Experimental[4]

***o*-Bromobenzoyldurene.**—A mixture of 1.02 g. of *o*-bromobenzoyldurene and 5 ml. of 4.7 *N* potassium methoxide was heated under reflux for one hour. The rate of precipitation of potassium bromide indicated that reaction was rapid and was complete at the end of 15 minutes. The reaction mixture was cooled and diluted with 30 ml. of water. The crude *o*-methoxybenzoyldurene, isolated by filtration, weighed 0.81 g. (95%) and melted at 122–125°. After two recrystallizations from ethanol it melted at 125–126°.

Anal.[5] Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.60; H, 7.70.

Acidification of the filtrate with 3 ml. of glacial acetic acid precipitated 0.023 g. of a compound melting at 93–96°. A mixture with an authentic specimen of *o*-hydroxybenzoyldurene melted at 94–97°.

Volumetric determination of bromide ion showed that 99.1% of the bromine in the original sample had been displaced. Similarly it was found that, when 1.08 g. of *o*-bromobenzoyldurene was heated for five hours with a 2.3 *N* solution of potassium methoxide only 16% of the halogen was displaced.

When a mixture of 110 g. of *o*-bromobenzoyldurene, 152 g. of solid sodium methoxide and 460 ml. of methanol was heated under reflux, *o*-methoxybenzoyldurene was obtained in an 80% yield.

Heating 3.0 g. of the methoxybenzoyldurene with a solution of 8 ml. of glacial acetic acid and 6 ml. of 48% hydrobromic acid under reflux for two hours caused the separation of an oil, which crystallized on cooling.[6] When the mixture was poured into 100 ml. of water, 2.8 g. (97%) of a white solid was isolated. After recrystallization from petroleum ether (b.p. 45–60°) it melted at 100–101.5°. A mixture with an authentic specimen of *o*-hydroxybenzoyldurene melted at 100–101°. The infrared spectra of the two samples are identical, and the absorption band at 1624 cm.$^{-1}$ indicates that the molecule is strongly hydrogen-bonded.

o-Bromobenzoyldurene was prepared in a yield of 75% by slowly adding a solution of 16 g. (0.12 mole) of durene in 40 ml. of carbon disulfide to a mixture of 22 g. (0.10 mole) of *o*-bromobenzoyl chloride, 4.6 g. (0.11 mole) of aluminum chloride and 50 ml. of carbon disulfide and stirring at room temperature for four hours. After recrystallization from ethanol the product melted at 134–135°.

Anal. Calcd. for $C_{17}H_{17}OBr$: C, 64.36; H, 5.40. Found: C, 64.55; H, 5.46.

o-Hydroxybenzoyldurene was prepared in a yield of 48% by a method similar to that used for the preparation of *o*-hydroxybenzophenone.[7] A solution of 10 g. (0.06 mole) of *o*-methoxybenzoyl chloride in 40 ml. of carbon disulfide was slowly added to a mixture of 9.4 g. (0.07 mole) of durene, 9.3 g. (0.07 mole) of aluminum chloride and 40 ml. of carbon disulfide. After being stirred at room temperature for five hours, the reaction mixture was decomposed with dilute hydrochloric acid and the product isolated in the usual manner. After several recrystallizations from aqueous ethanol it melted at 101–102°.

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.06; H, 7.33.

***p*-Bromobenzoylmesitylene.**—By a treatment similar to that described for *o*-bromobenzoyldurene, 1.01 g. of *p*-bromobenzoylmesitylene was converted in 94% yield to a solid, which after several recrystallizations from ethanol melted at 76.5–77°. *p*-Methoxybenzoylmesitylene has been reported to melt at 78°.[8]

Titration of the bromide ion in the filtrate showed that 92% of the bromine in the bromo ketone had been displaced.

***m*-Bromobenzoylmesitylene.**—A mixture of 15 g. of *m*-bromobenzoylmesitylene, 0.3 g. of powdered copper and 75 ml. of 6 *N* potassium methoxide solution was heated under reflux for 48 hours. The product was a yellow, viscous oil which distilled at 120–122° (0.5 mm.). The infrared spectrum was identical with that of benzoylmesitylene.[9] Seeding with crystals of this ketone (m.p. 35°) caused crystallization. The solid so obtained melted at 29–30°.

A nitro derivative was prepared by treating 1 g. of the product with a mixture of concentrated sulfuric acid and fuming nitric acid at 0°. It melted at 202–204°, which is the melting point reported for a trinitrobenzoylmesitylene.[10]

Titration of the filtrate showed that 78% of the bromine had been displaced. In subsequent experiments, carried out under varying conditions, the amount of displacement varied from 53 to 95%. The use of powdered copper appeared to promote the conversion slightly.

***o*-Bromobenzophenone.**—A mixture of 10 g. of *o*-bromobenzophenone and 40 ml. of 5.3 *N* potassium methoxide was heated to boiling, whereupon a vigorous reaction took place with the formation of a heavy precipitate. After the reaction had moderated, the mixture was warmed gently for 30 minutes. Addition of 100 ml. of water to the cold reaction mixture caused the solid to dissolve and precipitated an oil, which distilled at 116–118° (1 mm.). The infrared spectrum indicated the presence of a ketone and a carbinol. A semicarbazone after two recrystallizations from ethanol and water had a melting point of 163–164°, which corresponds to the melting point of 164° reported for benzophenone semicarbazone.

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.06; H, 5.31; N, 17.51.

A 2,4-dinitrophenylhydrazone, prepared in 72% yield, melted at 239–240°. The reported melting point of the 2,4-dinitrophenylhydrazone of benzophenone is 239°. Seeding with crystals of benzophenone caused the oil to crystallize; m.p. 44–46°. The product is a mixture of 75% benzophenone probably accompanied by benzohydrol. Titration of the aqueous solution from the reaction showed that 97% of the bromine had been displaced.

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[4] All melting points are corrected.

[5] The microanalyses were performed by Miss Emily Davis, Miss Rachel Kopel and Mrs. Jean Fortney.

[6] R. Stoermer, *Ber.*, **41**, 321 (1908).

[7] F. Ullmann and I. Goldberg, *ibid.*, **35**, 2811 (1902).

[8] R. C. Fuson and R. Gaertner, *J. Org. Chem.*, **13**, 496 (1948).

[9] The infrared spectra were determined and interpreted by Miss Elizabeth Petersen.

[10] R. C. Fuson and M. D. Armstrong, THIS JOURNAL, **63**, 2652 (1941).

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Basic Derivatives of Coumarilic Acids

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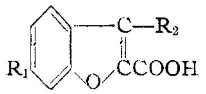
Previous investigations of basic esters and amides derived from the coumarin nucleus[1] have been extended in the present work to similar derivatives of certain coumarilic acids, I. Since a coumarilic acid contains the carbon chain of cinnamic acid, it was expected that in analogy with, *e. g.*, Apothesine, local anesthetic activity would be found in this series. This expectation was fully realized. The simple basic esters of coumarilic acid were very active, both topically and by infiltration. However, the compounds proved to be very irritating, and the series was not extended to more than a few examples.


I

Experimental[2]

Coumarilic Acids.—These compounds were prepared by the usual method[3] from the corresponding coumarin intermediates. From 4,7-dimethylcoumarin was obtained an 83% yield of 3,6-dimethylcoumarilic acid, m.p. 214–216° (dec.) (lit.[4] m.p. *ca.* 212° (dec.)). The reaction between

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[1] Clinton and Laskowski, THIS JOURNAL, **71**, 3602 (1949); Laskowski and Clinton, *ibid.*, **72**, 3987 (1950).

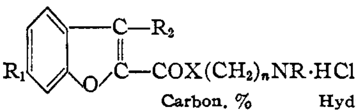
[2] All melting points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

[3] *Cf.* Fuson, Kneisley and Kaiser, *Org. Syntheses*, **24**, 33 (1944).

[4] Fries and Fickewirth, *Ann.*, **362**, 50 (1908); Dey, *J. Chem. Soc.*, **107**, 1647 (1915).

TABLE I

DERIVATIVES OF COUMARILIC ACIDS



R_1, $C-R_2$, $C-COX(CH_2)_nNR\cdot HCl$, O

R_1	R_2	X	*n*	R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	H	O	2	$(CH_3)_2$	187.5–188.8	$C_{13}H_{16}ClNO_3$	57.89	58.08	5.98	5.96	13.11	13.22
H	H	O	2	C_7H_{14}[a]	207.6–208.8	$C_{18}H_{24}ClNO_3$	63.99	64.04	7.16	7.24	10.50	10.42
H	H	O	3	C_6H_{12}[b]	180.0–181.2	$C_{18}H_{24}ClNO_3$	63.99	64.12	7.16	7.07	10.50	10.34
H	H	S	2	$(C_2H_5)_2$	209.5–210.5	$C_{15}H_{20}ClNO_2S$	[c]	[c]	..	..	11.30	11.10
H	H	S	4	$(C_2H_5)_2$	153.1–153.9	$C_{17}H_{24}ClNO_2S$	[d]	[d]	..	..	10.37	10.10
H	H	NH	3	$(C_2H_5)_2$	81.0– 84.0	$C_{16}H_{23}ClN_2O_2$	...	...	..	..	11.41	11.26
CH_3	CH_3	O	2	$(CH_3)_2$	187.4–188.8	$C_{15}H_{20}ClNO_3$	60.50	60.34	6.77	6.73	11.91	11.76
CH_3	CH_3	O	3	C_6H_{12}[b]	184.0–185.2	$C_{20}H_{28}ClNO_3$	65.65	65.94	7.71	7.63	9.69	9.38
C_4H_9O	CH_3	O	2	$(CH_3)_2$	158.0–160.0	$C_{18}H_{26}ClNO_4$	60.75	60.85	7.37	7.25	9.96	9.77
C_4H_9O	CH_3	O	3	C_6H_{12}[b]	168.7–169.9	$C_{23}H_{34}ClNO_4$	65.15	65.08	8.08	7.83	8.36	8.10

[a] 2,6-Dimethyl-1-piperidyl. [b] 2-Methyl-1-piperidyl. [c] Calcd.: S, 10.22. Found: S, 10.30. [d] Calcd.: S, 9.38. Found: S, 9.48.

7-hydroxy-4-methylcoumarin, *n*-butyl benzenesulfonate and anhydrous potassium carbonate in *m*-xylene solution gave a 61% yield of 7-butoxy-4-methylcoumarin, m.p. 51–52° (lit.[5] m.p. 51°). From this was obtained a 44% yield of **6-butoxy-3-methylcoumarilic acid**, m.p. 130.2–131.2°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.42. Found: C, 67.50; H, 6.46.

Derivatives.—The coumarilic acids were converted to the acid chlorides by means of thionyl chloride. The crude crystalline acid chlorides then reacted directly, in benzene solution, with an alcohol, thiol or amine. The compounds prepared are listed in the accompanying Table I.

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(5) Bose, Sen and Chakravarti, *Ann. Biochem. Exptl. Med.*, **5**, 1 (1945).

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Synthesis of β-(6-Methoxy-1-naphthoyl)-propionic Acid

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The preparation of β-(6-methoxy-1-naphthoyl)-propionic acid is a continuation of an earlier investigation in this Laboratory[1] on the use of organocadmium reagents for the preparation of substituted β-aroylpropionic acids. It has been previously reported[1,2,3] that poor yields of the diaryl cadmium derivative were obtained when the latter was prepared from the aryl iodide, whereas the corresponding bromide gave good results. These results suggested the need for a suitable method of synthesis of 1-bromo-6-methoxynaphthalene. This latter compound has been previously prepared[4] in the standard fashion in 4% yield. The bromide has now been prepared in a 34% yield employing the mercuric bromide double salt method of Schwechten.[5,6] Conversion of the 1-bromo-6-methoxynaphthalene to its cadmium derivative and subsequent reaction with β-carbomethoxypropionyl chloride[7] resulted in a 44% yield of the β-(6-methoxy-1-naphthoyl)-propionic acid.

Subsequently, it has been found that the keto acid can be prepared in 41% yield by the addition of 6-methoxy-1-naphthylmagnesium iodide to a suspension of succinic anhydride[8] in an ether–benzene solution. Although the yield of product is slightly higher employing the cadmium reaction, the more efficient preparation of the iodide[9] (65% compared with 34%) makes the inverse Grignard the more preferable method.

Reduction of the carbonyl by either the modified Wolff–Kishner[10] method or by hydrogenolysis[11] gave γ-(6-methoxy-1-naphthyl)-butyric acid in yields of 83 and 53%, respectively.

Experimental[12]

1-Bromo-6-methoxynaphthalene.—To an orange-colored solution of 6-methoxy-1-naphthyldiazonium chloride, prepared according to the procedure of Wilds and Close,[9] from 50 g. (0.238 mole) of 6-methoxy-1-naphthylamine hydrochloride, was added with stirring a cold suspension of mercuric bromide[6] formed by treating 80.0 g. (0.246 mole) of mercuric nitrate with 113.6 g. (1.226 moles) of sodium bromide in 240 ml. of water. The product was processed according to the method of Newman and Wise.[6] The yield of air-dried complex varied from 96–112 g. (90–115% calculated on the basis of $(C_{11}H_9ON_2Br)_2HgBr_2$).

For the decomposition, the mercuric bromide double salt was finely ground and added in several portions through a wide rubber tube[13] to a flask fitted with a reflux condenser and containing 200 ml. of dimethylaniline heated to 110–120°. After each addition of complex, a vigorous nitrogen evolution occurred; heating was continued until no further reaction was noticed. The time for the decomposition varied between two and three hours, depending upon the amount of double salt employed. The reaction mixture was digested with benzene, the benzene extract washed with dilute acid and alkali and the benzene removed. The residue of 1-bromo-6-methoxynaphthalene was purified by vacuum distillation, b.p. 124.5–126.0° (0.8 mm.), $n^{26}D$ 1.6481, yield 18.0–19.2 g. (32–34%).

Anal. Calcd. for $C_{11}H_9OBr$: Br, 33.71. Found: Br, 33.83. The picrate melts at 104.8–105.5° (alc.). Cohen, *et al.*[4] report 105–106°.

β-(6-Methoxy-1-naphthoyl)-propionic Acid. A. By the Cadmium Reaction.—The procedure of Dauben and Tilles[1] was followed for the preparation of the diaryl cadmium de-

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[1] W. G. Dauben and H. Tilles, *J. Org. Chem.*, **15**, 785 (1950).

[2] J. Cason, THIS JOURNAL, **68**, 2070 (1946); *Chem. Revs.*, **40**, 15 (1947).

[3] H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

[4] A. Cohen, J. W. Cook, C. L. Hewett and A. Girard, *J. Chem. Soc.*, 653 (1934).

[5] H. W. Schwechten, *Ber.*, **65**, 1605 (1932).

[6] M. S. Newman and P. H. Wise, THIS JOURNAL, **63**, 2847 (1941).

[7] J. Cason, "Org. Syntheses," Vol. 25, John Wiley and Sons, Inc., New York, N. Y., p. 19.

[8] M. S. Newman, R. B. Taylor, T. Hodgson and A. B. Garrett, THIS JOURNAL, **69**, 1784 (1947).

[9] A. L. Wilds and W. J. Close, *ibid.*, **69**, 3079 (1947).

[10] Huang-Minlon, *ibid.*, **68**, 2487 (1946).

[11] E. C. Horning and D. B. Reisner, *ibid.*, **71**, 1036 (1949).

[12] Microanalyses by the Microanalytical Laboratory of the Department of Chemistry, University of California. All melting points are corrected; all boiling points are uncorrected.

[13] L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., Boston, Mass., 1941, p. 287.