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Succinoylation of 2-Methoxynaphthalene

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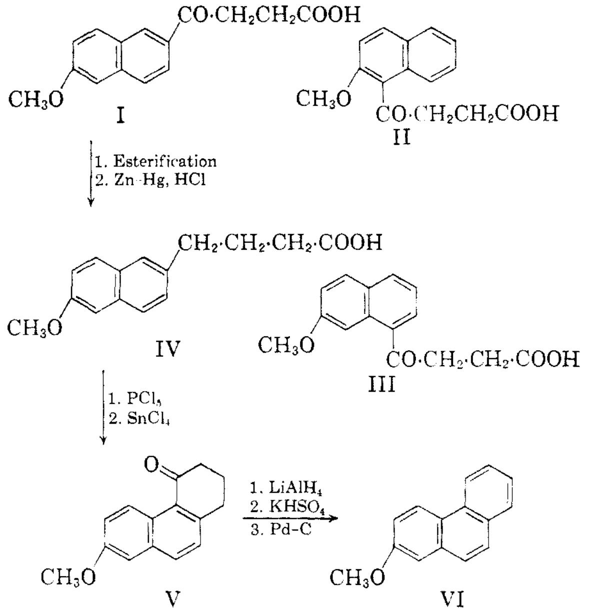
Succinoylation of 2-methoxynaphthalene has been studied in nitrobenzene, carbon disulfide, and tetrachloroethylene. When nitrobenzene was used as solvent, two products, β-(2-methoxy-6-naphthoyl)propionic acid (I) and β-(2-methoxy-1-naphthoyl)propionic acid (II) were obtained; in tetrachloroethylene II was the sole product; whereas, in carbon disulfide, the main compound isolated was II with traces of I. This is in close agreement to the results of Short, *et al.*[1] The reported β-(7-methoxy-1-naphthoyl)propionic acid[2] could not be obtained. This acid has been synthesized by an unambiguous route, and found different from the acids isolated by us. Additional evidence for the structure of β-(2-methoxy-6-naphthoyl)propionic acid is provided by its conversion to 2-methoxyphenanthrene. The effect of solvents on the orientation of substitution has been discussed.

The Friedel-Crafts reaction between 2-methoxynaphthalene and succinic anhydride in carbon disulfide was studied by Short, *et al.*[1] and later by Bachmann and Horton.[2] The former reported β-(2-methoxy-1-naphthoyl)propionic acid (II), m.p. 138°, as the only product. Its constitution was established by hypochlorite oxidation to the corresponding naphthoic acid. In contradiction to this report, the later workers obtained a product with m.p. 148°. They conclusively proved it to be β-(7-methoxy-1-naphthoyl)propionic acid (III), not only by hypochlorite oxidation to 7-methoxy-1-naphthoic acid, but also by reduction to γ-(7-methoxy-1-naphthyl)butyric acid, which in turn was synthesized through unambiguous routes for comparison.

In view of the above contradictory reports, the study of succinoylation of 2-methoxynaphthalene in different solvents was undertaken. In nitrobenzene, two products were isolated having m.p. 149–150° and m.p. 138° (*cf.* Short, *et al.*[1]). In tetrachloroethylene, only one acid, m.p. 138°, identical with the acid of same melting point from condensation in nitrobenzene was obtained. In carbon disulfide, again, both the acids resulted; but the higher melting acid could be isolated only in traces, the main product being the acid of m.p. 138°.

The higher melting acid was proved to be β-(2-methoxy-6-naphthoyl)propionic acid (I) by hypochlorite oxidation to 2-methoxy-6-naphthoic acid, and also by conversion to 2-methoxyphenanthrene[3] as described in accompanying formulas. Miyasaka[4] obtained 4-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (V) using a similar procedure. Our results are at variance with those obtained by the Japanese worker. According to him, V melts at 56°, while our compound melts at 168°. Clemmensen reduction of I gave a poor yield (32%) of IV. But, when the ethyl ester of I was reduced, IV was obtained in 75.5% yield. Cyclization of IV to V was effected with stannic chloride. Reduction of V with lithium aluminum hydride, followed by dehydration and dehydrogenation gave 2-methoxyphenanthrene, which was identical with an authentic specimen kindly supplied by Dr. D. K. Banerjee of the College of Engineering and Technology, Calcutta 32, India.



Hypochlorite oxidation of the acid, m.p. 138°, afforded 2-methoxy-1-naphthoic acid, m.p. 173–175°, and was quite different from 7-methoxy-1-naphthoic acid (VII), m.p. 170.5, prepared according to the method of Fieser and Holmes[5]—a fact which was demonstrated by their mixed melting point and their Debye-Scherrer photographs. Evidence in favor of structure II for the

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[1] Short, Stromberg, and Wiles, *J. Chem. Soc.*, 319 (1936).

[2] Bachmann and Horton, *J. Am. Chem. Soc.*, **69**, 58 (1947).

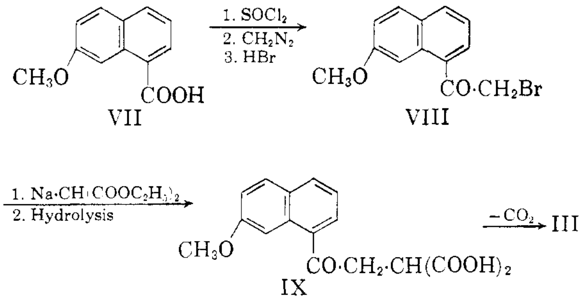
[3] Ghosal and Bagchi, *Science and Culture*, **19**, 49 (1953).

[4] Miyasaka, *J. Pharm. Soc. Japan*, **59**, 278 (1939); *C.A.* **34**, 1012 (1940).

[5] Fieser and Holmes, *J. Am. Chem. Soc.*, **58**, 2319 (1936).

acid, m.p. 138°, has already been provided by the experiments of Gilmore and Horton.[6] In no case could we isolate Bachmann and Horton's acid, m.p. 148°, although experimental conditions were varied in a number of ways such as time and temperature of reaction, order of addition of the reactants, *etc.*

For direct comparison, Bachmann and Horton's acid (III) was synthesized through the following unambiguous route from the Fieser and Holmes' acid (VII):



The final product melted at 147.5° in conformity with the observation of Bachmann and Horton.

In view of our experiences, we are forced to conclude that Bachmann and Horton's observation represents a rather unusual variation of the course of the reaction, and may be due to the presence of foreign matters in the catalyst. Instances are known in the literature[7] where employment of different Friedel-Crafts' catalysts led to different products. In fact, in the course of the present work, using different brands of anhydrous aluminum chloride for the succinoylation of 2-methoxynaphthalene in nitrobenzene, we observed variation. In some experiments, the acids (I) and (II) were obtained in the ratio 2.5:1. Subsequently, it was uniformly observed that the lower melting acid (II) was the main product (I:II:1:3). Particular care was taken to ascertain whether this was due to any other factor than the quality of the catalyst. Experiments under carefully controlled conditions compels us to believe that this may be the only reason for the variation observed.

The cutting down of the reaction time to two hours (one half hour in freezing mixture and one and a half hours at room temperature) as against 120 hours at 0° recommended by the previous workers does not materially affect the yield so long as the same grade of aluminum chloride is used. In fact, employment of shorter reaction periods facilitates the isolation of the products in purer condition. The initial supposition that β-(2-methoxy-1-naphthoyl) propionic acid may be converted into the 6-isomer in the presence of anhydrous aluminum chloride was disproved by keeping the 1-acid with aluminum chloride in nitrobenzene for 96 hours, when the 1-acid was recovered quantitatively.

DISCUSSION

Acylation of naphthalene and its derivatives are anomalous in the sense that orientation of substitution depends to a large extent on the solvent employed. It has been suggested that acylation at the β-position is favored in nitrobenzene medium, because the aluminum chloride–acyl chloride complex gets solvated to form a bulky complex.[8] As the α-position is relatively hindered, a complex with large steric requirements cannot attack this position. This simple theory is unable to explain the formation of large quantities of β-(2-methoxy-1-naphthoyl)propionic acid in nitrobenzene medium as observed by us.

It would therefore be worthwhile to try to interpret the results in terms of the more recent generalizations on the mechanism of Friedel-Crafts reaction.[9,10] It is now believed that Friedel-Crafts acylation reactions may proceed *via* two alternative mechanisms, *viz.* substitution (S) and ionic (I). The reaction proceeds primarily *via* S mechanism when the aromatic substrate is comparatively unreactive, such as benzene, toluene, *etc.*, whereas I mechanism becomes important only when a sterically hindered acyl halide is used, the aromatic substrate is reactive, or a sterically hindered position is being acylated.

The reactive hydrocarbon 2-methoxynaphthalene should undergo Friedel-Crafts substitution by the I mechanism. Acylation of this compound yields the 1- and 6-substitution products. Because the electron density at the 1-position is considerably greater than that at the 6-, a competing ionic substitution should predominantly yield the 1-substitution product. It is so when carbon disulfide and tetrachloroethylene are used as solvents. If the substitution at the 6-position is considerably large, it is highly probable that substitution at this unhindered and relatively unreactive position has taken place by the S mechanism. The preponderence of succinoylation and acetylation at the 6-position in nitrobenzene medium may be easily explained with this hypothesis.

The Friedel-Crafts complex between aluminum chloride and a succinic anhydride is practically insoluble in carbon disulfide and tetrachloroethylene. Hence, the little that goes into solution may be considered to be highly dissociated to yield acylonium ion. It is therefore reasonable to expect acylation through I mechanism, which is supported by substitution taking place exclusively at the hindered 1-position of a reactive substrate.

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(6) Gilmore and Horton, *J. Am. Chem. Soc.*, **72**, 733 (1950).

(7) Gutsche and Lauck, *Chem. and Ind.*, 116 (1559).

(8) Baddeley, *J. Chem. Soc.*, 599 (1949).

(9) Brown, Pearsall, Eddy, Wallace, Grayson, and Nelson, *Ind. Eng. Chem.*, **45**, 1462 (1953).

(10) Gore, *Chem. Rev.*, **55**, 229 (1955).

The isolation of a very small quantity of the 6-isomer shows that substitution at the 6-position by I mechanism is negligible, or the simultaneous S reaction proceeds to a very limited extent. In nitrobenzene, in which the Friedel-Crafts complex is soluble, the presence of a considerable amount of undissociated complex is expected. This could lead to acylation at the 6-position (comparatively unreactive and free) through the S mechanism. This would explain the formation of a larger proportion of the 6-isomer in comparison to the product obtained by carrying out the reaction in other solvents.

2-Methoxynaphthalene is acetylated at the 6-position in nitrobenzene medium.[11,12] That no isomeric 1-derivative is formed is a sharp contrast to succinoylation of the same compound. If we compare the structures of the two Friedel-Crafts complexes, we would find that the electron releasing character of the methyl group in the case of the complex between acetyl chloride and aluminum chloride, and the electron withdrawing character of the carboxyl in the case of the complex between succinic anhydride and aluminum chloride, would respectively retard and favor the formation of the acylonium ion. We should therefore expect much less contribution of the I mechanism in the case of acetyl chloride, resulting in the acylation proceeding predominantly at the 6-position through the S-mechanism.

Results given in the literature indicate that naphthalene shows a greater tendency to be acylated at the β-position than 2-methoxynaphthalene. This may be attributed to the comparatively unreactive character of naphthalene.

It has been pointed out before that the purity of the catalyst plays a very important part in determining the course of the reaction. This may be due to the fact that minor constituents in the catalyst might to some extent promote or retard the I- and S-reaction carried out in otherwise similar conditions. In that case, the variations observed by a different set of workers for reactions carried out between the same reactants and in the same solvent may find an explanation.

EXPERIMENTAL[13]

Succinoylation of 2-methoxynaphthalene. A. *In nitrobenzene.* To a solution of aluminum chloride (29.4 g.) in nitrobenzene (98 ml.) succinic anhydride (10 g.) was added. The mixture was cooled below 0°, and 2-methoxynaphthalene (15.8 g.) was slowly added. After stirring for 0.5 hr., the cooling bath was removed; the reaction mixture was decomposed after 1.5 hr. with ice and hydrochloric acid. On working up in the usual manner, a solid acid was obtained which was methylated with 20 ml. of dimethyl sulfate. The product was then esterified with ethanol (50 ml.), benzene (75 ml.), and concd. sulfuric acid (1 ml.) for 5 hr. The benzene layer was washed with water and dilute ammonia. On removal of the solvent, the residue crystallized partially. The crystals were collected (4 g.), and washed with a little ethanol; m.p. 107°. Recrystallization from ethanol gave pure ethyl β-(2-methoxy-6-naphthoyl)propionate, m.p. 111–12°. This ester on hydrolysis with alcoholic potassium hydroxide gave a quantitative yield of β-(2-methoxy-6-naphthoyl)propionic acid, which on recrystallization from glacial acetic acid, melted at 148–149°. This acid on oxidation with sodium hypochlorite afforded 2-methoxy-6-naphthoic acid m.p. 200° (lit. 205°).

The liquid ester obtained after filtration of ethyl β-(2-methoxy-6-naphthoyl)propionate was distilled and the fraction (11.9 g.) b.p. 215–222°/4.0 mm. was collected. This on saponification gave an acid, m.p. 137–138°, not depressed by admixture with β-(2-methoxy-1-naphthoyl)-propionic acid.

Total yield of the esters was 56%.

In two experiments, aluminum chloride (58.8 g.), nitrobenzene (194 ml.), succinic anhydride (20 g.), and 2-methoxynaphthalene (31.6 g.) afforded 17.3 g. of the 6-isomer, m.p. 149°, and 6.6 g. of the 1-isomer, m.p. 139–140°. In this case, the total yield of the acids was 45%.

B. *In carbon disulfide.* Succinic anhydride (5 g.) was allowed to react with 2-methoxynaphthalene (8 g.) in carbon disulfide (30.4 g.) in the presence of anhydrous aluminum chloride (14.7 g.) under conditions identical with those described by Short, *et al.*[1] An acidic product, m.p. 108–109.5°, (4.5 g.) was obtained. This was esterified with alcoholic hydrochloric acid (9 ml., 5%) to give 3.5 g. of ester, b.p. 210–214°/3 mm. On being left for 7 days in contact with a little methanol, traces of solid, m.p. 111–112°, separated. This was removed by filtration and washed with a little methanol. Mixed melting point with ethyl β-(2-methoxy-6-naphthoyl)propionate did not show any depression. The filtrate from above was redistilled after removal of methanol when the distillate solidified on cooling, m.p. 37–38° (lit.[1] m.p. 40–41°). This was hydrolyzed with alcoholic potassium hydroxide, when 3.0 g. of solid acid were obtained. On crystallization from methanol, the first crop of β-(2-methoxy-1-naphthoyl)propionic acid (1 g.) melted at 139–140°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.77; H, 5.43. Found: C, 69.61; H, 5.65.

The acid in the mother liquor was subjected to fractional crystallization, but no other product could be obtained.

The keto acid (1 g.), on oxidation with alkaline sodium hypochlorite gave 2-methoxynaphthoic acid, which was crystallized from ethyl acetate, m.p. 173–175° (lit.[1] m.p. 174–175°).

C. *In tetrachloroethylene.* Succinic anhydride (10 g.) was added to a cold suspension of aluminum chloride (29.4 g.) in tetrachloroethylene (147.8 g.). The suspension was then cooled in a freezing mixture, and 2-methoxynaphthalene (15.8 g.) was slowly added with stirring, keeping the temperature below 0°. The reaction mixture was kept below 0° for 2 hr., and then kept overnight. On working up in the usual manner, an acid was obtained which on crystallization from acetic acid gave crystals (3.5 g.) m.p. 126–127°. On recrystallization from 95% ethanol the melting point rose to 138°. Admixture with β-(2-methoxy-1-naphthoyl)propionic acid did not depress the melting point. The crude acids obtained from the mother liquor was esterified and worked up as described above, but no solid product could be isolated, demonstrating the absence of the 6-isomer.

γ-(2-Methoxy-6-naphthyl)butyric acid (IV). Amalgamated zinc (100 g.), water (16 ml.), concd. hydrochloric acid (150 ml.), toluene (175 ml.), acetic acid (75 ml.), ethanol (90 ml.), and ethyl β-(2-methoxy-6-naphthoyl)propionate (25 g.) were refluxed for 60 hr. The toluene layer was separated, washed with water. The water layer and the washings were extracted with ether, and the ether extract combined with the toluene. After removal of toluene by steam distillation, the product was methylated with 30 ml. of di-

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(11) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

(12) Robinson and Rydon, *J. Chem. Soc.*, 1394 (1939).

(13) All melting points are uncorrected.

methyl sulfate and alkali. The crude acid (23.5 g.) was sublimed under reduced pressure to afford a 75% yield of pale yellow solid m.p. 129–131.5°, which was crystallized from benzene-ligroin to yield shiny white crystals, m.p. 136°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.78; H, 6.56. Found: C, 73.51; H, 6.62.

4-Keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene (V). To γ-(2-methoxy-6-naphthyl)butyric acid (1.5 g.) suspended in 30 ml. of thiophene free benzene, phosphorus pentachloride (2.5 g.) was added. The mixture was allowed to stand for 0.5 hr. at room temperature, heated at 60° for 1 hr., and then subsequently heated for 5 min. on steam bath. The mixture was then cooled, and anhydrous stannic chloride (0.74 ml.) in thiophene free benzene (6 ml.) was added with shaking. After 10 min. the reaction mixture was decomposed with ether (9 ml.) and hydrochloric acid (9 ml.). The ether-benzene extract was washed thrice with hydrochloric acid (1:1), once with distilled water, and finally three times with dilute ammonia. On removal of the solvent, a white crystalline product, m.p. 146–152°, was obtained. Crystallization from benzene-alcohol afforded the pure ketone (0.7 g.), m.p. 168°. A 0.3-g. of sample of the impure ketone could be recovered from the mother liquor.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19. Found: C, 79.41; H, 6.30.

The ultraviolet absorption curve shows maxima at 216 (log ϵ 4.57), 251.5 (4.37), 317 (3.69), and 354 (3.52) mμ.

The oxime, m.p. 216°, was crystallized from alcohol-dioxane.

Anal. Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 5.80.

2-Methoxyphenanthrene (VI). The above ketone (0.5 g.) in dry ether (70 ml.) was reduced with lithium aluminum hydride (0.1 g.). After decomposition with 10% sulfuric acid, the ether layer was separated and washed with water. On removal of ether, white solid m.p. 120–122° was obtained. This was heated with fused potassium hydrogen sulphate for 30 min., and the product (0.2 g.) m.p. 127–128°, was purified by sublimation. This was then dehydrogenated for 1 hr. at 300–350° with palladium-charcoal (30%, 0.2 g.). The product was purified by sublimation and crystallized from ethanol to obtain white crystals (0.1 g.), m.p. 98°; the melting point was not depressed on admixture with an authentic specimen of 2-methoxyphenanthrene.

Anal. Calcd. for $C_{15}H_{12}O$: C, 86.54; H, 5.77. Found; C, 86.31; H, 5.88.

The picrate, m.p. 125°, was crystallized from ethanol. Mixed melting point with the picrate of 2-methoxyphenanthrene was undepressed.

Anal. Calcd. for $C_{21}H_{15}N_3O_8$: N, 9.6. Found: N, 9.8.

2-Methoxy-8-bromoacetyl naphthalene (VIII). To a suspension of 7-methoxynaphthoic acid (2.6 g.) in dry thiophene free benzene (10 ml.), thionyl chloride (2.5 g.) was slowly added with shaking. After standing for 30 min., the mixture was maintained at 60° for 30 min. Then the solvent was removed with the help of a water pump. Benzene (15 ml.) was again added and removed, the operation being repeated thrice. The acid chloride was diluted with dry ether (15 ml.) and added to a cooled solution of diazomethane from nitrosomethylurea (7 g.) in ether (50 ml.), and left overnight. Hydrobromic acid (48%, 3 ml.) was added to the above solution. After the evolution of nitrogen was complete, the ethereal solution was washed first with water and then with alkali. On removal of ether, the bromoketone was obtained as solid, and was directly employed in the next step.

β-(2-Methoxy-8-naphthoyl)-α-carboxypropionic acid (IX). To a suspension of ethyl sodio malonate prepared from pulverized sodium (0.47 g.), and ethyl malonate (3.3 ml.) in dry benzene (15 ml.), the solution of the above bromoketone was added with slight cooling. The mixture was refluxed for 4.5 hr. and then decomposed with ice water. The benzene layer was separated, and the residue obtained on removal of benzene was directly hydrolyzed with methanolic potassium hydroxide (40 ml., 10%) for 3.5 hr. Crystals of the potassium salt separated on cooling. After removal of the methanol, the salt was dissolved in water and the solution carefully acidified with cooling, when precipitation took place in two distinct stages. These were separately collected. The first crop (2 g.), m.p. 107°, was found to be impure 7-methoxy-naphthoic acid. The second crop (0.9 g.), m.p. 177° dec., insoluble in benzene and chloroform, was crystallized from methanol twice to yield the pure compound, m.p. 179°.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 63.6; H, 4.6. Found: C, 64.1; H, 4.8.

β-(7-Methoxy-1-naphthoyl)propionic acid (III). The crude malonic acid IX (m.p. 177°, 0.9 g.) was decarboxylated at 180° for 30 min. The product was extracted with bicarbonate. Acidification gave a white solid (0.4 g.) m.p. 145°. After two crystallizations from methanol, colorless crystals were obtained, m.p. 147.5° (lit.[2] m.p. 148°). This acid showed depression in melting point on admixture with both I and II.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.42. Found: C, 69.55; H, 5.45.

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