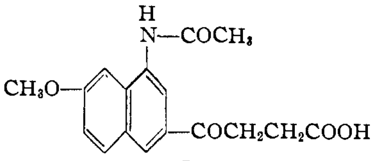
[Contribution from the Noyes Chemical Laboratory, University of Illinois]

The Succinoylation of 1-Acetylamino-6-methoxynaphthalene and 1-Acetylamino-8-methoxynaphthalene

By Leonard E. Miller, Arthur S. Neave, Jr., Grace E. Szosz and L. H. Wiedermann

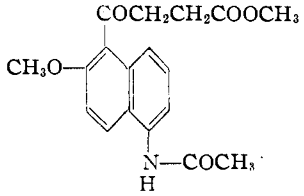
In a previous communication[1] it was shown that the reaction of 1-acetylamino-7-methoxynaphthalene with succinic anhydride in nitrobenzene in the presence of aluminum chloride proceeds at 0° in an 86% yield to give only β-(1-acetylamino-7-methoxy-3-naphthoyl)-propionic acid (I).


I

In this instance, substitution may be considered to have occurred in a position para to the methoxyl group by the principle of vinylogy.

In order to continue the study of the relative directive influences of the methoxyl and acetylamino groups on the naphthalene nucleus during succinoylation in nitrobenzene, the procedure used to prepare (I) has been extended to two additional isomers.

When 1-acetylamino-6-methoxynaphthalene was succinoylated under these conditions, methyl β-(2-methoxy-5-acetylamino-1-naphthoyl)-propionate (II) was isolated in 74% yield. Apparently esterification occurred during recrystallization from methanol.


II

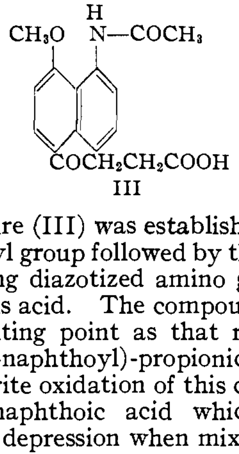
In another larger run where the product was isolated by a slightly modified procedure the free acid corresponding to (II) was obtained in a 62% yield.

The structure of (II) was established by its conversion into the known β-(2-methoxy-1-naphthoyl)-propionic acid by the hydrolysis of the acetyl group and deamination of the resulting diazotized amino group with hypophosphorous acid.

Substitution in this case occurred in a position ortho to the methoxyl group. An explanation for the difference in orientation of these isomers may be in the steric hindrance of the acetylamino group. In the precursor of (I), the position ortho to the methoxyl group may be sterically hindered by the acetylamino group in the *peri*-position; in the precursor of (II), the 6-position (para to the methoxyl group by the principle of vinylogy) may be similarly hindered by the acetylamino group ortho to it.

It may be pointed out that although naphthalene itself will undergo succinoylation when treated under similar conditions to give a mixture of α- and β-naphthoylpropionic acids, several attempted succinoylations of 1-acetylaminonaphthalene under identical circumstances were unsuccessful; the starting material was isolated unchanged.[1a]

That the directive influence of the methoxyl group is of prime importance when succinoylation is carried out in this manner is further shown by the succinoylation of 1-acetylamino-8-methoxynaphthalene. The product of this reaction, isolated in 88% yield, was β-(4-methoxy-5-acetylamino-1-naphthoyl)-propionic acid (III).


III

The structure (III) was established by hydrolysis of the acetyl group followed by the deamination of the resulting diazotized amino group with hypophosphorous acid. The compound formed had the same melting point as that reported for β-(4-methoxy-1-naphthoyl)-propionic acid. Alkaline hypochlorite oxidation of this compound gave 4-methoxy-1-naphthoic acid which showed no melting point depression when mixed with a sample prepared from 4-acetyl-1-methoxynaphthalene.

Experimental[2]

1-Acetylamino-6-methoxynaphthalene.—This material was prepared according to the procedure of Wilds and Close.[3] After sublimation at 170–190° (0.03 mm.), the product was recrystallized from methanol, m. p. 140–141°.

β-(2-Methoxy-5-acetylamino-1-naphthoyl)-propionic Acid.—To a dry 2-liter three-necked, round-bottomed flask fitted with a glass-sleeve mechanical stirrer, a thermometer and a flask for adding the solid reactants, was added 450 ml. of freshly distilled nitrobenzene and 142 g. (1.065 moles) of powdered anhydrous aluminum chloride. The solution was cooled to 0° and the stirrer started. A mixture of 64.5 g. (0.30 mole) of 1-acetylamino-6-methoxynaphthalene and 31 g. (0.31 mole) of succinic anhydride was added in small portions. The addition required about twenty-five minutes. The solution darkened almost

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[1] Miller and Morello, This Journal, **70**, 1900 (1948).

[1a] L. E. Miller and D. L. Dorward, unpublished experiments.

[2] All melting points are uncorrected.

[3] Wilds and Close, This Journal, **69**, 3080 (1947).

immediately. After this addition the thermometer was replaced by a calcium chloride tube, the flask by a rubber stopper and the mixture was stirred for forty hours at 0°. At this time, 750 g. of ice containing 7.5 ml. of concentrated hydrochloric acid was added to the reaction mixture and the flask was shaken well. The mixture was then subjected to distillation at 33° (22 mm.). Water was added from time to time until most of the nitrobenzene had been distilled. The solid residue was separated on a filter and the filtrate distilled with water once more to remove the residual nitrobenzene. The combined solid residue was extracted several times with aqueous sodium carbonate. The insoluble material, consisting of starting material and aluminum hydroxide, was extracted several times with ether. The alkaline filtrate was then washed with ether and separated. Upon pouring the aqueous solution into excess dilute hydrochloric acid, a light yellow solid separated. It was collected on a filter, washed well with water and permitted to dry. The solid was crystallized from methanol (Norite); yield 55 g. or 58.3%, m. p. 208-210°. After four recrystallizations, the m. p. was 212-213°. From the combined ether extracts 2.7 g. of 1-acetylamino-6-methoxynaphthalene was isolated in pure condition, m. p. 140-141°. The yield of the Friedel-Crafts reaction based upon the amount of starting material consumed was 61.5%.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.44; N, 4.44. Found: C, 64.37; H, 5.78; N, 4.41.

Methyl β-(2-Methoxy-5-acetylamino-1-naphthoxyl)-propionate.—The procedure used in this case was similar to that given for the preceding compound except that 300 ml. of nitrobenzene, 94.6 g. (0.71 mole) of aluminum chloride, 43.0 g. (0.20 mole) of 1-acetylamino-6-methoxynaphthalene and 21 g. (0.21 mole) of succinic anhydride were used. Upon acidification of the aqueous solution of the sodium salt of the succinoylation product, a colorless solid separated. It was collected on a filter and permitted to dry. The solid was recrystallized from methanol (Norite) to give small colorless needles, m. p. 141-142°; the yield was 47 g. (70%). After three additional recrystallizations from methanol, the ester, methyl β-(2-methoxy-5-acetylamino-1-naphthoyl)-propionate, melted at 144.5-145.5°.

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.69; H, 5.84; N, 4.47.

Apparently, the impure succinoylation product contained a trace of hydrochloric acid, and during recrystallization from methanol was esterified.

From the combined ether extracts 1.5 g. of 1-acetylamino-6-methoxynaphthalene was isolated in pure condition, m. p. 140-141°. The yield based upon the amount of starting material consumed was 74%.

This methyl ester was also prepared from the pure acid (see above) by treatment with diazomethane.

β-(2-Methoxy-1-naphthoyl)-propionic Acid.—A mixture of 30 g. (0.095 mole) of β-(2-methoxy-5-acetylamino-1-naphthoyl)-propionic acid, 110 ml. of water and 220 ml. of concentrated hydrochloric acid was heated under reflux for one hour. The mixture was cooled in ice and the solid amine hydrochloride collected on a filter. The product was recrystallized from water to which a small amount of concentrated hydrochloric acid had been added (Norite) to give small pink plates, m. p. 258-259° (dec.). The yield was 28.2 g. or 95.7%.

A mechanically stirred mixture of 10.9 g. (0.035 mole) of the hydrochloride of β-(2-methoxy-5-amino-1-naphthoyl)-propionic acid, 100 ml. of glacial acetic acid and 75 ml. of concentrated hydrochloric acid was cooled to 5° in an ice-bath. To the suspension of the hydrochloride, 2.9 g. (0.042 mole) of sodium nitrite in 14 ml. of water was added dropwise until a positive test with starch-iodide paper was obtained. The mixture was stirred for one-half hour longer. At this time 87 ml. (0.84 mole) of ice-cold hypophosphorous acid (50%) was added over a fifteen-minute period. During this addition bubbles of nitrogen were observed. After another one-half hour of stirring, the reaction mixture was heated on a steam-cone until the bubbles of nitrogen subsided.[4] Immediately following, most of the liquid was removed at 32° (22 mm.). The product was then dissolved in aqueous sodium carbonate and filtered. The alkaline solution was poured into excess dilute hydrochloric acid and the acid separated on a filter.

The crude β-(2-methoxy-1-naphthoyl)-propionic acid was treated with an ethereal solution of diazomethane. After five minutes, the excess diazomethane was destroyed by the addition of several drops of glacial acetic acid. The ether solution was washed several times with aqueous sodium bicarbonate, with cold 2% potassium hydroxide and finally with water. The ether was removed by distillation and the residue was purified by evaporative distillation at 190° (0.02 mm.).

To a solution of the liquid methyl-β-(2-methoxy-1-naphthoyl)-propionate in 100 ml. of methanol was added 1 ml. of 40% potassium hydroxide. The solution was heated under reflux for one hour. The methanol was removed by distillation and the residue dissolved in 100 ml. of water. On acidification with hydrochloric acid, the β-(2-methoxy-1-naphthoyl)-propionic acid separated and was collected on a filter. The acid crystallized from benzene (Norite) in small white needles, m. p. 134-135° (reported: 131°[5]; 136.5-137.5°[6]). The yield was 1.6 g. or 17.7% based upon the amine hydrochloride. There was no depression of the melting point when this material was mixed with an authentic sample prepared by the succinoylation of 2-methoxynaphthalene[6] in carbon bisulfide solution.

1-Acetylamino-8-methoxynaphthalene.—Using 1-naphthylamine-8-sulfonic acid,[7] this material was prepared by the procedure of Wilds and Close for the 1,6-isomer. After evaporative distillation at 180-190° (0.03 mm.) and recrystallization from methanol, the product was isolated as large prisms; m. p. 128.5-129°.

β-(4-Methoxy-5-acetylamino-1-naphthoyl)-propionic Acid.—The procedure used here was similar to that employed in the case of the 1,6-isomer. The succinoylation was permitted to proceed for forty-eight hours using 43 g. (0.2 mole) of 1-acetylamino-8-methoxynaphthalene, 21 g. (0.21 mole) of succinic anhydride and 94.6 g. (0.71 mole) of anhydrous aluminum chloride in 300 ml. of freshly distilled nitrobenzene. The solid product was washed thoroughly with water on a filter and permitted to dry. Flocculent needles were formed when the yellow solid was crystallized from methanol (Norite). Since the solid was slightly soluble in hot methanol, the compound had to be crystallized in several small portions, m. p. 222-224° (dec.). The yield was 55.7 g. (88.4%).

Anal. Calcd. for $C_{17}H_{17}NO_5$; C, 64.75; H, 5.44; N, 4.44. Found: C, 64.78; H, 5.63; N, 4.56.

β-(4-Methoxy-1-naphthoyl)-propionic Acid.—A mixture of 20.0 g. (0.062 mole) of the succinoylation product, 75 ml. of water and 150 ml. of concentrated hydrochloric acid was heated under reflux for one hour. During this period the solid was dissolved completely. As the dark-orange solution was cooled slowly, light tan needles crystallized. The solid was separated by filtration, crystallized (Norite) and recrystallized from a water-hydrochloric acid solution (1:2). The pink crystals were collected on a filter and dried in air. The yield was 18.3 g. (92.1%).

This amine hydrochloride was treated in the same manner with the same quantities of reagents as the previous isomer already described above. The only difference in this instance was that the diazonium salt-hypophosphorous acid mixture was placed in a refrigerator for sixteen hours before being heated on a steam-bath. After deamination, esterification, washing, saponification

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(4) When the reaction mixture was permitted to remain cold for several hours in the standard procedure, see "Organic Reactions," Adams, *et al.*, Vol. II, John Wiley and Sons, Inc., New York, N. Y., (1944), pp. 294-297, a lower yield (10%) was obtained.

(5) Desai and Wali, *J. Univ. Bombay*, **5**, 73 (1936).

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

(7) Purchased from the Eastman Kodak Company.

and acidification the light yellow precipitate of crude β-(4-methoxy-1-naphthoyl)-propionic acid which formed was separated by filtration and crystallized from methanol (Norite). The product was collected on a filter and recrystallized from methanol. Observed melting points when the melting point tubes were placed in the bath at 160° were: 171.5-172° and 174-174.5° (reported m. p. 171°,[8] 172°,[9] 177-178°[5]). The yield was 1.86 g. (20.7%) based upon the amine hydrochloride.

4-Methoxy-1-naphthoic Acid. **(1) Hypochlorite Oxidation of β-(4-Methoxy-1-naphthoyl)-propionic Acid.**—One gram of β-(4-methoxy-1-naphthoyl)-propionic acid was dissolved in 100 ml. of freshly prepared sodium hypochlorite solution (made by dissolving 5.8 g. of sodium hydroxide in 100 ml. of water and adding 1.8 g. of chlorine to the solution); this solution was approximately 0.25 *N* with respect to sodium hypochlorite and 0.5 *N* with respect to sodium hydroxide. The mixture was heated gently in a water-bath (80-82°) for twenty minutes, boiled under reflux on a sand-bath for twenty minutes, allowed to cool slightly and was filtered. Sulfur dioxide was bubbled into the cooled filtrate until the solution was acid to congo red paper. The white solid which deposited was separated on a filter, and thoroughly washed with water. The precipitate was crystallized twice from methanol, m. p. 236-239° (inserted into the bath at 220°). The compound darkened upon melting and bubbles of gas appeared (reported, 230°,[10] 232°,[11] 234°,[8] 239°,[12] and 242-243°[13]). The yield was 0.16 g. (20.5%).

(2) Hypochlorite Oxidation of 4-Methoxy-1-acetonaphthone.—To a solution of 1 g. of 4-methoxy-1-acetonaphthone[14] in 10 ml. of methanol, 35 ml. of "Chlorox" (5.25% by weight of sodium hypochlorite) was added slowly in small portions at room temperature over a thirty minute period. After the addition of all the sodium hypochlorite solution, 10 ml. of methanol was added. After heating the solution for forty minutes (as above), a dark yellow layer which had formed at the bottom of the flask was removed by extraction with ether and discarded. The product was isolated from the aqueous layer, using the procedure given in the preceding preparation, and was recrystallized from methanol; m. p. 236-240° (inserted into the bath at 220°). The compound darkened upon melting and bubbles of gas appeared.

A mixed melting point of the hypochlorite oxidation products of β-(4-methoxy-1-naphthoyl)-propionic acid and 4-methoxy-1-acetonaphthone showed no melting point depression. The infrared absorption spectra of the two compounds were identical; both showed very strong absorption at 1677 cm.$^{-1}$, 1268 cm.$^{-1}$ and 768 cm.$^{-1}$.[15]

Summary

The succinoylation of 1-acetylamino-6-methoxynaphthalene in nitrobenzene in the presence of aluminum chloride at 0° gave β-(2-methoxy-5-acetylamino-1-naphthoyl)-propionic acid.

The succinoylation of 1-acetylamino-8-methoxynaphthalene in nitrobenzene in the presence of aluminum chloride at 0° gave β-(4-methoxy-5-acetylamino-1-naphthoyl)-propionic acid.

No other isomers were found in either instance.

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(8) Ruzicka and Waldman, *Helv. Chim. Acta*, **15**, 907 (1932).

(9) Fieser and Hershberg, THIS JOURNAL, **58**, 2316 (1936).

(10) Rousset, *Bull. soc. chim.*, [3] **17**, 309 (1897).

(11) Gattermann and Hess, *Ann.*, **244**, 73 (1888).

(12) Herz, Schulte and Zerweck, U. S. Patent 1,669,297, May 8, 1928; *C. A.*, **22**, 2170 (1928).

(13) Spaith, Geissman and Jacobs, *J. Org. Chem.*, **11**, 399 (1946).

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

(15) The authors are indebted to Mrs. A. Johnson for the interpretation of the infrared spectra.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Synthesis of 1-Methoxypropyl Ketones[1]

BY HENRY R. HENZE, GEORGE W. BENZ AND GEORGE L. SUTHERLAND

It has been demonstrated that many, although not all, ketones can be converted into 5,5-disubstituted hydantoins by means of the Bucherer method[2] or through the improvements upon the latter developed by Henze and Long.[3] Since a series of 5-alkoxymethyl-5-phenylhydantoins has been shown[4] to possess a high degree of anticonvulsant activity, the latter varying with the degree of branching at the α-carbon of the alkoxy group, it was desirable to prepare isomeric and homologous ketones for subsequent conversion, if possible, into hydantoin derivatives.

The present investigation dealt with the synthesis of fifteen 1-methoxypropyl ketones. With respect to the other grouping present in these mixed ketones, six are straight chain alkyl, seven are branched chain alkyl, one is cycloalkyl, and one is phenyl. These ketones resulted from a sequence of steps: (a) preparation of 1-chloropropyl methyl ether; (b) conversion of the latter into 1-methoxybutyronitrile; (c) interaction of the alkoxynitrile with appropriate Grignard reagents to yield the keto ethers.

Experimental

Preparation of 1-Chloropropyl Methyl Ether.—This chloro ether was prepared according to the method of Henry[5] by saturating with dry hydrogen chloride a well-stirred mixture of methanol (224 g., 7 moles) and propionaldehyde (406 g., 7 moles) in a container chilled by a salt-ice-bath. After about six hours, the two-phase mixture was separated, the top (chloro ether) layer was dried over anhydrous calcium chloride in a refrigerator, and was fractionated. After removal of about 110 g. of lower boiling material, there was collected 250 g. (33% yield) of material boiling through the range 96-108° (747 mm.).

The chloro ether could not be preserved without evidence of decomposition; hence, was converted as soon as possible to the alkoxy nitrile, which can be purified readily through fractional distillation.

Preparation of 1-Methoxybutyronitrile.—The procedure most commonly employed for the conversion of α-chloro ethers into the corresponding alkoxynitriles is that of

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(1) From the M.A. thesis of G. W. B., August, 1946, and of G. L. S., August, 1947.

(2) Bucherer and Lieb, *J. prakt. Chem.*, [2] **141**, 5 (1934).

(3) Henze and Long, THIS JOURNAL, **63**, 1936, 1941 (1941).

(4) Henze, Melton and Forman, *ibid.*, **70**, 2438 (1948); Merritt, Putnam and Bywater, *J. Pharmacol.*, **84**, 67 (1945).

(5) Henry, *Compt. rend.*, **100**, 1007 (1885).