in the work, Dr. A. C. Osterberg, Pharmacology Department, Experimental Therapeutic Section, for the activity data, Mr. L. Brancone and his associates for the analyses, and Mr. W. L. McEwen and his staff for certain large scale preparations of intermediates.

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(4) A satisfactory bromine analysis was not obtained.

Heterocyclic Compounds. VIII. 2-(2-Thenoyl)-1-naphthoic Acid and 1-(2-Thenoyl)-2-naphthoic Acid[1]

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Projected syntheses of certain benzothiophanthrene derivatives required that we prepare 2-(2-thenoyl)-1-naphthoic acid (IX) and 1-(2-thenoyl)-2-naphthoic acid (X) as intermediates. New methods for obtaining these known[2a,2b] acids are reported at this time.

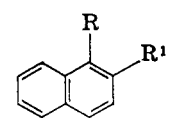
As the first step toward the synthesis of IX, commercially available 2-aminonaphthalene-1-sulfonic acid (I) was acetylated and the product was isolated either as the free acid (II) or its pyridinium salt. The latter was readily handled but the free acid was not recrystallized successfully without decomposition.

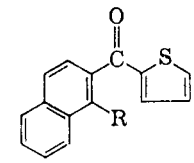
Excellent yields of 2-acetylamino-1-chloronaphthalene (III), 2-acetylamino-1-bromonaphthalene (IV), and 2-acetylamino-1-iodonaphthalene (V) were obtained rapidly from either II or its pyridinium salt merely by treatment in aqueous solution at room temperature with chlorine, bromine, and iodine monochloride, respectively. This halogenation reaction was suggested by the observation that the sulfonic acid group can be removed quantitatively from 2-amino-1-naphthalenesulfonic acid by means of bromine in aqueous solution at room temperature.[3] The sulfonic acid group was recovered quantitatively as sulfate ion but the fate of the organic nucleus was not reported at that time.

Halides III, IV, and V were identical with those obtained previously by halogenation of 2-acetylaminonaphthalene.[4-8] The method we report is advantageous, however, because halogenation is accomplished in water rather than in acetic acid, is not accompanied by dihalogenation, and affords superior yields of products.

Known methods[9,10] were employed to convert IV to 1-bromo-2-naphthoic acid, the chloride of which condensed with thiophene in the presence of anhydrous stannic chloride to give an excellent yield of 1-bromo-2-(2-thenoyl)-naphthalene (VII). Treatment of VII with cuprous cyanide in pyridine gave ketonitrile VIII, which was subsequently hydrolyzed with boiling aqueous sulfuric acid to produce 2-(2-thenoyl)-1-naphthoic acid (IX).

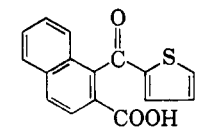
The isomeric 1-(2-thenoyl)-2-naphthoic acid (X) was isolated in 27% yield when thiophene was allowed to react with 1,2-naphthalic anhydride[11] in carbon disulfide, under the catalytic influence of aluminum chloride. This yield is nearly double that reported for this isomer from other methods of preparation.[1,2]





I. R = SO_3H; R^1 = NH_2
II. R = SO_3H; R^1 = $NHCOCH_3$
III. R = Cl; R^1 = $NHCOCH_3$
IV. R = Br; R^1 = $NHCOCH_3$
V. R = I; R^1 = $NHCOCH_3$
VI. R = Br; R^1 = COCl

VII. R = Br
VIII. R = CN
IX. R = COOH



X

EXPERIMENTAL[12]

Acetylation of 2-amino-1-naphthalenesulfonic acid. (a) Pyridinium 2-acetylamino-1-naphthalenesulfonate. To a suspension of technical 2-amino-1-naphthalenesulfonic acid (250 g.) in acetic anhydride (125 ml.) was added a mixture of pyridine (125 ml.) and acetic anhydride (125 ml.). Heat was evolved and all solid material dissolved. Upon standing at room temperature the solution deposited large colorless crystals of pyridinium 2-acetylamino-1-naphthalenesulfo-

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(12) Melting points are uncorrected. Microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, and by Micro-Tech Laboratories, Skokie, Ill.

nate. The product was twice washed by suspension in cold acetone and finally oven dried; yield, 247 g. (64%), m.p. 128–134°. After two crystallizations from ethanol the m.p. was 135–136°.

Anal. Calcd. for $C_{17}H_{16}N_2O_4S$: N, 8.13; S, 9.31. Found: N, 7.82; S, 9.28.

The reaction mixture from which the aforementioned salt had been filtered, together with the acetone washings, was diluted with ten to fifteen volumes of water to precipitate 40 g. of 2-acetylaminonaphthalene. After crystallization from ethanol, this amide melted at 133–134° and did not depress the melting point when mixed with authentic 2-acetylaminonaphthalene.

(*b*) *2-Acetylamino-1-naphthalenesulfonic acid* (II). When pyridine (87 ml.) was added to a suspension of 2-amino-1-naphthalenesulfonic acid (158 g.) in acetic anhydride (190 ml.), considerable heat was generated and all of the solid dissolved. The mixture was heated to reflux for 1 hr. and then 36% hydrochloric acid (480 ml.) was added with efficient cooling of the reaction mixture in order to minimize elimination of the sulfonic acid group. Upon standing in the cold the solution deposited 118 g. (63%) of II as a white powder of suitable purity to be directly halogenated. Dilution of the filtrate with water caused precipitation of varying quantities of 2-acetylaminonaphthalene.

Although the 2-acetylamino-1-naphthalenesulfonic acid was not successfully recrystallized without decomposition, a sample was prepared for analysis by solution in the minimum quantity of cold water and precipitation with 36% hydrochloric acid. The sample was then dried *in vacuo* over solid potassium hydroxide.

Anal. Calcd. for $C_{12}H_{11}NO_4S$: S, 12.08. Found: S, 11.62.

2-Acetylamino-1-chloronaphthalene (III) was instantaneously precipitated when 250 ml. of water saturated with chlorine at room temperature was poured slowly, with stirring, into a solution of 5 g. of 2-acetylamino-1-naphthalenesulfonic acid (II) in 200 ml. of water. After 10 min. the precipitate was collected, washed with water and with potassium bisulfite solution, and again with water. The dried material (3.5 g., 85%) melted at 143–147°. Crystallization from absolute ethanol raised the m.p. to 146–147°, which was not depressed when authentic 2-acetylamino-1-chloronaphthalene, prepared by the method of Franzen and Stäuble[4] was admixed.

When the pyridinium salt of II was chlorinated in exactly the same manner as for the free acid, 2-acetylamino-1-chloronaphthalene was again obtained in 85% yield.

2-Acetylamino-1-bromonaphthalene (IV) was precipitated in quantitative yield when a solution of bromine (5–10% excess) in acetic acid (15 ml.) and water (1 ml.) was added slowly at room temperature, with stirring, to a solution of 2-acetylamino-1-naphthalenesulfonic acid II (10 g.), or an equivalent weight of the pyridinium salt of II, in water (200 ml.). Recrystallization from absolute ethanol readily gave IV in colorless needles, m.p. 140–141°, which did not depress the melting point of authentic IV prepared by the method of Langenbeck and Hölscher.[5]

2-Acetylamino-1-iodonaphthalene (V) was obtained in exactly the same manner (80% yield) by addition of iodine monochloride (7 g.), dissolved in a mixture of acetic acid (20 ml.) and water (3 ml.), to a solution of II (10 g.), or an equivalent weight of the pyridinium salt in water (200 ml.); m.p. 155–162°. Recrystallization from absolute ethanol raised the melting point to 163°, which was not depressed by admixture of authentic V prepared by the method of Willstaedt and Scheiber.[3]

1-Bromo-2-(2-thenoyl)naphthalene (VII). 2-Acetylamino-1-bromonaphthalene (IV) was hydrolyzed[9] and the resulting amine was converted to 1-bromo-2-naphthoic acid by the method of Boyes, Grieve, and Rule.[10] The acid chloride (VI) was formed when a mixture of 145 g. of 1-bromo-2-naphthoic acid and 290 g. of thionyl chloride was allowed to stand for 24 hr. at room temperature. Evaporation under reduced pressure and crystallization of the residue once from heptane gave 147 g. (95%) of material of sufficient purity for the subsequent Friedel-Crafts reaction.

Anhydrous stannic chloride (26 g.) was added dropwise, during a period of 30 min., to a stirred mixture of 1-bromo-2-naphthoyl chloride (VI, 27 g.), thiophene (8.4 g.) and benzene (100 ml.) maintained at a temperature of 10°. After being stirred for 2 hr. the mixture was hydrolyzed with dilute hydrochloric acid. Evaporation of the organic layer, which had been washed with aqueous sodium carbonate, left a residue which crystallized from ethanol to give 26.5 g. (83%) of 1-bromo-2-(2-thenoyl)naphthalene (VII), m.p. 95–96°.

Anal. Calcd. for $C_{15}H_9BrOS$: Br, 25.20; S, 10.11. Found: Br, 25.42; S, 10.51.

An *oxime of* VII crystallized from ethanol, m.p. 191–192°.

Anal. Calcd. for $C_{15}H_{10}BrNOS$: N, 4.22. Found: N, 4.25.

2-(2-Thenoyl)-1-naphthonitrile (VIII) was prepared by heating a mixture of VII (5 g.), cuprous cyanide (1.6 g.), and pyridine (15 ml.) to reflux for 16 hr. in an atmosphere of nitrogen. The nitrile (3.3 g., m.p. 128–132°) obtained by diluting the reaction mixture with water and extracting with ether was crystallized from aqueous ethanol or from a mixture of benzene and petroleum ether; yield, 2.6 g., m.p. 131.5–132.5°.

Anal. Calcd. for $C_{16}H_9NOS$: C, 72.98; H, 3.44; N, 5.32. Found: C, 73.14; H, 3.31; N, 5.31.

The nitrile (VIII, 9.5 g.) hydrolyzed slowly when heated to reflux with sulfuric acid (20 g.), water (260 ml.), and ethanol (280 ml.). After a reflux period of 6 days a 62% yield of *2-(2-thenoyl)-1-naphthoic acid* (IX) was obtained by distilling the ethanol and extracting the residual mixture with benzene. The benzene solution was extracted with 10% aqueous sodium carbonate and acid IX was precipitated by acidification of the alkaline solution; m.p. 155–157°. Recrystallization from acetic acid raised the melting point to that reported by Sandin and Fieser.[1]

1-(2-Thenoyl)-2-naphthoic acid (X). A mixture of 1,2-naphthalic anhydride (10 g.), thiophene (4.2 g.), and carbon disulfide (100 ml.) was heated on a steam bath and stirred vigorously while anhydrous aluminum chloride (11.4 g.) was added in small portions over a period of 2 hr. The mixture was heated for 2.5 hr., then cooled, and the carbon disulfide layer was decanted. Hydrolysis of the residue with ice and hydrochloric acid yielded a crude organic acid that was purified by crystallization of the sodium salt as described by Sandin and Fieser.[1] The only isomer obtained was 1-(2-thenoyl)-2-naphthoic acid (X), m.p. 220–222°; yield, 3.8 g. (27%).

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An Improved Synthesis of Glycerylphosphorylcholine

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Recent investigation in this laboratory has demonstrated a pronounced effect of synthetic lecithin on blood cholesterol levels. This lecithin also has shown definite ability to dissolve experimentally produced atheromatous plaques in rabbits' aortas. Consequently, it became desirable to extend the investigations to related substances such as glycerylphosphorylcholine.