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

Directive Influence of the Acetylamino Group in the Friedel–Crafts Acylation of the Acetylaminonaphthalenes

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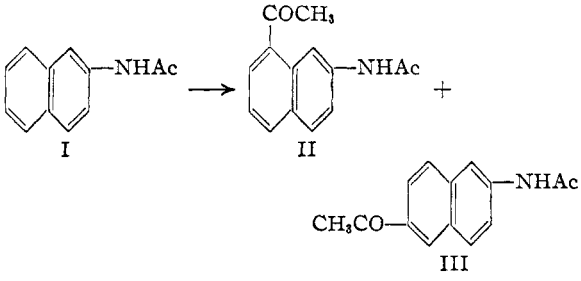
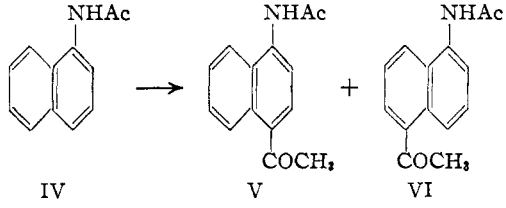
The structure of the main product of Friedel–Crafts acetylation of acet-2-naphthalide (I) was recently established[2] as 7-acetylamino-1-acetonaphthone (II). The structure of the secondary product obtained in the same reaction[3] has now been established as 6-acetylamino-2-acetonaphthone (III). The primary and secondary products of Friedel–Crafts acetylation of acet-1-naphthalide (IV) have been proved to be 4-acetylamino-1-acetonaphthone (V) and 5-acetylamino-1-acetonaphthone (VI).





The isolation of an isomeric acetylaminoacetonaphthone, along with the main product (II)[2] of the Friedel–Crafts acetylation of I, was previously realized by Brown, Jacobs, Winstein, Levy, Moss and Ott.[3] They suggested that the isomer was probably the 6-substituted product, and this assumption has now been proved correct. The minor product (III) was converted to 6-hydroxy-2-acetonaphthone, which was methylated to give 6-methoxy-2-acetonaphthone, and this was oxidized to 6-methoxy-2-naphthoic acid. All three compounds were known previously, and direct comparison with an authentic sample of the acid was also possible. The ratio of the products II and III of ring-acetylation was approximately 12:1 (on the basis of amounts isolated after hydrolysis). The reaction proceeded in an identical manner when 2-naphthylamine was used and acet-2-naphthalide was formed *in situ*.

Since the β-acetylamino group was found to direct substitution entirely in the unsubstituted ring, it was of interest to determine the directive influence of the acetylamino group in the α-position. The products of Friedel–Crafts acetylation of acet-1-naphthalide (IV) were V and VI, isolated as 4-amino-1-acetonaphthone and 5-amino-1-acetonaphthone in a ratio of approximately 4:1. The reaction proceeded in an identical manner when 1-naphthylamine was used and acet-1-naphthalide was formed *in situ*. The structure of 4-amino-1-acetonaphthone was proved by conversion to a hydroxyacetonaphthone and a methoxyacetonaphthone identical with compounds prepared by the Friedel–Crafts acetylation of 1-methoxynaphthalene,[4] the structures of which had been established unequivocally as 4-hydroxy-1-acetonaphthone and 4-methoxy-1-acetonaphthone. The structure of the 5-isomer was proved by replacement of the amino group by chlorine, followed by hypochlorite oxidation to the known 5-chloro-1-naphthoic acid.

When the results of the Friedel–Crafts acetylation of the acetylaminonaphthalenes are compared with those of other electrophilic substitution reactions (*e. g.*, nitration) of the acetylaminonaphthalenes, it is apparent that an additional factor must be considered in the reaction involving aluminum chloride—probably the steric effect of the amino group or its large complex with aluminum chloride. The β-acetylamino group usually directs electrophilic substitution at the 1-, 6- and 8-positions, with the 1-position favored, but in the Friedel–Crafts acetylation substitution occurs only at the unhindered 6- and 8-positions. The α-acetylamino group usually directs electrophilic substitution at the 2-, 4- and 5-positions, but in the Friedel–Crafts acetylation substitution occurs only at the unhindered 4- and 5-positions.

Experimental[5]

Friedel–Crafts Acetylation of Acet-2-naphthalide. 6-Amino-2-acetonaphthone.—The Friedel–Crafts acetylation of acet-2-naphthalide was carried out according to the method of Brown and his co-workers.[3] After hydrolysis two aminoacetonaphthones were isolated: 7-amino-1-acetonaphthone, m. p. 108.5–110°,[2] and a position isomer. It was found necessary to purify the isomer through its hydrochloride. The contaminating hydrochloride of 7-amino-1-acetonaphthone was less soluble in water and the major portion was removed by fractional crystallization. Precipitation of the more soluble hydrochloride with ammonia gave the free base, which was recrystallized from ethanol as pale yellow prisms, m. p. 166.5–168° (reported, 163–164°).[3]

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 78.00; H, 6.15; N, 7.70.

(1) Present address: Ammonia Department, E. I. du Pont de Nemours and Co., Wilmington, Delaware.

(2) Leonard and Hyson, *J. Org. Chem.*, **13**, 164 (1948).

(3) Brown, Jacobs, Winstein, Levy, Moss and Ott, *ibid.*, **11**, 163 (1946).

(4) Witt and Braun, *Ber.*, **47**, 3219 (1914).

(5) All melting points are corrected.

Proof of Structure of 6-Amino-2-acetonaphthone

Conversion to 6-Hydroxy-2-acetonaphthone.—Four-tenths of a gram of the amine was precipitated as the hydrochloride in finely divided form and was diazotized by the addition of sodium nitrite in the usual manner. The diazonium salt solution was allowed to stand overnight at room temperature, after which the diazonium reaction was completely destroyed by heating the solution for one hour on the steam-bath. Two volumes of ethanol were added, and the solution was decolorized, filtered, and cooled. The precipitate was recrystallized from aqueous ethanol, then from benzene; m. p. 170–171° (reported, 171°).[4]

6-Methoxy-2-acetonaphthone.—This compound was prepared from 6-hydroxy-2-acetonaphthone by alternate additions of 2.5 *N* sodium hydroxide solution and dimethyl sulfate at steam-bath temperature until the addition of base no longer produced any yellow color. When the reaction was complete, sufficient hot methanol was added to dissolve all oily material, and the solution was cooled. The colorless, flaky crystals which separated melted at 104.5–105.5° (reported, 105°).[6]

6-Methoxy-2-naphthoic Acid.—The 6-methoxy-2-acetonaphthone in methanol solution was oxidized in the usual manner with a solution of sodium hypochlorite (commercial Clorox). The acid was recrystallized from ethanol; m. p. 209–210.5°, after sintering (reported, 209°,[6] 205°).[7] It was identical with an authentic sample of 6-methoxy-2-naphthoic acid.

Friedel-Crafts Acetylation of 2-Naphthylamine.—To a cooled mixture of 14.3 g. (0.1 mole) of 2-naphthylamine, 67 g. (0.5 mole) of anhydrous aluminum chloride and 400 ml. of carbon disulfide under anhydrous conditions was added 15 g. (0.24 mole) of redistilled acetyl chloride over a period of thirty minutes. The reaction was allowed to proceed at room temperature for three hours and then at reflux temperature for three hours. The cooled solvent was decanted and the residue was decomposed by the addition of 500 g. of cracked ice followed by 200 ml. of 10 *N* hydrochloric acid. The mixture was heated on the steam-bath until all the solid dissolved. The hot solution was decolorized, filtered, and cooled. The precipitated hydrochloride was separated, suspended in water, and neutralized by the addition of ammonia to give 8.5 g. of crude aminoacetonaphthone. After one recrystallization from benzene, the compound melted at 109–110° and was identical with an authentic sample of **7-amino-1-acetonaphthone**. The acetyl derivative was also identical with authentic 7-acetylamino-1-acetonaphthone. The acidic filtrate from the precipitated hydrochloride was treated with excess aqueous potassium hydroxide, and the solid which separated was extracted with acetone. The acetone extract was evaporated, and the residue was treated with hot 2 *N* hydrochloric acid. The acid extract was decolorized and cooled, with deposition of 1.8 g. of hydrochloride, identified as **6-amino-2-acetonaphthone** hydrochloride by conversion to 6-methoxy-2-naphthoic acid as previously described.

Friedel–Crafts Acetylation of Acet-1-naphthalide. 4-Amino-1-acetonaphthone and 5-Amino-1-acetonaphthone.—The same molar proportions and the same conditions were used as in the Friedel–Crafts acetylation of 2-naphthylamine. The reaction mixture was cooled, the carbon disulfide was decanted, and the complex was decomposed by the addition of ice. The insoluble material was collected and 19 g. of this crude product was subjected to hydrolysis by refluxing forty-five minutes with 500 ml. of 1.5 *N* hydrochloric acid. The solution was refluxed an additional twenty minutes with 8 g. of decolorizing carbon and was filtered hot. The solid hydrochloride (A) which separated on cooling was removed by filtration, and the acidic filtrate (B) was retained. The solid (A) was suspended in water and the mixture was made basic with ammonia to precipitate the free amine. Recrystallization from benzene–ligroin gave 7 g. of **4-amino-1-acetonaphthone** (31% yield based on acet-1-naphthalide) as yellow prisms, m. p. 135.5–136.5°.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 77.69; H, 5.81; N, 7.43.

The filtrate (B) from the separation of the 4-amino-1-acetonaphthone hydrochloride was rendered basic with ammonia and the yellow precipitate (3.5 g.) was removed by filtration. The ammoniacal filtrate was extracted with ether and the ethereal solution was evaporated to give a greenish oil. More such oil was obtained from the mother liquor remaining after the recrystallization of the yellow precipitate. The combined oil was dissolved in hot 1.5 *N* hydrochloric acid, from which 1.8 g. of colorless crystalline hydrochloride separated on cooling (9% yield based on acet-1-naphthalide). This **5-amino-1-acetonaphthone hydrochloride** was recrystallized from ethanol–ether; m. p. 248–251°, with decomposition.

Anal. Calcd. for $C_{12}H_{12}ClNO$: C, 65.00; H, 5.46; N, 6.32. Found: C, 64.92; H, 5.65; N, 6.59.

5-Amino-1-acetonaphthone was liberated from its hydrochloride by treatment with aqueous ammonia, followed by cooling. The yellowish plates which separated were recrystallized from benzene–ligroin; m. p. 96.5–97.5°.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.80; H, 5.99; N, 7.57. Found: C, 77.68; H, 6.02; N, 7.62.

Proof of Structure of 4-Amino-1-acetonaphthone

Conversion to 4-Hydroxy-1-acetonaphthone.—Two grams of 4-amino-1-acetonaphthone, m. p. 135.5–136.5°, was precipitated as the hydrochloride in finely divided form and was diazotized by the addition of sodium nitrite in the usual manner. The solution of the diazonium salt was added dropwise, with stirring, to 50 ml. of 4 *N* sulfuric acid heated to the boiling point. After the addition was complete, the mixture was heated for an additional five minutes and was then cooled. The solid which separated was dissolved in hot 2 *N* sodium hydroxide and was reprecipitated by acidification of the decolorized solution. Recrystallization from benzene–ligroin gave 1.0 g. of long, silky, colorless needles, m. p. 197.5–199°. The compound gave no melting point depression when mixed with an authentic sample of 4-hydroxy-1-acetonaphthone prepared by the method of Witt and Braun.[4]

4-Methoxy-1-acetonaphthone.—The compound was made from 4-hydroxy-1-acetonaphthone by the same method which was employed for the methylation of 6-hydroxy-2-acetonaphthone, and was purified by recrystallization from ligroin; m. p. 69–71°. The compound gave no melting point depression when mixed with an authentic sample of 4-methoxy-1-acetonaphthone prepared by the method of Witt and Braun.[4]

Proof of Structure of 5-Amino-1-acetonaphthone

Conversion to 5-Chloro-1-naphthoic Acid.—One-half gram of the amine hydrochloride, m. p. 248–251°, was suspended in 10 *N* hydrochloric acid and solid sodium nitrite was added in small portions until diazotization was complete. The excess nitrous acid was destroyed by the addition of urea. One-half gram of copper bronze powder was added to the solution of the diazonium salt, and the mixture was warmed on the steam-bath until the evolution of nitrogen ceased. The cooled reaction mixture was extracted with two 25-ml. portions of carbon tetrachloride. The combined extracts were washed with 2 *N* sodium hydroxide and finally with water. The carbon tetrachloride solution was evaporated, leaving a small amount of reddish oil which was oxidized in methanol solution by sodium hypochlorite in the usual manner. When the reaction was complete, the excess hypochlorite was destroyed by the addition of bisulfite and the solution was acidified with mineral acid. The precipitated organic acid, after recrystallization from aqueous ethanol, then from benzene, melted at 251–252°. The melting point of the compound was not depressed on admixture with an authentic sample of 5-chloro-1-naphthoic acid. The authentic sample was prepared in an unequivocal manner starting with 1,5-dinitronaphthalene. 5-Nitro-1-naphthylamine was prepared from the dinitro compound by the

(6) Fries and Schimmelschmidt, *Ber.*, **58**, 2835 (1925).

(7) Short, Stromberg and Wiles, *J. Chem. Soc.*, 319 (1936).

method of Hodgson and Walker.[8] The preparation of 5-chloro-1-nitronaphthalene was carried out by replacing the amino group of 5-nitro-1-naphthylamine by chlorine,[9] followed by reduction of the nitro group to form 5-chloro-1-naphthylamine.[10] 5 - Chloro - 1 - naphthonitrile[11] was formed by replacement of the amino group by nitrile through the diazonium salt and was finally hydrolyzed to 5-chloro-1-naphthoic acid by the method of Gomberg and Blicke.[12]

Friedel–Crafts Acetylation of 1-Naphthylamine.—The same molar proportions of reactants, conditions of reaction, and methods of hydrolysis and isolation were employed as in the Friedel–Crafts acetylation of the acet-1-naphthalide. The products, in somewhat lower yields, were identified as 4-amino-1-acetonaphthone and 5-amino-1-acetonaphthone by comparison with the samples isolated previously.

7-Bromo-1-nitronaphthalene.—This compound was prepared from 8-nitro-2-naphthylamine[13] by the method which Hodgson and Walker[14] applied to the preparation of 2-bromo-1-nitronaphthalene.

7-Bromoacet-1-naphthalide.—A mixture of 1 g. of 7-bromo-1-nitronaphthalene 20 ml. of glacial acetic acid, 4 ml. of acetic anhydride and 2 g. of iron powder was heated at reflux temperature for one hour. Additional iron powder (3 g.) was added and refluxing was continued an additional hour. The mixture was poured into 150 ml. of water and the whole was cooled in an ice-bath. The precipitate (0.8 g.) was recrystallized from ethanol as colorless needles, m. p. 195.5–196.5°.

Anal. Calcd. for $C_{12}H_{10}BrNO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.24; H, 3.60; N, 5.13.

7-Bromo-1-naphthylamine.—The acetyl derivative in aqueous ethanol was heated under reflux with 10 *N* hydrochloric acid for five hours. The clear solution, upon cooling, deposited the amine hydrochloride as glistening plates, m. p. 260°, with decomposition. The free base was precipitated by treatment of the hydrochloride in aqueous solution with aqueous sodium carbonate. Recrystallization from aqueous ethanol gave colorless needles, m. p. 65–66°.

Anal. Calcd. for $C_{10}H_8BrN$: C, 54.08; H, 3.63; N, 6.31. Found: C, 53.78; H, 3.33; N, 6.31.

The **benzoyl** derivative was obtained in the usual manner and was recrystallized from ethanol and benzene; m. p. 211–212°.[15]

Anal. Calcd. for $C_{17}H_{12}BrNO$: C, 62.59; H, 3.71; N, 4.29. Found: C, 62.85; H, 3.80; N, 4.56.

Attempted Preparation of 2-Amino-1-acetonaphthone by a Bucherer Type Reaction.—Two grams of 2-hydroxy-1-acetonaphthone[16,17] was placed in a mortar and was finely ground with 8 g. of calcium chloride ammonia complex which had been prepared by the addition of pulverized anhydrous calcium chloride to liquid ammonia.[18] The mixture was placed in a bomb of 37 ml. capacity and was heated at 200° for seven hours. After cooling, the solid was removed and was pulverized in a mortar. This powder was extracted with two 100-ml. portions of moist ether and the ether was removed. The residue after ether evaporation was extracted with 300 ml. of hot 3 *N* hydrochloric acid. The hot acid extract was filtered and the filtrate was cooled and neutralized with ammonia. The precipitate was recrystallized three times from benzene–ligroin to give 1.0 g. of colorless plates, m. p. 126–127.5°.

Anal. Calcd. for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.88. Found: C, 83.18; H, 6.17; N, 5.02.

The analysis indicated that the material could be an equimolar mixture of 2-naphthol and 2-naphthylamine. Equivalent quantities of pure 2-naphthol and pure 2-naphthylamine were mixed and the mixture was recrystallized from benzene–ligroin. The melting point of the colorless plates which separated was 126–128°, and the melting point of a mixture of this product with the material described above was identical.

The Bucherer reaction was repeated using seven and one-half times the previous quantities of reactants in a 250-ml. bomb. From this reaction there was isolated 6.4 g. of 2-naphthylamine, as determined by mixed melting point.[19]

Summary

1. The structure of the product formed in lesser amount, along with 7-acetylamino-1-acetonaphthone, in the Friedel–Crafts acetylation of acet-2-naphthalide in carbon disulfide solution has been established as 6-acetylamino-2-acetonaphthone.

2. The products of the Friedel–Crafts acetylation of acet-1-naphthalide have been proved to be 4-acetylamino-1-acetonaphthone and 5-acetylamino-1-acetonaphthone, with the former in preponderance.

3. The results indicate that the acetyl group does not enter a position *ortho* to the acetylamino group.

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(8) Hodgson and Walker, *J. Chem. Soc.*, 1346 (1933).

(9) Ferraro and Caflisch, *Helv. Chim. Acta*, **11**, 803 (1928).

(10) Friedländer, Karamessinis and Schenk, *Ber.*, **55**, 45 (1922).

(11) Eckstrand, *J. prakt. Chem.*, [2] **38**, 139 (1888).

(12) Gomberg and Blicke, THIS JOURNAL, **45**, 1765 (1923).

(13) Saunders and Hamilton, *ibid.*, **54**, 636 (1932).

(14) Hodgson and Walker, *J. Chem. Soc.*, 1620 (1933).

(15) 2-Bromo-1-benzoylaminonaphthalene melts at 179° (Dziewonski and Sternbach, *Bull. intern. acad. polonaise*, **1931A**, 59). Melting point comparison of the N-benzoyl derivatives of 7-bromo-1-naphthylamine and 2-bromo-1-naphthylamine thus provides a means of distinguishing between these compounds which was previously lacking, since the 7-bromo- and 2-bromo-1-naphthylamines melt at 65–66° (see above) and 65–67° (Hodgson and Hathway, *J. Chem. Soc.*, 538 (1944)), and the corresponding acetyl derivatives melt at 195.5–196.5° and 196.5–197°.

(16) Chattaway, *J. Chem. Soc.*, 2495 (1931).

(17) Fries, *Ber.*, **54**, 709 (1921).

(18) Fries and Hübner, *ibid.*, **39**, 444 (1906).

(19) The intermediate in the modified Bucherer reaction is probably the 1,3-diketonic form of 2-hydroxy-1-acetonaphthone, which should be quite susceptible to cleavage by ammonia. The β-naphthol thus formed could undergo normal conversion (partial or total) to β-naphthylamine.