to give 5-(p-chlorobenzyl)-2-hydroxybenzaldehyde. The chemistry of this compound has been investigated, especially its use for the synthesis of a large number of coumarin and coumarone derivatives bearing a p-chlorobenzyl substituent, which were needed for biological studies. Similar arylalkylations of other aldehydes are described.

Friedel-Crafts alkylations or arylalkylations of aromatic aldehydes have hitherto met with little success. Gilman and Burtner,[1] for instance, obtained only very small amounts of the corresponding m-alkylbenzaldehydes in the reaction of isopropyl and *tert*-butyl chloride with benzaldehyde in the presence of aluminum chloride. The presence of phenolic groups, however, facilitates such reactions, and recently the present authors reported briefly[2] the preparation in high yields of 5-benzyl-2-hydroxybenzaldehyde from benzyl chloride and salicylaldehyde in the presence of zinc chloride. This work is now extended to other aldehydes as well as to substituted benzyl chlorides.

p-Hydroxybenzaldehyde could not be benzylated in this way, but, surprisingly, 3-benzyl-4-methoxybenzaldehyde (I) was readily obtained with anisaldehyde. Salicylaldehyde, on the other hand, reacted with p-chlorobenzyl chloride to give 5-(p-chlorobenzyl)-2-hydroxybenzaldehyde (II) in good yield; the constitution of this compound was established by a Kishner-Wolff reduction to the already known 4-(p-chlorobenzyl)-2-methylphenol.[3] Methylation afforded 5-(p-chlorobenzyl)-2-methoxybenzaldehyde, which could also be obtained, though in lower yield, by direct arylalkylation of o-methoxybenzaldehyde. It is possible that such Friedel-Crafts reactions are facilitated by the ability of the arylalkyl substituent to enter a position that is at the same time *meta* to the formyl radical and *para* to a hydroxy group, but more experimental evidence would be needed before this could be definitely proven. This type of condensation did not succeed, however, with more complex arylmethyl chlorides such as 2,4-dichlorobenzyl chloride and α-chloromethylnaphthalene, both of which failed to react with salicylaldehyde.

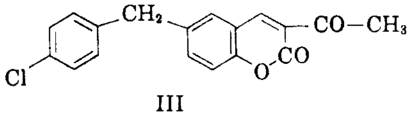


I

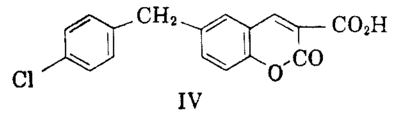


II

5 - (p - Chlorobenzyl) - 2 - hydroxybenzaldehyde proved a convenient intermediate for the synthesis of various coumarin and coumarone derivatives bearing a p-chlorobenzyl radical, which were required for testing for possible biological activities, such as spasmolytic or growth-regulating properties.[4] A piperidine-catalyzed Knoevenagel condensation[5] of this aldehyde with ethyl acetoacetate afforded 3-acetyl-6-(p-chlorobenzyl)coumarin (III), and a similar reaction with ethyl malonate[6] gave the ethyl ester of 6-(p-chlorobenzyl)-coumarin - 3 - carboxylic acid (IV). Another route to coumarins was the alkali-catalyzed condensation of 5-(p-chlorobenzyl)-2-methoxybenzaldehyde with arylacetonitriles, and conversion of the diarylacrylonitriles (V) thus obtained to 3-aryl-6-(p-chlorobenzyl)coumarins (VI) by demethylation with



III



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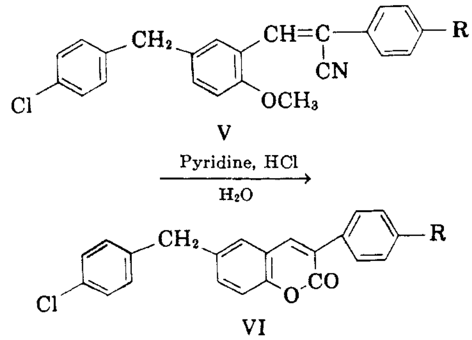

V

VI

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(1) Gilman and Burtner, *J. Am. Chem. Soc.*, **57**, 909 (1935).

(2) Buu-Hoï, Loc, and Xuong, *Compt. rend.*, **242**, 1331 (1956).

(3) Huston, *et al.*, *J. Am. Chem. Soc.*, **55**, 2146, 4639 (1933).

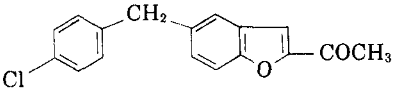
(4) *Cf.* Kuhn, *Naturwissenschaften*, **31**, 468 (1943); Veldstra and Havinga, *Enzymologia*, **11**, 373 (1945); Buu-Hoï, Royer, Lecocq, and Guettier, *Bull. soc. chim.*, **14**, 128 (1947).

(5) Knoevenagel, *Ber.*, **31**, 732 (1898).

(6) Knoevenagel, *Ber.*, **31**, 2610 (1898).

pyridine hydrochloride and hydrolysis of the coumarin-imines thus obtained.

The Rap-Stoermer condensation[7] of the potassium salt of 5-(*p*-chlorobenzyl)-2-hydroxybenzaldehyde with chloroacetone readily gave 2-acetyl-5-(*p*-chlorobenzyl)coumarone (VII). It is worth mention that several 2-acylcoumarones possess khellin-like activity.[8]



VII

Other compounds of biological interest, such as the tuberculostatic thiosemicarbazone of aldehyde I and the isonicotinylhydrazone of aldehyde II, were also prepared in the course of this work.

EXPERIMENTAL

3-Benzyl-4-methoxybenzaldehyde (I). A solution of 20 g. of anisaldehyde and 20 g. of benzyl chloride in dry chloroform was refluxed for 20 hours with 7.5 g. of finely powdered anhydrous zinc chloride. After cooling, water was added, and the organic layer was washed successively with dilute hydrochloric acid, water, aqueous sodium carbonate, and again water, then dried over sodium sulfate. The residue from distillation of the solvent was purified by vacuum-distillation, and was crystallized from petroleum ether in colorless needles, m.p. 66°. Yield, 11 g. A similar reaction with *p*-hydroxybenzaldehyde failed.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.5; H, 6.2.

The corresponding *isonicotinylhydrazone* crystallized from ethanol in colorless needles, m.p. 195°.

Anal. Calc'd for $C_{21}H_{19}N_3O_2$: N, 12.2. Found: N, 12.2.

The *thiosemicarbazone* crystallized from ethanol in fine, colorless prisms, m.p. 183°.

Anal. Calc'd for $C_{16}H_{17}N_3OS$: N, 14.1. Found: N, 14.0.

Condensation of equimolar amounts of this thiosemicarbazone and chloroacetic acid[9] in the presence of sodium acetate in ethanol gave in quantitative yield *the 4-keto-Δ^2-thiazolin-2-ylhydrazone* of 3-benzyl-4-methoxybenzaldehyde, crystallizing from acetic acid in silky, colorless needles, m.p. 249°.

Anal. Calc'd for $C_{18}H_{17}N_3O_2S$: N, 12.4. Found: N, 12.1.

5-(p-Chlorobenzyl)-2-hydroxybenzaldehyde (II). A solution of 80 g. of *p*-chlorobenzyl chloride and 60 g. of freshly redistilled salicylaldehyde in 400 ml. of chloroform was refluxed for 24 hours with 30 g. of zinc chloride. After addition of water, the chloroform layer was washed with dilute hydrochloric acid, then with water, dried over sodium sulfate, and the residue from distillation of the solvent was vacuum-fractionated. Yield, 65 g. of an aldehyde, b.p. 229–231°/20 mm., crystallizing from methanol in long colorless needles, m.p. 54°. Kishner-Wolff reduction[10] gave 4-(*p*-chlorobenzyl)-2-methylphenol.[3]

Anal. Calc'd for $C_{14}H_{11}ClO_2$: C, 68.2; H, 4.5. Found: C, 68.1; H, 4.4.

The corresponding *isonicotinylhydrazone* crystallized from ethanol in yellowish prisms, m.p. 183°.

Anal. Calc'd for $C_{20}H_{16}ClN_3O_2$: N, 11.5. Found: N, 11.8.

The *thiosemicarbazone* crystallized from ethanol in fine colorless prisms, m.p. 265–266°.

Anal. Calc'd for $C_{15}H_{14}ClN_3O\ S$: N, 13.1. Found: N, 13.4.

The *4-keto-Δ^2-thiazolin-2-ylhydrazone* crystallized from acetic acid in silky colorless needles, m.p. 290–292°.

Anal. Calc'd for $C_{17}H_{14}ClN_3O_2S$: N, 11.7. Found: N, 11.4

5-(p-Chlorobenzyl)-2-methoxybenzaldehyde was obtained by heating for 3 hours 12 g. of the foregoing aldehyde and 8 g. of methyl iodide in an ethanolic solution of 2.4 g. of sodium hydroxide. Yield, 11 g. of an aldehyde, b.p. 244–245°/20 mm., crystallizing from ethanol in shiny colorless prisms, m.p. 87°.

Anal. Calc'd for $C_{15}H_{13}ClO_2$: C, 69.1; H, 5.0. Found: C, 69.0; H, 5.1.

*2-Acetyl-5-(*p*-chlorobenzyl)coumarone* (VII). A solution of 5 g. of 5-(*p*-chlorobenzyl)-2-hydroxybenzaldehyde and 1.2 g. of potassium hydroxide in 20 ml. of ethanol was refluxed for 30 minutes with 1.8 g. of chloroacetone. After cooling, water was added, and the precipitate which formed after standing overnight was collected, washed with water, and recrystallized from ethanol. Yield, 4.7 g. of shiny colorless prisms, m.p. 105°.

Anal. Calc'd for $C_{17}H_{13}ClO_2$: C, 71.7; H, 4.6. Found: C, 71.4; H, 4.5.

3-Bromo-5-(p-chlorobenzyl)-2-hydroxybenzaldehyde. To a solution of 2.5 g. of aldehyde II in 10 ml. of acetic acid, 2 g. of bromine was added with stirring. The precipitate obtained on dilution with water was collected, washed with water, and crystallized from ethanol, giving shiny colorless prisms, m.p. 121°.

Anal. Calc'd for $C_{14}H_{10}BrClO_2$: C, 51.6; H, 3.1. Found: C, 51.3; H, 2.9.

The *isonicotinylhydrazone* crystallized from ethanol in fine yellowish prisms, m.p. 231°.

Anal. Calc'd for $C_{20}H_{15}BrClN_3O_2$: N, 9.4. Found: N, 9.3.

The *thiosemicarbazone* crystallized from acetic acid in yellowish needles, m.p. 264°.

Anal. Calc'd for $C_{15}H_{13}BrClN_3OS$: N, 10.5. Found: N, 10.2.

3-Acetyl-6-(p-chlorobenzyl)coumarin (III). A mixture of 4 g. of aldehyde II, 4 g. of ethyl acetoacetate, and 4 drops of piperidine was left to stand for one week at room temperature; a few ml. of ethanol then was added, and the solid obtained on scratching with a glass rod was collected and recrystallized from ethanol, giving 3.5 g. of shiny colorless needles, m.p. 175°.

Anal. Calc'd for $C_{18}H_{13}ClO_3$: C, 69.1; H, 4.2. Found: C, 69.4; H, 4.1.

Ethyl 6-(p-chlorobenzyl)coumarin-3-carboxylate. A mixture of 2.5 g. of aldehyde II, 2.4 g. of ethyl malonate, and 3 g. of piperidine was kept for 3 days at room temperature. The solid formed gave on recrystallization from ethanol 3.5 g. of fine, colorless prisms, m.p. 136°.

Anal. Calc'd for $C_{19}H_{15}ClO_4$: C, 66.6; H, 4.4. Found: C, 66.9; H, 4.6.

6-(p-Chlorobenzyl)coumarin-3-carboxylic acid (IV). This compound, obtained on saponification of 3 g. of the foregoing ester with 0.8 g. of potassium hydroxide in aqueous ethanol, and subsequent acidification with hydrochloric acid, crystallized from ethanol in shiny colorless prisms, m.p. 217°. Yield: 2 g.

Anal. Calc'd for $C_{17}H_{11}ClO_4$: C, 64.9; H, 3.5. Found: C, 64.9; H, 3.3.

1-Phenyl-2-(5-p-chlorobenzyl-2-methoxyphenyl)acrylonitrile (V; R = H). To a warm solution of 5 g. of 5-(*p*-chlorobenzyl)-2-methoxybenzaldehyde and 5 g. of benzyl cyanide in ethanol, a few drops of 25% aqueous sodium hydroxide were added with shaking. The mixture was left overnight at

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[7] Rap, *Gazz. chim. ital.*, **25**, II, 285 (1895); Stoermer, *Ann.*, 312, 333 (1900); Bisagni, Buu-Hoï, and Royer, *J. Chem. Soc.*, 3688 (1955).

[8] Buu-Hoï, Royer, Bisagni, and Routier, Unpublished results.

[9] *Cf.* Buu-Hoï, Xuong, and Binon, *J. Chem. Soc.*, 713 (1956).

[10] *Cf.* Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

room temperature, then poured in water. The precipitated oil solidified slowly, and was recrystallized from ethanol. Yield, 7 g. of silky, pale yellow needles, m.p. 87°.

Anal. Calc'd for $C_{23}H_{18}ClNO$: C, 76.8; H, 5.0. Found: C, 76.7; H, 5.2.

6-(p-Chlorobenzyl)-3-phenylcoumarin (VI; R = H). A mixture of 5 g. of the foregoing acrylonitrile and 50 g. of redistilled pyridine hydrochloride was refluxed for 15 minutes. Dilute hydrochloric acid was added after cooling, and the precipitate which formed was crystallized from ethanol. Yield, 3 g. of shiny colorless prisms, m.p. 99°.

Anal. Calc'd for $C_{22}H_{15}ClO_2$: C, 76.2; H, 4.3. Found: C, 76.4; H, 4.6.

1-p-Chlorophenyl-2-(5-p-chlorobenzyl-2-methoxyphenyl)-acrylonitrile (V; R = Cl) was prepared similarly from *p*-chlorobenzyl cyanide. This compound crystallized from ethanol in pale yellow needles, m.p. 124°.

Anal. Calc'd for $C_{23}H_{17}Cl_2NO$: C, 70.0; H, 4.3. Found: C, 69.6; H, 4.2.

6-(p-Chlorobenzyl)-3-p-chlorophenylcoumarin (VI; R = Cl) was recrystallized from ethanol in shiny colorless prisms, m.p. 130°.

Anal. Calc'd for $C_{22}H_{14}Cl_2O_2$: C, 69.3; H, 3.7. Found: C, 69.1; H, 4.0.

1-p-Bromophenyl-2-(5-p-chlorobenzyl-2-methoxyphenyl)-acrylonitrile (V; R = Br), prepared from *p*-bromobenzyl cyanide, crystallized from ethanol in fine yellowish prisms, m.p. 133°.

Anal. Calc'd for $C_{23}H_{17}BrClNO$. C, 62.9; H, 3.9. Found: C, 62.6; H, 3.9.

6-(p-Chlorobenzyl)-3-p-bromophenylcoumarin (VI; R = Br) crystallized from ethanol in shiny colorless needles, m.p. 146°.

Anal. Calc'd for $C_{22}H_{14}BrClO_2$: C, 62.0; H, 3.3. Found: C, 62.3; H, 3.6.

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