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THE CHEMISTRY OF 1-NAPHTHALENEACETIC ACID DERIVATIVES

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The ferric oxide-potassium bromide-catalyzed condensation of naphthalene with chloroacetic acid yielding 1-naphthaleneacetic acid (1) together with 1,5-naphthalenediacetic acid (2) was an object of study here. Related reactions such as those of naphthalene with α-halo fatty acids or that of 1-methylnaphthalene with chloroacetic acid (2) also have been studied in this laboratory. The present paper is an extension which deals with the condensation of chloroacetic acid with 1-halo-, 1-methoxy-, and 2-methoxy-naphthalene. The halogenation, nitration, and sulfonation of 1-naphthaleneacetic acid and some reactions of the product formed have also been investigated.

The patent literature (3) describes the non-catalytic condensations of chloroacetic acid with 1-chloro- and 1-bromo-naphthalene. There were claimed chloronaphthaleneacetic acid of m.p. 124° and bromonaphthaleneacetic acid of m.p. 122–128°, respectively. From our results, however, these products appear to be mixtures of corresponding isomers. The report that 4-bromo-1-naphthaleneacetic acid (m.p. 149–150°) was synthesized by way of bromomethylation (4) seems unsatisfactory with respect to the method used for determining the structure of the product. There is little literature regarding the halogenation, nitration, and sulfonation of 1-naphthaleneacetic acid. As described in the following pages, these electrophilic substitutions occur in the 4- or 5-position, just as those in 1-methylnaphthalene.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Syntheses described below are those under optimum conditions. Asterisks indicate new compounds.

Materials. Materials used are substantially the same as those in the previous paper (2). *1-Naphthaleneacetic acid* was prepared by reaction of naphthalene with chloroacetic acid, m.p. 126–128°. *1-Chloronaphthalene* (b.p. 253–257°) and *1-bromonaphthalene* (b.p. 175–180°/80 mm.) were prepared by chlorination (5) and bromination (6) of naphthalene, respectively. *1-Methoxynaphthalene* (b.p. 260–264°) and *2-methoxynaphthalene* (m.p. 70–72°) were prepared by methylating appropriate naphthols (7).

*4-Chloro-1-naphthaleneacetic acid.** (*a*) *Chlorination of 1-naphthaleneacetic acid.* 1-Naphthaleneacetic acid (10 g.) was dissolved in 15 cc. of glacial acetic acid, 0.2 g. of iodine was added, and then chlorine was introduced for three hours with gentle boiling. After standing overnight, a greenish black precipitate of crude 4-chloro-1-naphthaleneacetic acid (m.p. *ca.* 146°) was collected. The yield is 2.6 g. (22%). The crude product was recrystallized several times from aqueous acetic acid yielding colorless needles melting at 172–174°. Each recrystallization involved about a 25% loss of material. Titration gave the molecular weight 222; Calc'd for the monobasic acid, $C_{12}H_9ClO_2$: 221.

The *potassium salt* of this acid was dry-distilled. The oily product thus obtained formed a picrate, m.p. 119–121° from methanol, which showed no depression upon admixture with the authentic *picrate** of *1-methyl-4-chloronaphthalene* prepared by the chlorination of 1-methylnaphthalene (8). There is no description of the determination of the structure of the authentic material, which, however, was identified again in our hands; *i.e.*, it gave 4-chloro-1-naphthoic acid by boiling with 6% nitric acid for 30 hours, m.p. 209–211°; literature m.p. 210° (9).

(*b*) *Condensation of 1-chloronaphthalene with chloroacetic acid.* A mixture of 1-chloronaphthalene (18 g.), chloroacetic acid (7.0 g., 2/3 equivalent), ferric oxide (0.031 g.), and potassium bromide (0.155 g.) was refluxed for 20 hours. The temperature was adjusted so as to attain 203° after 10 hours and 222° after 20 hours. The reaction mixture was then vacuum-distilled. After recovering unreacted chloronaphthalene (10 g.), 7 g. (58%) of crude chloronaphthaleneacetic acids boiling at 220–250° (45 mm.) was obtained. The crude product was extracted with aqueous alkali, filtered, precipitated again by hydrochloric acid, and then crystallized repeatedly from ether and aqueous acetic acid. The m.p. was thus raised to 172° with slight previous softening. The m.p. was not depressed by admixture of 4-chloro-1-naphthaleneacetic acid described in (*a*). From the mother liquor, colorless crystals of m.p. 144–146°, with slight previous softening, were isolated. The molecular weight, 220, found by acidimetric titration, was in agreement with that of chloronaphthaleneacetic acid, 221.

*4-Bromo-1-naphthaleneacetic acid.** (*a*) *Bromination of 1-naphthaleneacetic acid.* 1-Naphthaleneacetic acid (10 g.) was dissolved in glacial acetic acid, bromine (8.5 g., theoretical amount) was added, and the mixture was heated in a water-bath at 60–80° for 2 hours. After standing overnight, crude 4-bromo-1-naphthaleneacetic acid (m.p. *ca.* 166°) was precipitated. The yield amounted to 6.7 g. (47%). Crystallization from aqueous acetic acid yielded the pure acid as needles melting at 174.5–175.5°; recrystallization loss, *ca.* 30%. Titration gave the molecular weight 262. Calc'd for the monobasic acid, $C_{12}H_9BrO_2$: 265.

The position occupied by the bromine atom on the naphthalene nucleus was determined by dry distillation of the potassium salt. The distillate gave a picrate of m.p. 122–124°, which showed no depression after admixture of 1-methyl-4-bromonaphthalene picrate [m.p. 122–124°; literature m.p. 124° (10) and 127° (11)] prepared by the bromination of 1-methylnaphthalene.

(*b*) *Condensation of 1-bromonaphthalene with chloroacetic acid.* A mixture of 1-bromonaphthalene (47 g.), chloroacetic acid (14.3 g., 2/3 equivalent), ferric oxide (0.077 g.), and potassium bromide (0.385 g.) was heated for 20 hours. The temperature rose to 195° after 10 hours, and to 217° after 20 hours. After distilling unreacted bromonaphthalene (32 g.), 11.5 g. (29%) of a crude mixture of bromonaphthaleneacetic acids (b.p. 210–250°/12 mm.) was obtained. Treatment as described for chloronaphthaleneacetic acid gave a pure acid melting at 174–175°. Recrystallization involved more than 60% loss. The mother liquor gave an isomeric acid melting at 131–133° with slight previous softening; titration gave a molecular weight of 262 for this substance (Calc'd for $C_{12}H_9BrO_2$: 265).

2-Methoxy-1-naphthaleneacetic acid and 2-hydroxy-1-naphthaleneacetic acid lactone.* A mixture of 2-methoxynaphthalene (30 g.), chloroacetic acid (9 g., 1/2 equivalent), ferric oxide (0.049 g.), and potassium bromide (0.245 g.) was refluxed for 20 hours, the temperature rising to 195° after 10 hours and to 212° after 20 hours. The alkaline extract of the reaction product gave on acidification 14 g. (68%) of crude 2-methoxy-1-naphthaleneacetic acid, while non-catalytic condensation afforded only 7% yield. From the extraction residue 12 g. of unreacted methoxynaphthalene was recovered by distillation. The crude acid was vacuum-distilled; the main fraction, 7 g. (b.p. 255–270°/53 mm.), was crystallized twice from acetic acid to yield 2.1 g. of fine laminae, m.p. 211–213°. The colorless acid tended to be bluish on standing. Titration gave the molecular weight 213 (Calc'd for $C_{13}H_{12}O_3$: 216).

Distillation of the potassium salt from 2.5 g. of the acid gave 0.4 g. of crystals from which 1-methyl-2-methoxynaphthalene (m.p. 41–42°) was obtained by recrystallization, and it was identical (m.p. and mixture m.p.) with a specimen prepared by the successive reaction of 2-naphthol with formaldehyde, zinc powder, and methyl sulfate (12).

2-Methoxy-1-naphthaleneacetic acid (0.3 g.) was suspended in 5 parts of conc'd hydriodic acid (_sp. gr._ 1.70) and boiled gently on an oil bath for _ca._ one hour. The product (0.25 g.), after thoroughly washing with water, was crystallized from aqueous acetic acid to give crystals of m.p. 103–104°, difficultly soluble in water and cold aqueous alkali but soluble in boiling aqueous alkali. These properties agree with those of 2-hydroxy-1-naphthaleneacetic acid lactone [literature m.p. 103–104° (13)].

Anal. Calc'd for $C_{12}H_8O_2$: C, 78.23; H, 4.38.
Found: C, 78.18; H, 4.38.

_4- and 5-Methoxy-1-naphthaleneacetic acid;_* _4- and 5-hydroxy-1-naphthaleneacetic acid._* A mixture of 1-methoxynaphthalene (30 g.), chloroacetic acid (9 g., 1/2 equivalent), ferric oxide (0.049 g.), and potassium bromide (0.245 g.) was refluxed for 20 hours. The temperature reached 190° after 10 hours and 210° after 20 hours. After recovery of unreacted methoxynaphthalene (15 g.), a mixture of methoxynaphthaleneacetic acids (10 g., 49%) was distilled at 220–250° (35 mm.). The yield was very poor in the absence of these catalysts. The distillate was worked up as already described. Recrystallization from aqueous acetic acid provided comparatively soluble needles of m.p. 141–143° (I) together with less soluble laminae of m.p. 194–195° (II). The evidence presented below appears to show that the former is 4-methoxy-1-naphthaleneacetic acid and the latter is the 5,1-isomer. Titration gave molecular weights of 218 (I) and 215 (II) (Calc'd for $C_{13}H_{12}O_3$: 216).

Dry distillation of the potassium salt of acid I gave an oily substance (III). Demethylation of III with conc'd hydriodic acid gave 1-methyl-4-hydroxynaphthalene, whose _picrate_* melted at 163–165° and showed no depression after admixture with the picrate of authentic 1-methyl-4-hydroxynaphthalene [m.p. 82–84°; literature m.p. 84–85° (14), 84° (15), and 79–81° (16)] prepared by successive sulfonation and potassium hydroxide fusion of 1-methylnaphthalene. Furthermore the picrate of III, m.p. 141–143° was identical (m.p. and mixture m.p.) with the picrate of 1-methyl-4-methoxynaphthalene [m.p. in literature, 146–147° (17)] prepared by the methylation of 1-methyl-4-hydroxynaphthalene with methyl sulfate. The hydriodic acid treatment of I (0.1 g.) gave _4-hydroxy-1-naphthaleneacetic acid_* (0.05 g.). When recrystallized from water, it gave pure material in the form of laminae, m.p. 190–192° (dec.) (open) and 192–194° (block).

The distillate from the potassium salt of acid II was solid, and, after recrystallization from aqueous acetic acid, it gave laminae, m.p. 54–55°. It probably is _1-methyl-5-methoxynaphthalene_* (IV), since the m.p. is different from those of 1,2- (liquid) (18), 1,4- (liquid) (17), 1,6- (48°) (19), and 1,7-methylmethoxynaphthalene (46–48°) (20), and the formation of the 1,3- or 1,8-isomer seems less probable.

Anal. Calc'd for $C_{12}H_{12}O$: C, 83.68; H, 7.02.
Found: C, 84.19; H, 6.93.

The _picrate_* _of IV_ melted at 144–145°. Demethylation of IV by refluxing with hydriodic acid followed by an alkaline extraction and reprecipitation with hydrochloric acid yielded crystals of m.p. 91–93°, which showed a depression on admixture of authentic 4-hydroxy-1-methylnaphthalene. The m.p. of 5-hydroxy-1-methylnaphthalene in the literature (21) is 97°. The hydriodic acid treatment of II (0.3 g.) afforded 5-hydroxy-1-naphthaleneacetic acid (0.22 g.), which, on recrystallization from very dilute methanol, gave crystals of m.p. 196–198° (dec.) (open) and 197–198° (block).

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.27; H, 4.99.
Found: C, 71.84; H, 5.02.

_4-Nitro-1-naphthaleneacetic acid._* To a stirred solution of 1-naphthaleneacetic acid (10 g.) in 20 cc. of glacial acetic acid was added 5 g. (1.5 equivalents) of fuming nitric acid (_sp. gr._ 1.52) at 25–30° over a period of one hour. After stirring for more two hours at the same temperature, the mixture was allowed to stand at about 20° for one day. The yellow crystals deposited amounted to 3.4 g. (28%), m.p. _ca._ 143°. The m.p. could be raised to 154.5–156.5° by repeated crystallizations from aqueous acetic acid. The loss of each recrystallization was about 30%. The pure product forms light yellow laminae. Titration gave the molecular weight 228 (Calc'd for $C_{12}H_9NO_4$: 231).

The pyrolytic product from the potassium salt of the above acid was recrystallized to give light-yellow needles of m.p. 71–72°, identical (m.p. and mixture m.p.) with authentic 1-methyl-4-nitronaphthalene [m.p. 72°; literature m.p. 72° (22)] prepared by the nitration of 1-methylnaphthalene.

*4-Amino-1-naphthaleneacetic acid.** Pure 4-nitro-1-naphthaleneacetic acid (5 g.), tin foil (9 g., 1.3 equivalents), and 30% hydrochloric acid (20 cc., 3 equivalents) were heated under reflux to *ca.* 80°. After cessation of the vigorous reaction the reduction was completed by heating on the water-bath for about 2 hours. The reaction mixture was then treated with 30% hydrochloric acid (50 cc.) and allowed to stand overnight. The white precipitate thus obtained amounted to 4.9 g. (86%), m.p. *ca.* 190° (dec.). Recrystallization from conc'd hydrochloric acid afforded pure *4-amino-1-naphthaleneacetic acid hydrochloride,** m.p. 211–213° (dec.), with *ca.* 50% loss on recrystallization.

Anal. Calc'd for $C_{12}H_{12}ClNO_2$: C, 60.64; H, 5.89.

Found: C, 61.12; H, 5.78.

The *hydrochloride* was converted to the free base by the addition of an equivalent amount of aqueous sodium hydroxide. After purification by recrystallization from ether, the *free base* melted at 119–121°. Diazotized 4-amino-1-naphthaleneacetic acid produced dyestuffs when coupled with 1-naphthol (red), 2-naphthol (orange), naphthol AS (brown), H-acid (deep violet), chromotropic acid (light violet), G-acid (brown), *m*-xylidine (yellowish orange), 1-naphthylamine (brown), and diphenylamine (brown).

1-Naphthaleneacetic acid-5-sulfonic acid, 5-hydroxy- and 5-methoxy-naphthaleneacetic acids.* Into 20 g. (4 equivalents) of conc'd sulfuric acid was added with stirring 10 g. of 1-naphthaleneacetic acid. The mixture was heated at 40–50° for 8 hours. The reaction product was poured into water, neutralized with barium carbonate, filtered, and evaporated to dryness. The dibarium salt of 1-naphthaleneacetic acid-5-sulfonic acid (19.7 g., 89%) (V) thus obtained contains one molecule of water of crystallization, determined by the weight decrease of a sample when air-dried at 150° for 30 minutes. Weight decrease calc'd for $C_{12}H_8BaO_5S \cdot H_2O$: 4.3%. Found: 4.2%. The barium was estimated by the weight of barium carbonate precipitated from the anhydrous salt with sodium carbonate.

Anal. Calc'd for $C_{12}H_8BaO_5S$: Ba, 34.22. Found: Ba, 33.93.

From the reaction of an aqueous solution of V with sodium carbonate, *ca.* 15 g. of disodium salt was obtained as hygroscopic crystals. To a melted mixture of potassium hydroxide (50 g.) and water (5 cc.) was added the disodium salt (10 g.) in several portions at 230–240°. After brown oily matter appeared floating on the surface (about 20 minutes), stirring was continued for 5 to 10 minutes. The reaction mixture was dissolved in water, filtered, acidified with hydrochloric acid and allowed to stand overnight. The precipitate of crude white 5-hydroxy-1-naphthaleneacetic acid (m.p. *ca.* 156°) was collected; yield, 2.3 g. (35%). The crude hydroxy acid (5 g.) was methylated with methyl sulfate (8 g.) in sodium hydroxide (2.5 g.) and water (15 cc.) at 0–5° in the usual way (7). After completing the reaction, the solution was boiled with the addition of 50 cc. of 10% sodium hydroxide to insure hydrolysis of the methyl ester. Acidification of the solution gave a precipitate of crude 5-methoxy-1-naphthaleneacetic acid; yield, 3.7 g. (69%), m.p. *ca.* 187°. Recrystallization from aqueous acetic acid afforded pure crystals, m.p. 192–194° (block), which showed no depression upon admixture of the 5-methoxy-1-naphthaleneacetic acid described before. Recrystallization resulted in about a 30% loss of material.

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SUMMARY

1. The ferric oxide-potassium bromide-catalyzed condensations of chloroacetic acid with substituted naphthalenes have been studied. 1-Chloro-4-naphthaleneacetic acid has been prepared from 1-chloronaphthalene, 1-bromo-4-naphthalene-

acetic acid from 1-bromonaphthalene, 2-methoxy-1-naphthaleneacetic acid from 2-methoxynaphthalene, and 1-methoxy-4- and probably 1-methoxy-5-naphthaleneacetic acid from 1-methoxynaphthalene. The structures of these products have been established.

2. The following new compounds have been synthesized from 1-naphthaleneacetic acid using well-known procedures: 4-chloro-, 4-bromo-, 4-nitro-, and 4-amino-1-naphthaleneacetic acid; the dibarium salt of 1-naphthaleneacetic acid-5-sulfonic acid; and 1-methyl-5-methoxynaphthalene.

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