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

PRODUCTS OF FRIEDEL-CRAFTS ACYLATION OF β-SUBSTITUTED NAPHTHALENES

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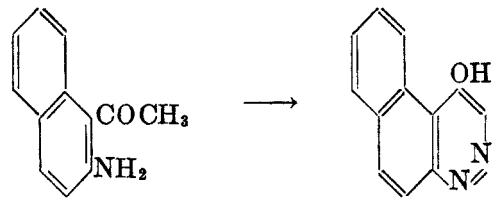
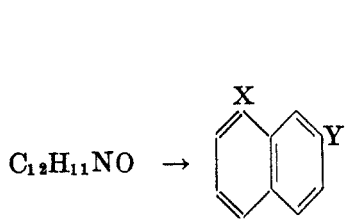
The diazotization and subsequent cyclization of *o*-aminoaryl alkyl ketones with the formation of 4-hydroxycinnolines is of such generality (1, 2, 3) as to serve as a positive indication of the vicinal arrangement of the amino and acyl groups on the aromatic nucleus in such compounds. When it was discovered (4) that the compound reported to have the structure 2-amino-1-acetonaphthone (I) (5) did not form a 4-hydroxycinnoline (II) under the usual diazotization and cyclization conditions, there was reasonable doubt as to the validity of the assigned structure of this aminoacetonaphthone. The compound (III), which had been



I II

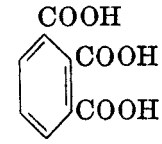
obtained by Friedel-Crafts acetylation of acet-2-naphthalide followed by hydrolysis (2, 5), was therefore subjected to degradative study to determine the position at which the acetyl group had entered the molecule.

Removal of the amino group of III by diazotization and subsequent treatment with hypophosphorous acid led to the formation of 1-acetonaphthone (IV), which was identified by the melting point of its picrate and by the melting point of the 1-naphthoic acid (V) formed by hypochlorite oxidation. The attachment of the acetyl group at an *alpha* position was thus indicated. Replacement of the amino group of III by a hydroxyl group gave a hydroxyacetonaphthone (VI) (4) which was oxidized by permanganate to hemimellitic acid (VII). With the



III

	X	Y
IV	$COCH_3$	H
V	COOH	H
VI	$COCH_3$	OH
VIII	$COCH_3$	OCH_3
IX	COOH	OCH_3
X	COOH	OH
XI	COOH	NH_2



VII

position of attachment of the acetyl group thus limited to the 5- or the 8-position relative to the 2-amino group in III, the final distinction was possible through recourse to mild oxidation reactions. Conversion of VI to the methoxyaceto-

naphthone VIII was followed by hypochlorite oxidation to the known 7-methoxy-1-naphthoic acid (IX) (6), and the acid hydrolysis product of IX was identified as 7-hydroxy-1-naphthoic acid (X) (6, 7). The product of hypoiodite oxidation of the acetyl derivative of III was identified as 7-acetylamino-1-naphthoic acid and was hydrolyzed to the known 7-amino-1-naphthoic acid (XI) (8).

The accumulation of corroberative evidence for 7-amino-1-acetonaphthone as the structure of III was considered desirable because this conclusion makes necessary the revision of the structures of numerous related naphthalene derivatives described in the literature as 1,2-substituted compounds.

The evidence that the "2-amino-1-acetonaphthone" of Brown, Jacobs, Winstein, Levy, Moss, and Ott (5), obtained by Friedel-Crafts acetylation of acet-2-naphthalide followed by hydrolysis, is in reality 7-amino-1-acetonaphthone suggests that the derived "2-halo-1-acetonaphthones" are likewise 1,7-isomers. These workers (5) prepared a bromoacetonaphthone from III by diazotization followed by a Sandmeyer reaction. The compound obtained was found to be identical with one of the bromoacetonaphthones prepared by Friedel-Crafts acetylation of 2-bromonaphthalene and previously assigned the structure 2-bromo-1-acetonaphthone (9).

Dziewonski and Sternbach (9) converted their 2-bromoacetonaphthone to the oxime and thence by a Beckmann rearrangement to a 2-bromoacetnaphthalide. Hydrolysis gave a 2-bromonaphthylamine, the benzoyl derivative of which melted at 220°. More recently, 2-bromo-1-naphthylamine was prepared from 1-nitro-2-naphthylamine (10) and the melting point of the benzoyl derivative was found to be 179°. Hence, the 2-bromonaphthylamine of Dziewonski and Sternbach could not be 2-bromo-1-naphthylamine and, in turn, their 2-bromoacetonaphthone could not be 2-bromo-1-acetonaphthone.

The same 2-bromoacetonaphthone was converted by nitric acid oxidation to a 2-bromonaphthoic acid, m.p. 233° (9). Prior to the work of Dziewonski and Sternbach, neither 2-bromo-1-naphthoic acid nor 7-bromo-1-naphthoic acid had been described in the literature. However, in 1938 Goldstein and Fischer (11) prepared 7-bromo-1-naphthoic acid and reported the melting point 237° (cor.). The proximity of melting points is suggestive of identity inasmuch as in the chloro series 7-chloro-1-naphthoic acid melts at 243° (11) and 2-chloro-1-naphthoic acid melts at 153° (12). A similar disparity would also be expected with the corresponding bromonaphthoic acids, which indicates that the bromonaphthoic acid obtained by Dziewonski and Sternbach is not 2-bromo-1-naphthoic acid but more likely 7-bromo-1-naphthoic acid. The synthesis of the 1,2-acid by an unequivocal method would eliminate any doubt.

Dziewonski and Sternbach (9) also converted their 2-bromonaphthylamine to a dibromonaphthalene, m.p. 68°, and reported this compound to be identical with a dibromonaphthalene described by Guareschi (13). Meldola (14) prepared 1,2-dibromonaphthalene and originally reported the melting point 63°. Further purification was found to raise the melting point to 67–68° (15). 1,7-Dibromonaphthalene is reported to melt at 74° (16) and 75° (17). It is possible that the melting point (68°) of the dibromonaphthalene prepared by Dziewonski and

Sternbach could likewise be revised upward to correspond to the melting point of the 1,7-compound, with which it should be identical on the basis of all other evidence presented. According to Armstrong and Rossiter (16), little or no reliance can be placed on either the appearance or melting point of the dibromonaphthalenes, as a slight impurity suffices to produce very misleading changes.

In Table I are assembled and compared the melting points of authentic 1,7-compounds, of corresponding authentic 1,2-compounds, and of those supposedly "1,2-compounds" which now must be regarded as 1,7.

Applying these findings to correction of the literature, the 2-amino-1-acetonaphthone (2) and hydroxyacetonaphthone (4) of Leonard and Boyd become 7-amino-1-acetonaphthone and 7-hydroxy-1-acetonaphthone, respectively. All of the naphthalene compounds described by Brown, Jacobs, Winstein, Levy, Moss and Ott (5) as "1,2-compounds" are actually 1,7-compounds; these include the substituted acetonaphthones, the derived ω-bromoacetonaphthones, bromohydrins, dialkylammonium bromides, and the final dialkylamino alcohols

TABLE I

COMPARISON OF 1,7- AND 1,2-NAPHTHALENE DERIVATIVES

	MELTING POINTS, °C	
Authentic 1,7-Compound	"1,2-Compd."	1,2-Compd.
7-Bromo-1-naphthylamine, N-benzoyl	220	179
7-Bromo-1-naphthoic Acid, 237	233	
7-Chloro-1-naphthoic Acid, 243		153
1,7-Dibromonaphthalene (a)	68	63
1,7-Dibromonaphthalene (b) 74, 75		67, 68

(a) First report, (b) Report following further purification.

which were tested for antimalarial activity. The 2-bromo-1-acetonaphthone of Dziewonski and Sternbach (9) is actually 7-bromo-1-acetonaphthone and all of the compounds derived from this bromo ketone (9) must now be regarded as 1,7-compounds. Revision of structure is also necessary for two compounds obtained by Anderson and Johnston (18) from the 2-bromo-1-acetonaphthone of Dziewonski and Sternbach: 1-(2-bromonaphthyl)diphenylchloromethane is, instead, 1-(7-bromonaphthyl)diphenylchloromethane, and 1-(2-bromonaphthyl)-diphenylcarbinol is 1-(7-bromonaphthyl)diphenylcarbinol.

In the Friedel-Crafts acylation of naphthalenes substituted in the β-position by halogen or acetylamino we have shown that substitution occurs preferentially in the unsubstituted ring. This orientation may be due to the deactivation of the substituted ring toward electrophilic substitution. Such deactivation would be due to the halogen atom in the 2-halonaphthalenes and to aluminum chloride complex formation by the 2-acetylamino group in acet-2-naphthalide. Two factors influence the position in the unsubstituted ring at which acylation will then occur. One is the orientation effect of the 2-halo or acetylamino group, which will favor substitution in the 6- or 8-position. The other is the usual

α-orientation effect of the naphthalene nucleus, which will encourage substitution in the 5- or 8-position. The two effects supplement each other in directing substitution at the 8-position, which explains the formation of the 2,8 (or 1,7)-disubstituted naphthalenes in preponderant yield in the acylation of these β-substituted naphthalenes. It is interesting and not altogether consistent with these observations that the 1-halonaphthalenes undergo Friedel-Crafts acylation predominantly in the 4-position. Yet there appears to be no question as to the established structure of these 1,4-compounds (19).

In the Friedel-Crafts acylation of naphthalenes substituted in the β-position by methoxyl, the products obtained are more diverse, and the orientation effect of the methoxyl group appears to be more important than any aluminum chloride-complexing effect in deciding the position of substitution. One complicating factor in the study has been the cleavage by aluminum chloride of the ether linkage in the β-alkoxynaphthalenes (20). With a monofunctional acylating agent, substitution on 2-methoxynaphthalene occurred at the 1-position (21, 22, 23). With a bifunctional acylating agent such as oxalyl chloride or malonylchloride, substitution occurred at both 1- and 8-positions relative to the 2-methoxyl group (24, 25, 26). Finally, there is conflicting evidence in the literature as to the structure of the compound produced in the reaction of 2-methoxynaphthalene in carbon disulfide with succinic anhydride in the presence of aluminum chloride. One group of investigators (27) indicated the 8-position, and another group (28) the 1-position as the point of substitution on the naphthalene nucleus, with no plausible explanation being advanced for these differing products.

EXPERIMENTAL[1]

Acet-2-naphthalide, m.p. 131–132°, was prepared by the method of Kaufman (29).

7-Amino-1-acetonaphthone, m.p. 108.5–110°, was prepared by Friedel-Crafts acetylation of acet-2-naphthalide according to the method of Brown and co-workers (5) and reported as 2-amino-1-acetonaphthone.

1-Acetonaphthone. Two grams of 7-amino-1-acetonaphthone was diazotized in the usual manner (4) and fifteen mole-equivalents of hypophosphorous acid was added to the cold solution during fifteen minutes. The reaction mixture was maintained at 0° for 24 hours, and the reddish brown oil which separated was extracted with ether. The ether solution was washed with 5 *N* sodium hydroxide, with water, and dried. An oil remained after the ether was evaporated.

The picrate was prepared by treating a small amount of the oil with picric acid in ether and was recrystallized from ether; m.p. 115.5°. Stobbe (30) reported the melting point 116°.

1-Naphthoic acid. About 0.3 g. of 1-acetonaphthone in aqueous methanol was treated with a solution of sodium hypochlorite (commercial Clorox) and the reaction mixture was worked up in the usual manner for hypochlorite oxidations. After purification, the acid obtained melted at 161°, and a mixed melting point with an authentic sample of 1-naphthoic acid showed no depression.

7-Hydroxy-1-acetonaphthone. The diazotization of 9.2 g. (0.05 mole) of 7-amino-1-acetonaphthone was carried out in the usual manner (4), and the solution was allowed to stand for two days at room temperature before heating on the steam-bath for one hour. Sufficient ethanol was added to dissolve the black precipitate, and the solution was filtered hot. The

[1] All melting points are corrected. Microanalyses by Miss Theta Spoor.

cooled filtrate was extracted with ether and the combined ether extracts were evaporated. The residue was dissolved in benzene, and the solution was filtered following decolorization with Darco. The crystals which formed when the filtrate was cooled were recrystallized from benzene-ligroin as pale yellow needles, m.p. 149–150.°

Hemimellitic acid (*31*). One gram of 7-hydroxy-1-acetonaphthone was subjected to vigorous alkaline permanganate oxidation followed by a short period of acidic oxidation. After removal of the precipitated manganese dioxide, the solution was evaporated nearly to dryness and 50 ml. of 12 *N* hydrochloric acid was added to the sludge. This mixture was extracted repeatedly with ether and ethyl acetate, and the combined extracts were evaporated to dryness. The residue was dissolved in a few ml. of hot water, decolorized with Darco, and filtered. An equal quantity of 12 *N* hydrochloric acid was added to the filtrate and the resulting yellow-green solution was placed in the ice-box overnight. Small white crystals appeared which melted at 184–197°. The material was dissolved in a small amount of water; the solution was saturated with hydrogen chloride and then placed in the ice-box overnight. The colorless crystals were collected and dried over phosphorus pentoxide at 100° for 15 hours; m.p. 195–196.5° (lit., 190°). Neutral equivalent: Calc'd for $C_9H_6O_6$: 70. Found: 70.5.

7-Methoxy-1-acetonaphthone. Two grams of 7-hydroxy-1-acetonaphthone was treated with sodium hydroxide and dimethyl sulfate until no yellow coloration was obtained upon addition of sodium hydroxide. Sufficient ethanol was added to create a clear solution at room temperature, and the solution was placed in the ice-box overnight. The white prisms, m.p. 62–63°, after recrystallization from aqueous ethanol, had the sharp m.p. 63°; yield, 1.8 g.

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.97; H, 6.00.
Found: C, 77.97; H, 6.11.

7-Methoxy-1-naphthoic acid (6). One gram of 7-methoxy-1-acetonaphthone was treated with a methanol-water solution of sodium hypochlorite (commercial Clorox), and the solution was worked up in the usual manner. One gram of an acid was obtained which melted at 165.5–168.5°. Recrystallization from aqueous ethanol gave long white needles, m.p. 168.5–169° (lit., 167–168°).

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.27; H, 4.99.
Found: C, 71.12; H, 5.03.

7-Hydroxy-1-naphthoic acid (6, 7). 7-Methoxy-1-naphthoic acid (0.24 g.) was treated with 25 ml. of 12 *N* hydrochloric acid, and the mixture was heated under reflux for three hours. The solution was filtered hot and a small amount of white flocculent precipitate appeared in the cooled filtrate; m.p. 253–255°. Recrystallization from acetone-ligroin gave a white powder which softened at 253° and melted at 256°. Recrystallization from chlorobenzene gave fine colorless needles, m.p. 254–255° (lit., 253–254°).

7-Acetylamino-1-acetonaphthone (5). 7-Amino-1-acetonaphthone was acetylated by the method of Kaufman (29) to give needles, m.p. 149–150°.

7-Acetylamino-1-naphthoic acid (8). 7-Acetylamino-1-acetonaphthone (2.5 g.) dissolved in 25 ml. of dioxane was placed in a flask fitted with a stirrer and a dropping-funnel and surrounded by an ice-bath. One hundred grams of a solution containing 12.5 g. of iodine and 50 g. of potassium iodide per 100 g. of water was added with stirring over a period of one hour. Five grams of sodium hydroxide in 25 ml. of water was added in portions during this period. After the addition of the iodine solution, the reaction mixture was allowed to stand at room temperature overnight. A small amount of sodium bisulfite was added to destroy any excess sodium hypoiodite and the precipitated iodoform was removed. The orange-red filtrate was extracted with two 50-ml. portions of ether. The ether was evaporated on the steam-bath and the red oily residue was extracted with aqueous sodium bicarbonate. The sodium bicarbonate solution was decolorized with Darco and filtered. The filtrate was acidified carefully with hydrochloric acid; the precipitated acid had the m.p. 231–233°; yield, *ca.* 0.30 g. After two recrystallizations from aqueous ethanol, the white needles melted at 237–238° (lit., 229–230°).

Anal. Calc'd for $C_{13}H_{11}NO_3$: C, 68.13; H, 4.84; N, 6.11.
Found: C, 68.38; H, 4.93; N, 6.26.

7-Amino-1-naphthoic acid (8). About 0.20 g. of 7-acetylamino-1-naphthoic acid was treated with dilute hydrochloric acid and warmed on the steam-bath for one-half hour. The solution was filtered and neutralized with sodium hydroxide, after which it was reacidified with a very slight excess of acetic acid. This solution was then extracted with three portions of ether. The combined ether extracts, which showed a blue-green fluorescence, were evaporated to dryness and the residue extracted with benzene. An equal volume of ligroin was added to the benzene solution and after evaporation of a considerable portion of the benzene, crystallization occurred.

The light tan needles were washed with ligroin; m.p. 228.5–230° (lit., 223–224°).

SUMMARY

The structure of the product of Friedel-Crafts acetylation of acet-2-naphthalide has been proved to be 7-amino-1-acetonaphthone. The product of analogous acetylation of 2-bromo- or 2-chloro-naphthalene has been shown to be the corresponding 7-halo-1-acetonaphthone.

These conclusions have made necessary the revision of the structures of numerous related naphthalene derivatives described in the literature as 1,2-substituted compounds.

The function of halogen, acetylamino, and methoxyl groups in β-substituted naphthalenes, in directing the position of attack during Friedel-Crafts acylation, has been discussed.

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