

accord with the conception that the mercury atom is so large that it absorbs much of the electron "pull" of the radical which otherwise would be more pronouncedly imparted to the -CN bond. The wide range of pK variation in the case of the amines is in agreement with the fact that the nitrogen atom, through which the effect of the radical is transmitted, is small.

Summary

1. It is shown that the cleavage of -CN from

RHgCN by hydrochloric acid in ethanol is reversible.

2. Equilibrium constants at 25° have been determined for this reaction in the case of the radicals cyclohexyl, ethyl, benzyl, 2-chlorobenzyl, *p*-tolyl, phenyl and alpha-naphthyl.

3. The equilibrium constants vary from radical to radical.

4. The order of the radicals is that previously established for other reversible processes.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

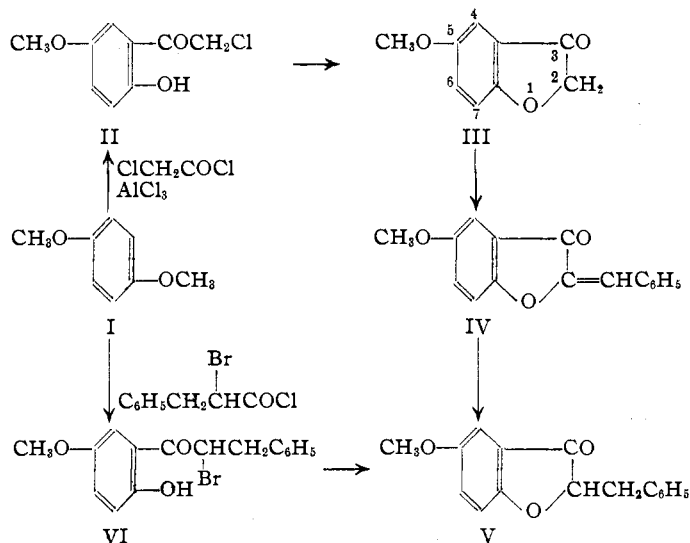
Derivatives of Coumaran. I. 2-Benzyl-5(and 6)-methoxycoumaran-3-one

BY R. L. SHRINER AND R. E. DAMSCHRODER

The synthesis of coumaran derivatives is of interest as bearing on the problem of the structure of certain naturally occurring substances, such as tectorigenin, which may be a substituted coumaran-3-one¹ or an isoflavone,² quebracho tannin, which may be a substituted coumaran-3-ol³ or a flavpinacol.⁴ Rotenone⁵ contains a coumaran nucleus with an unsaturated side chain in one portion of its structure.

aldehydes.⁶ If these unsaturated ketones could be reduced readily at the double bond, a useful method for the synthesis of coumaran-3-ones substituted in the 2-position would be available. The reduction of benzalcoumaranones has been reported in which platinum was used as the catalyst⁷ but Freudenberg⁸ found that side reactions occurred with platinum as the catalyst and hence used nickel on kieselguhr.

The present paper is concerned with the catalytic reduction of 2-benzal-5-methoxycoumaran-3-one IV, which was prepared by the method of von Auwers and Pohl.⁹ Hydroquinone dimethyl ether (I), chloroacetyl chloride and aluminum chloride yielded ω -chloro-2-hydroxy-5-methoxyacetophenone (II). The latter underwent ring closure upon treatment with alcoholic sodium acetate and the resulting 5-methoxycoumaran-3-one (III) was then condensed with benzaldehyde to yield IV. It was found that, in glacial acetic acid solution, the latter was reduced readily by platinum and hydrogen to the saturated ketone (V). An independent synthesis of V was carried out not only to establish the fact that reduction occurred as indicated



Since coumaran-3-ones contain active methylene groups, they readily condense with aromatic

(1) Shibata, *J. Pharm. Soc. Japan*, **47**, 380 (1927).

(2) Asahina, Shibata and Ogawa, *ibid.*, **48**, 1087 (1928).

(3) Nuñez, *Anales asoc. quím. argentina*, **24**, 159 (1936).

(4) Russell, *Chem. Rev.*, **17**, 155 (1935).

(5) La Forge, Haller and Smith, *ibid.*, **12**, 181 (1933).

(6) Kesselkaul and von Kostanecki, *Ber.*, **29**, 1890 (1896); Mameli, *Gazz. chim. ital.*, **52**, I, 322 (1922); Feist and Siebenlist, *Arch. Pharm.*, **265**, 196 (1927).

(7) Drumm, MacMahon and Ryan, *Proc. Roy. Irish Acad.*, **36B**, 149 (1924); Bargellini and Monti, *Gazz. chim. ital.*, **44**, II, 33 (1914).

(8) Freudenberg, Fikentscher and Harder, *Ann.*, **441**, 157 (1925).

(9) Von Auwers and Pohl, *ibid.*, **405**, 243 (1914); *Ber.*, **48**, 85 (1915).

but also to compare this method of synthesis with the two-step method of preparing 2-substituted coumaran-3-ones by ring closure of *o*-hydroxyaryl α -haloalkyl ketones.

Hydroquinone dimethyl ether (I) was treated with α -bromo- β -phenylpropionyl chloride in the presence of aluminum chloride. The mixture was heated for ten to twelve hours to cause cleavage of the adjacent methoxyl group in order to obtain the compound VI. Treatment of the latter with alcoholic sodium acetate produced 2-benzyl-5-methoxycoumaran-3-one. A mixed melting point of the product of this reaction with that obtained by catalytic reduction of IV showed no depression. The synthesis of 2-benzyl-6-methoxycoumaran-3-one was also carried out by both methods using resorcinol dimethyl ether as the starting material. In both cases the yields of product by the first method were better than those obtained by the second even though several additional steps are involved in the preparation of the benzalcoumaranones.

The possibility of the direct alkylation of the coumaranone (III) to the substituted benzylcoumaranone (V) by treatment of III with sodium ethoxide and benzyl chloride was also investigated. None of the 2-benzyl-5-methoxycoumaran-3-one could be isolated, the chief product being a bimolecular condensation product from two moles of the coumaranone.

Experimental

2-Benzal-5-methoxycoumaran-3-one.—A 75% yield of this derivative melting at 109–110° (corr.) was obtained by following the procedure described by von Auwers and Pohl.⁹

2-Benzyl-5-methoxycoumaran-3-one.—A solution of 6.3 g. of 2-benzal-5-methoxycoumaran-3-one in 200 cc. of glacial acetic acid was reduced with hydrogen at a pressure of 2 to 3 atmospheres in the presence of platinum oxide catalyst.¹⁰

The yellow solution became colorless in ten minutes, at which time the theoretical amount of hydrogen had been absorbed. The reduction mixture was filtered and the clear filtrate was poured into 600 cc. of cold water. The rather gummy precipitate solidified on standing and was removed by filtration. It was crystallized from ethanol. The yield of white needles melting at 76–77° (corr.) was 4.2 g. or 66% of the theoretical.

Anal. Calcd. for C₁₆H₁₄O₃: C, 75.56; H, 5.53. Found: C, 75.59; H, 5.68.

2-Benzal-6-methoxycoumaran-3-one.—A 70% yield of this compound was obtained from 6-methoxycoumaran-3-

one and benzaldehyde. It melted at 144–145° (corr.), which checked the value of von Auwers.⁷

2-Benzyl-6-methoxycoumaran-3-one.—Exactly the same procedure described for the above 5-methoxy derivative was followed. A 69% yield of white needles melting at 92–93° (corr.) was obtained.

Anal. Calcd. for C₁₈H₁₆O₃: C, 75.56; H, 5.53. Found: C, 75.33; H, 5.74.

α -Bromo- β -phenylpropionyl Chloride.—A mixture of 110 g. of hydrocinnamic acid and 200 g. of thionyl chloride was heated at 60° for ten hours. Fractional distillation gave an 85% yield of β -phenylpropionyl chloride boiling at 115–118° at 16–17 mm.

One hundred twelve grams of bromine was dropped into 104 g. of β -phenylpropionyl chloride at a temperature of 65 to 70° over a period of three hours. The mixture was stirred during the addition of the bromine and for eight hours longer. The light red fuming liquid was distilled *in vacuo*, the fraction boiling at 113–115° at 5 mm. being α -bromo- β -phenylpropionyl chloride. Redistillation gave 114 g. of a clear colorless liquid with the following constants: d_{20}^{20} 1.5538; n_D^{20} 1.5768; M_D calcd., 52.8; found, 52.7.

This compound had been prepared previously by Fischer,¹¹ who recorded a boiling point of 132–133° at 12 mm. α -Bromo- β -phenylpropionamide was prepared as a derivative and found to melt at 126–127°, which checked that recorded in the literature.⁷

It may be mentioned that it is necessary to convert the hydrocinnamic acid into the acid chloride before bromination. Bromination by the modified Hell-Volhard-Zelinsky method¹² yields a considerable amount of the β -bromo derivative which loses hydrogen bromide during the distillation.

2-Benzyl-5-methoxycoumaran-3-one.—To a vigorously stirred cold solution of 6.9 g. of hydroquinone dimethyl ether and 12.35 g. of α -bromo- β -phenylpropionyl chloride in 40 cc. of carbon disulfide, 7 g. of aluminum chloride was added fractionally over a period of one hour. The reaction mixture was then warmed on an oil-bath until the carbon disulfide refluxed gently. After eight to ten hours the stirrer was stopped, but heating was continued for ten to twelve hours longer.

The carbon disulfide was removed by distillation and the dark brown residue was decomposed in the reaction flask by adding cautiously a warm dilute hydrochloric acid solution. A brown oil separated and was extracted with ether and dried over sodium sulfate. Removal of the ether by distillation left an oil which could not be crystallized. Repeated attempts to crystallize this from methanol failed. When subjected to distillation at 6 mm. decomposition took place. A solution of 8 g. of the oil and 10 g. of sodium acetate in 100 cc. of ethanol was boiled under reflux for ten hours. The dark red solution was poured into 400 cc. of water and the resulting brown oil extracted with ether. The ether solution was dried over sodium sulfate and the ether distilled. The oil so obtained distilled at about 200° under 4 mm. pressure with decomposition. The yellow oily distillate was dissolved in a

(11) Fischer, *Ber.*, **37**, 3062 (1904).

(12) Clarke and Taylor, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, 1932, p. 452.

(12) Clarke and Taylor, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, New York, 1932, p. 108.

small amount of hot ethanol. When cooled a yellow crystalline mass appeared. Repeated recrystallizations gave 1 g. of white needles melting at 76-77°. A mixed melting point with 2-benzyl-5-methoxycoumaran-3-one prepared by reduction of the benzal compound showed no depression.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.56; H, 5.53. Found: C, 75.50; H, 5.46.

2-Benzyl-6-methoxycoumaran-3-one.—The Friedel-Crafts reaction using resorcinol dimethyl ether and α -bromo- β -phenylpropionyl chloride proceeded exactly as that described for the hydroquinone dimethyl ether.

After the treatment with sodium acetate the mixture was poured into water and allowed to stand for four days. At the end of this time the oil had partially crystallized. The solid was removed by filtration and dissolved in hot ethanol. By very slow cooling the oil which came out first was allowed to settle and the solution decanted. Final cooling of the decanted solution in an ice-salt mixture caused a light yellow precipitate to form. This was recrystallized from ethanol again to gleaming white plates which melted at 92-93.5°. The yield of pure product was 1.1 g.

A mixed melting point with 2-benzyl-6-methoxycoumaran-3-one prepared by reduction of the corresponding benzal compound showed no depression.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.56; H, 5.53. Found: C, 75.39; H, 5.40.

Summary

The catalytic reduction of 2-benzal-5 (and 6)-methoxycoumaran-3-one to 2-benzyl-5 (and 6)-methoxycoumaran-3-one furnishes a better method for the synthesis of 2-substituted coumaran-3-ones than the Friedel-Crafts reaction in which hydroquinone dimethyl ether or resorcinol dimethyl ether is treated with α -bromo- β -phenylpropionyl chloride and aluminum chloride followed by ring closure of the resulting ω -chloro-2-hydroxy-5 (and 4)-methoxyacetophenones.

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N-Aralkylmorpholines¹

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Introduction

It has been shown previously that the introduction of the morpholine ring into a series of known local anesthetics does not destroy nor greatly alter the anesthetic activity. Gardner and co-workers² and Leffler and Brill³ have substituted the morpholine ring for the dialkylamino group of the procaine series and the first-mentioned authors later⁴ have extended this work to the "Nupercaine" type. In all of these cases, however, the anesthesia found was not due fundamentally to the morpholine structure, since the simple dialkylamino analogs are, of course, also local anesthetics. On the other hand, in the work now being described, N-benzylmorpholines were found to be local anesthetics, while corresponding N-benzyl-diethylamines showed no anesthetic effect.

The N-aralkylmorpholines were prepared in good yields by condensing the desired aralkyl halide with either morpholine or 2,6-dimethylmorpholine. The aminoaralkylmorpholines were,

(1) Presented before the Medicinal Division of the American Chemical Society at Rochester, N. Y., September 10, 1937.

(2) Gardner and co-workers, *THIS JOURNAL*, **53**, 2763 (1931); *ibid.*, **55**, 2999 (1933).

(3) Leffler and Brill, *ibid.*, **55**, 365 (1933).

(4) Gardner and Hammel, *ibid.*, **58**, 1360 (1936).

in general, conveniently formed by an iron-water reduction of the intermediate nitro compounds.

An interesting cleavage reaction occurred when an attempt was made to brominate *p*-amino-benzylmorpholine. Bromine-laden air led into an aqueous solution of the base at room temperature gave a practically quantitative yield of 2,4,6-tribromoaniline. This, however, is not entirely unexpected, in view of the general weakness of the benzyl linkage and its ease of hydrolysis by acid reagents. Bromination first would be expected to give *p*-amino-*m,m*-dibromobenzylmorpholine (I) which by further bromination and subsequent hydrolysis could yield the intermediate (II), 4-amino-3,5-dibromobenzoic acid, as postulated below. This acid previously has

