[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

Aroylation by Mesyl Chloride–Carboxylic Acid Mixtures in Pyridine. Synthesis of Depside Derivatives[1,2]

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Application of an aroylation procedure utilizing carboxylic acid–mesyl chloride–pyridine mixtures to β-naphthol and benzyl *p*-hydroxybenzoate is described. Debenzylation of appropriate benzyl esters has given the di- and tridepside derivatives *p*-(*p*'-mesyloxybenzoyloxy)-benzoic acid and *p*-[*p*'-(*p*"-mesyloxybenzoyloxy)-benzoyloxy]-benzoic acid.

Polycarboxylic ester formation by reaction of mesyl (methanesulfonyl) chloride with phenolic acids involves an uncontrolled aroylation process (preceding paper). This observation, combined with our previous one of the acetylating action of acetic acid–mesyl chloride in pyridine,[3] suggested the possible utility of such mixtures in aroylation procedures. An isolated instance of aroylation by a carboxylic acid in presence of a sulfonyl chloride has been recorded: namely, the formation of benzanilide from benzoic acid, tosyl chloride and aniline in pyridine.[4] While the present study was in progress, examples of acylating agents prepared from a carboxylic acid and an aromatic sulfonyl chloride in tertiary bases (including pyridine) were described in the patent literature.[5–7] Very recently a procedure for preparing esters and amides by reaction of carboxylic acids with alcohols, phenols and amides in presence of an aromatic sulfonyl halide has been reported.[8] The present paper describes an esterification procedure which utilizes a carboxylic acid–mesyl chloride mixture in pyridine and its application to the synthesis of depside derivatives.

A preliminary study was made with the readily available β-naphthol. Consecutive addition of benzoic acid and mesyl chloride to a pyridine solution of the phenol gave moderate yields of β-naphthyl benzoate. However, the identical procedure with acetic and propionic acids gave crude products melting over wide ranges, from which β-naphthyl methanesulfonate was isolated in low yield. β-Naphthyl acetate was prepared in fair yield by first preparing the acylation mixture of acetic acid and mesyl chloride in pyridine, then adding β-naphthol after 30 minutes.

(1) From the M.S. Thesis of Charles H. Hayes, University of Nebraska, 1955. Presented at the 16th Midwest Regional Meeting of the American Chemical Society, Omaha, Nebr., November 3, 1954; see Abstracts of Papers, p. 52.

(2) Financial support of this investigation by the Research Corporation is gratefully acknowledged.

(3) J. H. Looker and F. C. Ernest, THIS JOURNAL, **76**, 294 (1954).

(4) (a) F. Ullmann and G. Nadai, *Ber.*, **41**, 1870 (1908); see (b) C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 504.

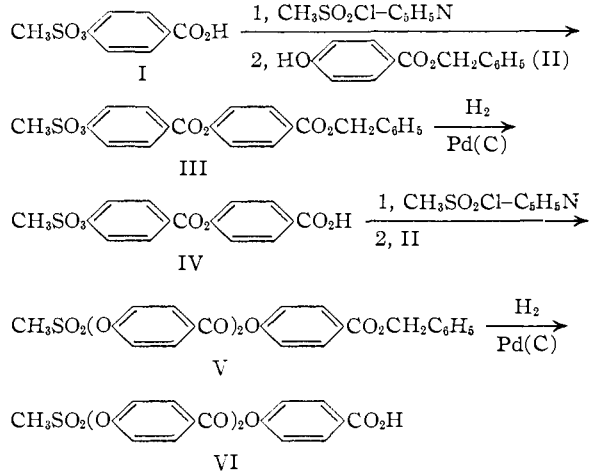
(5) British Patent 662,572; *C. A.*, **46**, 11245 (1952).

(6) Swiss Patent 279,167; *C. A.*, **47**, 6976 (1953).

(7) C. Gränacher, A. E. Siegrist and H. Bruengger, U. S. Patent 2,623,050; *C. A.*, **48**, 2778 (1954).

(8) J. H. Brewster and C. J. Ciotti, Jr., THIS JOURNAL, **77**, 6214 (1955). Several references to earlier work in the field of dehydration with aromatic sulfonyl halides in pyridine are cited by these authors. However, Brewster and Ciotti appear to have overlooked refs. 5, 6 and 7, all of which describe acylation procedures utilizing a carboxylic acid and an aromatic sufonyl halide. From the standpoint of reactants, the preparation of benzanilide given by these authors differs from that of Ullmann and Nadai (ref. 4a) only in the use of benzenesulfonyl chloride instead of *p*-toluenesulfonyl chloride. However, the more recent procedure gives a considerably better yield.

The general method outlined appeared ideal for synthesis of the depside derivatives required in our study of the mesylation product of *p*-hydroxybenzoic acid (preceding paper), obviating as it does the intermediate acid chlorides required in known syntheses. The aroylation procedure involves two steps: (1) preparation of the aroylation mixture



by reaction of the carboxylic acid with mesyl chloride in pyridine and (2) addition of the phenolic compound, in this case benzyl *p*-hydroxybenzoate (II), to be aroylated. The synthesis of II and its use in synthesis of didepsides have been described by Cavallito and Buck.[9] The acids I and IV, in conjunction with mesyl chloride, have been shown to be capable of O-aroylating II to give the benzyl esters (III and V) of the di- and tridepside derivatives IV and VI, respectively. Catalytic debenzylation[9] completed the preparation of IV and VI. An independent synthesis of III was effected from *p*-mesyloxybenzoyl chloride and II in boiling pyridine. An improved synthesis of I involves oxidation of *p*-mesyloxybenzaldehyde.

The aroylation procedure described very probably proceeds *via* a mixed carboxylic-sulfonic anhydride of the type $ArCOOSO_2CH_3$(VII), although the nature of the further involvement of VII in the aroylation is not clear. In addition to the possibility of direct reaction of VII with phenolic groups,[10] depending on rate considerations, VII could form an aroylating agent by reaction with unreacted carboxylic acid to give the carboxylic

(9) C. J. Cavallito and J. S. Buck, THIS JOURNAL, **65**, 2140 (1943).

(10) This possibility finds support in the reaction of alcohols and phenols with the anhydride of *o*-sulfobenzoic acid to give the carboxylic ester; C. F. van Duin, *Rec. trav. chim.*, **40**, 724 (1921); A. H. C. Heitman, THIS JOURNAL, **34**, 1591 (1912); ref. 4b, p. 556.

anhydride[8,11] or with the product pyridinium chloride to give the acid chloride.[12] Either VII or the acid chloride could undergo quaternization to give aroylpyridinium salts, which are known to be aroylating agents.[13] Reaction of sodium or potassium *p*-mesyloxybenzoate with excess mesyl chloride in boiling xylene afforded *p*-mesyloxybenzoic anhydride (VIII),[14] instead of the mixed anhydride.[15] The ester III has been obtained from the action of VIII on II in pyridine solution, thus showing that VIII is a possible active intermediate in the aroylation process. Further work is necessary, notably rate studies with pure carboxylic–methanesulfonic anhydrides, to establish conclusively the active intermediates in the aroylation process.

Experimental[16]

β-Naphthyl Benzoate.—To a solution of 1.44 g. (0.01 mole) of β-naphthol in 20 ml. of pyridine was added 2.44 g. (0.02 mole) of benzoic acid and then immediately 1.72 g. (0.015 mole) of mesyl chloride under ice cooling. Pyridine-insoluble material was present in the reaction mixture. After 20 hr. at room temperature, the mixture was poured into 200 ml. of water. The precipitated crude product was collected by filtration, washed free of pyridine with water and air-dried; yield quantitative, m.p. 75–85°. Two crystallizations from methanol gave pure β-naphthyl benzoate, recovery *ca.* 60%, m.p. and mixed m.p. 108–109° (lit. m.p.[17] 107°); mixed m.p. with β-naphthyl methanesulfonate,[18] 90–99°.

The identical procedure with acetic and propionic acids gave apparent quantitative yields of crude products, which, however, melted over wide ranges. Two crystallizations from methanol gave, in low yield, β-naphthyl methanesulfonate, m.p. and mixed m.p. 105–106.5° (lit. m.p.[18] 105°).

β-Naphthyl Acetate.—Glacial acetic acid (0.60 g., 0.01 mole) and mesyl chloride (0.86 g., 0.0075 mole) were dissolved in 10 ml. of pyridine and permitted to stand 30 minutes. Pyridine-insoluble material was present. β-Naphthol (freshly crystallized, 0.72 g., 0.005 mole) then was added with shaking and the resulting mixture permitted to stand 20 hr. at room temperature. The mixture was poured into water and the crude product collected, washed free of pyridine and air-dried overnight and at 60° for 1 hr., yield 0.83 g. (89%), m.p. 61–66°. Two crystallizations from methanol gave pure β-naphthyl acetate, m.p. and mixed m.p. 67.5–68° (lit. m.p.[19] 68.5°). Successive additions of water to the combined mother liquors gave three crops of impure β-naphthyl acetate, m.p.'s 62–66°, 63–68° and 59–63°, respectively. No pure β-naphthyl methanesulfonate proved isolable. The yield of pure β-naphthyl acetate isolated was still low.

***p*-Mesyloxybenzaldehyde.**—*p*-Hydroxybenzaldehyde (20 g.) was added slowly with stirring to a solution of mesyl chloride (37.6 g.) in 25 ml. of pyridine at 0°. After standing at room temperature for 1 hr., the reaction mixture was poured into 750 ml. of 6 *N* hydrochloric acid, to which crushed ice was added. The precipitated crude product was collected, washed well with water and air-dried; yield 30.7 g. (97%), m.p. 60–63°. Recrystallization from dilute ethanol gave the analytically pure aldehyde, m.p. 64–65°.

Anal. Calcd. for $C_8H_8O_4S$: C, 47.99; H, 4.03. Found: C, 48.36; H. 4.01.

***p*-Mesyloxybenzoic Acid** (I).—Crude *p*-mesyloxybenzaldehyde, m.p. 60–63° (30.7 g.), was added to a solution of potassium dichromate (16.1 g.) in 250 ml. of 30% sulfuric acid. The reaction mixture was heated on a steam-bath for 3 hr., cooled in ice and filtered to give the crude acid, which, after washing free of chromium salts and drying, weighed 30.3 g. (91.5% based on the aldehyde), m.p. 219–221°. Recrystallization from ethyl acetate gave the pure acid, m.p. 222–223° (cor.), lit. m.p.[20] 224°.

***p*-Mesyloxybenzoic Anhydride** (VIII).—*p*-Mesyloxybenzoic acid (1 g.) was added to 5 ml. of an aqueous solution containing 2 g. of sodium hydroxide. After complete solution of the acid, an approximately 3-l. volume of acetone was added immediately to precipitate the salt of the base-labile acid. The gelatinous salt was collected by filtration and added to a solution of mesyl chloride (1.05 g.) in 50 ml. of xylene (b.p. 137–140°), heated under reflux for 30 minutes, cooled to 0° and the resulting crude product collected by filtration. The crude anhydride was shaken with 50 ml. of water, collected and recrystallized from dioxane–water; yield 0.21 g. (22% based on *p*-mesyloxybenzoic acid), m.p. 172–174° (cor.). Further recrystallization from chloroform gave pure *p*-mesyloxybenzoic anhydride, m.p. 186–187° (cor.).

Anal. Calcd. for $C_{16}H_{14}O_9S_2$: C, 46.37; H, 3.41. Found: C, 46.47; H, 3.87.

p-Mesyloxybenzoic anhydride was prepared in 15.4% yield from potassium *p*-mesyloxybenzoate by the same general procedure and in 66% yield from *p*-mesyloxybenzoyl chloride by the procedure of Allen, *et al.*[21]

Benzyl *p*-(*p'*-Mesyloxybenzoyloxy)-benzoate (III).[22]—*p*-Mesyloxybenzoic acid (5.4 g., 0.025 mole) was added in portions with stirring over a period of 10 minutes to a solution of mesyl chloride (2.9 g., 0.025 mole) in 50 ml. of pyridine, in a system protected from atmospheric moisture, to form a pale yellow solution. Crystalline, pyridine-insoluble material was present. The mixture was permitted to stand undisturbed at 25° for 1 hr. Benzyl *p*-hydroxybenzoate[9] then was added in one portion with stirring to the mixture and allowed to stand at room temperature undisturbed for 20 hr. The heterogeneous reaction mixture then was poured into 500 ml. of 6 *N* hydrochloric acid to which crushed ice was added and the resulting precipitate collected by filtration. Recrystallization from methanol gave glistening white plates of the benzyl ester; yield 6.2 g. (58.5% based on *p*-mesyloxybenzoic acid), m.p. 93–95° (cor.). Further crystallization from methanol gave analytically pure ester, m.p. 97–98° (cor.).

Anal. Calcd. for $C_{22}H_{18}O_7S$: C, 61.96; H, 4.25. Found: C, 62.24; H, 4.40.

When the procedure outlined was carried out at 50°, a 49.5% yield of the benzyl ester was obtained.

Benzyl *p*-(*p'*-mesyloxybenzoyloxy)-benzoate was prepared from 4.0 g. of *p*-mesyloxybenzoyl chloride[23] and 6.0 g. of benzyl *p*-hydroxybenzoate in 100 ml. of pyridine at reflux temperature in 69% yield, m.p. 93–94° (uncor.) undepressed by admixture with analyt. pure material. The benzyl ester also was prepared in 63% yield by the action of *p*-mesyloxybenzoic anhydride on benzyl *p*-hydroxybenzoate in pyridine, m.p. 92° (cor.), raised to 97–98° (cor.) on crystallization from methanol.

***p*-(*p'*-Mesyloxybenzoyloxy)-benzoic Acid** (IV).—Benzyl *p*-(*p'*-mesyloxybenzoyloxy)-benzoate (2 g.) was subjected to

(11) Formation of carboxylic anhydrides from reaction of aromatic sulfonyl chlorides with salts of carboxylic acids has been reported: German Patent 123,052; *Chem. Zentr.*, **72**, II, 518 (1901).

(12) Chlorination of certain sulfonic esters by pyridinium chloride is well-known; for leading references see R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 108 (1953). It is considered possible that the chemistry of mixed carboxylic–sulfonic anhydrides will parallel that of the more reactive sulfonic esters.

(13) For leading references, see F. Kröhnke, *Angew. Chem.*, **65**, 605 (1953).

(14) This observation is not surprising; see ref. 11.

(15) Acetic–arenesulfonic- and acetic–alkanesulfonic anhydrides have been prepared in low yield from sodium acetate and the sulfonyl halide: A. Baroni, *Atti Accad. Lincei*, **17**, 1081 (1933); *C. A.*, **28**, 1660 (1934).

(16) All melting points are expressed in °C. and are uncorrected unless otherwise noted. Reagent grade pyridine was dried over potassium hydroxide prior to use. The methanesulfonyl chloride employed was freshly distilled *in vacuo*.

(17) Beilstein's "Handbuch der organischen Chem.," 1926, Vol. 9, p. 125.

(18) B. Helferich and P. Papalambrou, *Ann.*, **551**, 235 (1942).

(19) J. Kendall and J. E. Booge, THIS JOURNAL, **38**, 1720 (1916).

(20) C. Schall, *J. prakt. Chem.*, **48**, 241 (1893).

(21) C. F. H. Allen, *et al.*, *Org. Syntheses*, **26**, 1 (Procedure B) (1946).

(22) For other names for the CH_3SO_3– group, see preceding paper, footnote 6. One alternative name for III is benzyl *p*-(*p'*-methylsulfonyloxybenzoyloxy)-benzoate.

(23) J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **19**, 784 (1954).

hydrogenolysis over 2 g. of 10% palladium-on-charcoal in 100 ml. of reagent grade dioxane at 50° and 40 p.s.i.g. for 6 hr. The reaction mixture was heated, filtered to remove the catalyst and diluted with water to incipient turbidity. Upon cooling, there separated a colorless crystalline product, which was collected by filtration; yield 1.35 g. (88.5%), m.p. 227–229° (cor.). Recrystallization from 95% ethanol gave the analytically pure acid, m.p. 229–230° (cor.).

Anal. Calcd. for $C_{15}H_{12}O_7S$: C, 53.57; H, 3.59; S, 9.53. Found: C, 53.77; H, 3.66; S, 9.23.

Benzyl *p*-[*p'*-(*p"*-Mesyloxybenzoyloxy)-benzoyloxy]-benzoate (V).—*p*-(*p'*-Mesyloxybenzoyloxy)-benzoic acid (2.2 g., 0.0064 mole) was added to a solution of mesyl chloride (0.74 g., 0.0064 mole) in 15 ml. of pyridine, protected from atmospheric moisture and permitted to stand at 26° for 2 hr. Benzyl *p*-hydroxybenzoate (1.47 g., 0.0064 mole) then was added to the mixture thus prepared and the resulting mixture permitted to stand for 24 hr. The crude product was isolated in the usual manner by pouring the mixture into 200 ml. of 6 *N* hydrochloric acid. Recrystallization from methanol gave glistening white plates of the benzyl ester; yield 1.84 g. (51% based on *p*-(*p'*-mesyloxybenzoyloxy)-benzoic acid), m.p. 136–140° (cor.). Repeated crystallization from methanol and ethyl acetate gave the analytically pure ester, m.p. 139.5–140.5° (cor.).

Anal. Calcd. for $C_{29}H_{22}O_9S$: C, 63.73; H, 4.06; S, 5.87. Found: C, 63.84; H, 4.30; S, 6.02.

***p*-[*p'*-(*p"*-Mesyloxybenzoyloxy)-benzoyloxy]-benzoic Acid (VI).**—Benzyl *p*-[*p'*-(*p"*-mesyloxybenzoyloxy)-benzoyloxy]-benzoate (1.5 g.) was subjected to hydrogenolysis over 1.36 g. of 10% palladium-on-charcoal as previously outlined. Isolation in the usual manner gave 1.14 g. (92%) of the acid, m.p. 254–257° (uncor.). Recrystallization from glacial acetic acid gave the colorless, crystalline, analytically pure acid, m.p. 257–259° (uncor.).

Anal. Calcd. for $C_{22}H_{16}O_9S$: C, 57.89; H, 3.53. Found: C, 58.34; H, 3.56.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES INC.]

Benzylphenol Derivatives. VIII.[1] Carbamates

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A series of quaternary ammonium salts derived from N,N-dialkylcarbamates of phenolic Mannich bases is described; a number of these compounds display either parasympathomimetic or curare-like action. Several N-substituted carbamates of benzylphenols are also described.

Our investigation of the benzylphenols as starting materials for the synthesis of physiologically active compounds has continued and we wish to report the preparation of a number of N-substituted carbamates.

The fact that neostigmine, a parasympathomimetic agent, is a dimethylcarbamate of a phenolic quaternary ammonium compound,[2] and that the benzylphenols readily participate in the Mannich reaction[1] prompted us to prepare a series of quaternary ammonium compounds as follows: benzylphenol → phenolic Mannich base → N,N-dialkylcarbamate → quaternary.

Because of the thermal instability of the phenolic Mannich bases, most of them were not purified but were used in the crude form for the subsequent reaction. Two exceptions were 2-benzyl-4-chloro-6-dimethylaminomethylphenol, which could be crystallized,[1] and 4-benzyl-2-diethylaminomethylphenol, which was isolated as the crystalline hydrochloride. Conversion to the N,N-dialkylcarbamates was accomplished in fair yields by heating the appropriate phenol with an N,N-dialkylcarbamyl chloride or N,N-dialkylthiocarbamyl chloride. These reactions were carried out in pyridine on the steam-bath for some 16 hours; no attempts were made to recover any unreacted phenols. Quaternization (Tables I and II) proceeded with ease by treating the tertiary amino carbamates with an excess of methyl or ethyl iodide in a polar solvent such as isopropyl alcohol.

N,N-Disubstituted carbamates of the non-basic phenols, 2- and 4-benzylphenol and 2-benzyl-4-chlorophenol, were prepared similarly from the phenol and carbamyl chloride (Table III). In all these reactions, the yields reported represent only one experiment, and thus may not indicate the maximum yield possible. The two N-monosubstituted carbamates in Table III (19 and 20) were prepared by heating 4-benzylphenol with an isocyanate in an inert solvent. A few drops of triethylamine was added as a catalyst in the case of ethyl isocyanate. Appreciable amounts of 4-benzylphenol were recovered from these reactions.

Pharmacology.—Pharmacologic tests carried out with these compounds have shown that those in Table I exhibit curare-like properties. Although this activity is slight in most cases [3-benzyl-2-(dimethylcarbamyloxy)-benzyl] trimethylammonium iodide (compound 1) is quite effective in producing curare-like paralysis at low doses.

The compounds in Table II tend to exhibit neostigmine-like activity with [5-benzyl-2-(dimethylcarbamyloxy)-benzyl]-trimethylammonium iodide (compound 6) and [5-benzyl-2-(dimethylcarbamyloxy)-benzyl]-diethylmethylammonium iodide (compound 8) being practically as effective as neostigmine.

Acknowledgment.—The authors are indebted to Dr. H. L. Dickison for the above information on the pharmacologic activity of these compounds. Analyses were performed by Mr. R. M. Downing.

Experimental[3]

Phenolic Mannich Bases.—The preparation of 2-benzyl-6-dimethylaminomethylphenol and 2-benzyl-4-chloro-6-dimethylaminomethylphenol has been described previously.[1] In the same manner Mannich reactions were carried out to give three more basic phenols.

(1) Paper VII, W. B. Wheatley and L. C. Cheney, THIS JOURNAL, **74**, 2940 (1952).

(2) J. A. Aeschlimann and M. Reinert, *J. Pharm. Exp. Therap.*, **43**, 413 (1931).

(3) Melting points and boiling points are uncorrected.