[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

CONDENSATION OF NAPHTHALENES WITH α-HALO FATTY ACIDS AND RELATED REACTIONS

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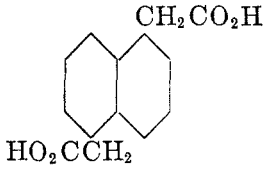
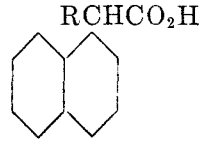
The preparation of α-naphthaleneacetic acid by the condensation of naphthalene with chloroacetic acid in the presence of ferric oxide and potassium bromide was recently reported (1). The promoting action of the bromide may be ascribed to its ability to convert chloroacetic acid to bromoacetic acid. The lower yield and melting point of the product obtained when the molar ratio of chloroacetic acid to naphthalene is increased from 1:3 to 1:1 may be attributed to disubstitution at the higher ratio. In the present paper it is shown that the two substituents enter the 1- and 5-positions mainly, yielding 1,5-naphthalenediacetic acid (I). Similar orientation occurs in disulfonation (2) and bis-chloromethylation (3) at low temperatures.



I



II R = CH_3
III R = C_2H_5

The similar condensation of naphthalene with α-halo fatty acids yields the corresponding naphthalene fatty acids, *e.g.* α-1-naphthalene propionic acid (II) and α-1-naphthalenebutyric acid (III). These acids have been prepared previously (4) from the corresponding 1-naphthalenemalonic acids by decarboxylation. The present method should prove simpler.

The patent literature (5) describes the preparation of 1-naphthaleneacetonitrile from naphthalene and chloroacetonitrile using ferric chloride as a catalyst. Our ferric oxide-potassium bromide catalyst also gives good results in this condensation.

Attempts to condense naphthalene derivatives or other aromatic compounds with chloroacetic acid have so far been unsatisfactory except with biphenyl and 1-methylnaphthalene. *p*-Xenylacetic acid so obtained from biphenyl has been prepared previously from methyl xenyl ketone through the Willgerodt reaction (6) and from *p*-xenylhydroxyacetic acid through reduction (7).

The synthesis of the above acids has been studied for the eventual purpose of preparing antispasmodics (4, 7).

EXPERIMENTAL

Materials. The naphthalene was purified by distillation to m.p. 80–81.5°. It contained about 0.0008% iron. The chloroacetic acid melted at 61–63°. α-Chloropropionic acid was obtained by reaction of calcium lactate with phosphorus pentachloride. It boiled at 185–190°. α-Bromobutyric acid, b.p. 146–151° (75 mm.), was prepared by brominating butyric

acid. Chloroacetonitrile, b.p. 123–127°, was prepared by the dehydration of chloroacetamide with phosphorus pentoxide (8). 1-Methylnaphthalene, b.p. 239–242° (uncorr.), was obtained in 70% yield by the dry distillation of potassium α-naphthaleneacetate.

1,5-Naphthalenediacetic acid. Naphthalene (128 g., 1 mole), chloroacetic acid (18 g., 2 moles), ferric oxide (0.4 g.), and potassium bromide (2 g.) were heated together at reflux for 20 hours in a flask equipped with a thermometer and an air-condenser. The temperature reached 208° after 15 hours and dropped to 198° at the end of the reaction. The cooled reaction mixture was extracted with aqueous sodium hydroxide, the extract filtered and acidified, and the precipitated crude acid (88 g.) collected. It was esterified by boiling for 2 hours with a 5-fold excess of methanol containing 10% of sulfuric acid. The excess methanol was evaporated. The residue was neutralized with aqueous alkali, washed with water, and extracted with benzene. The extract was dried over calcium chloride and distilled. The oily distillate (35 g.) boiling at 185–200° (20 mm.) was identified as methyl 1-naphthaleneacetate by alkaline hydrolysis to pure 1-naphthaleneacetic acid (m.p. 131°). Two higher-boiling fractions, b.p. 200–240° (20 mm.) (4 g.) and b.p. 240–260° (20 mm.) (11 g.) gave 1.3 g. and 5.6 g. respectively of crystals on cooling. These were combined and recrystallized from an 8-fold excess of kerosene. The product (dimethyl 1,5-naphthalenediacetate) separated as needles, m.p. 125–126.5°. The loss on recrystallization was 30%. Hydrolysis with 10% aqueous sodium hydroxide followed by acidification gave 3.7 g. of crude acid, m.p. *ca.* 244°. Recrystallization from dilute aqueous acetic acid gave m.p. 278–280°, which is in agreement with the literature value of 280° (3a). Titration of the potassium salt with 0.1 *N* oxalic acid using phenolphthalein as an indicator gave the molecular weight 242. Calc'd for the dibasic acid, $C_{14}H_{12}O_4$: 244.

The positions occupied by the substituents on the naphthalene nucleus were determined by distilling the potassium salt of the acid. The distillate gave crystals of m.p. 80–82° in good yield. These showed no melting point depression when mixed with an authentic sample of 1,5-dimethylnaphthalene (m.p. 80–82°) prepared by reduction of 1,5-bis(chloromethyl)naphthalene with zinc powder in alcohol saturated with hydrogen chloride (9, 3d).

α-1-Naphthalenepropionic acid. A mixture of naphthalene (38 g., 0.3 mole), α-chloropropionic acid (10.8 g., 0.1 mole), ferric oxide (0.061 g.). and potassium bromide (0.305 g.) was refluxed for 20 hours. The temperature was 195° after 10 hours and 210° after 20 hours. After the reaction was ended naphthalene (24 g.) was recovered by distillation. The residue was worked up as in the previous reaction. The precipitated acid was taken up in ether and the ether solution was distilled, eventually in a vacuum. The yield of acid, b.p. 224–230° (22 mm.), was 3.8 g. (19% based on the chloropropionic acid). Successive recrystallizations from kerosene and ether raised the m.p. to 149–150.5° which agrees with the literature value (4) for α-1-naphthalenepropionic acid (148–149°). The recrystallizations resulted in about a 30% loss of material. Titration gave the molecular weight 194. Calc'd for the monobasic acid, $C_{13}H_{12}O_2$: 200.

Distillation of the potassium salt of the acid gave an oily substance. Its picrate (from methanol), m.p. 97–99°, showed no melting point depression when mixed with the picrate [m.p. 100° (10)] of 1-ethylnaphthalene prepared by a Fittig synthesis.

α-1-Naphthalenebutyric acid. Naphthalene (46 g.), α-bromobutyric acid (20 g.), and ferric oxide (0.083 g.) were refluxed together at 180–190° for 20 hours. The reaction mixture was worked up as before, unreacted naphthalene and bromobutyric acid (2 g.) being recovered. The product, b.p. 215–224° (15 mm.), was obtained in a 5-g. yield (22% based on the bromobutyric acid reacted, 25% based on the naphthalene reacted). Slow recrystallization from a mixture of ethyl ether and petroleum ether gave prisms, m.p. 86–87° [literature 86–87° (4)]; loss about 50%. Titration gave the molecular weight 212. Calc'd for the monobasic acid, $C_{14}H_{14}O_2$: 214.

Dry distillation of the potassium salt yielded an oil which gave a picrate (from methanol) melting at 90–92°. This agrees with the literature value of 91–92° (10) for the picrate of 1-*n*-propylnaphthalene.

1-Naphthaleneacetonitrile. A mixture of naphthalene (51 g.), chloroacetonitrile (10 g.), ferric oxide (0.076 g.), and potassium bromide (0.380 g.) was refluxed for 20 hours. The temperature rose from 177° after 10 hours to 220° after 20 hours. The product on distillation yielded unreacted naphthalene (37.4 g.) and pure 1-naphthaleneacetonitrile (9.3 g., 42% based on chloroacetonitrile, and 51% based on naphthalene reacted).

The 1-naphthaleneacetonitrile was identified as follows. Hydrolysis of a 2-g. sample by refluxing with 12 cc. of 40% aqueous potassium hydroxide solution for 6 hours followed by acidification gave 2 g. of 1-naphthaleneacetic acid, m.p. 127°. The recrystallized acid, m.p. 132°, showed no melting point depression when mixed with an authentic specimen (1).

p-Xenylacetic acid. A mixture of biphenyl (25 g.), chloroacetic acid (7.7 g.), ferric oxide (0.041 g.), and potassium bromide (0.205 g.) was refluxed for 20 hours, the temperature rising to 205° after 10 hours and to 225° after 20 hours. The reaction yielded unreacted biphenyl (18 g.) and a product (5.3 g.) which melted at 159–161° after recrystallization from acetic acid-water (1:2). The loss on recrystallization was 75%. The melting point corresponds to the literature value (161–162°) (7, 11b) and showed no depression when the product was mixed with an authentic sample of *p*-xenylacetic acid prepared by the chloromethylation procedure (11).

1-Methyl-4- and 1-methyl-5-naphthaleneacetic acids. A mixture of 1-methylnaphthalene (20 g.), chloroacetic acid (6.7 g.), ferric oxide (0.033 g.), and potassium bromide (0.165 g.) was refluxed for 20 hours. The temperature was 190° after 10 hours and 205° after 20 hours. The product was added to 10 cc. of 40% aqueous sodium hydroxide and steam-distilled to remove unreacted 1-methylnaphthalene (14 g.). The residual solution was clarified with activated charcoal and acidified to obtain 4.3 g. of crude acid. The acid was esterified by refluxing it with a 5-fold excess of methanol containing 10% of sulfuric acid. The ester was distilled, b.p. 172–182° (10 mm.) and isolated in a yield of 2.6 g. It was hydrolyzed by refluxing with aqueous alkali and then acidifying. The yield of acid was 2.3 g.

The product was a mixture which melted over a range of 100°. Separation was not easy but was effected by repeated recrystallizations from acetic acid-water (1:3) and washing with ether. Needles, m.p. 178–179° (a) and m.p. 155–157° (b) were obtained, the latter from the mother liquor. Titration gave molecular weights of 194 (a) and 194 (b). Calc'd for the monobasic acid, $C_{13}H_{17}O_2$: 200.

Distillation of the potassium salt of acid (a) gave an oil which did not solidify at −18° and which formed a picrate, m.p. 142–143°. The picrate of 1,4-dimethylnaphthalene melts at 142–144° (3d, 12). In the same way the potassium salt of acid (b) yielded 1,5-dimethylnaphthalene, m.p. 80–82°, picrate, m.p. 137–139°. Literature values are respectively 80–82° and 138–139° (3d, 9). Mixture melting points with authentic samples were not depressed. It is probable that substitution occurred at the α-positions in both cases and that acid (a) is 1-methyl-4-naphthaleneacetic acid and acid (b) is 1-methyl-5-naphthaleneacetic acid.

Other experiments. α-Bromosiovaleric acid was recovered almost unchanged in an attempted reaction with naphthalene; the desired condensation product was obtained in very poor yield. Benzene, toluene, xylene, anisole, nitrobenzene, dimethylaniline, chlorobenzene, tetralin, 1-nitronaphthalene, diphenylmethane, dibenzyl, and thiophene reacted not at all or only slightly with chloroacetic acid under the conditions described above. The same was true of an attempted condensation between naphthalene and methyl chloroacetate. Phenol condensed with chloroacetic and bromoacetic acids to form phenyl chloroacetate and phenoxyacetic acid respectively. 2-Naphthol reacted with chloroacetic acid in the absence of catalysts for form 2-naphthol-1-acetic acid.

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SUMMARY

The catalyst ferric oxide-potassium bromide has been used to effect condensation between naphthalene and chloroacetic acid to yield 1,5-naphthalenediacetic acid. Similarly α-1-naphthalenepropionic acid has been obtained in 19% yield from naphthalene and α-chloropropionic acid, α-1-naphthalenebutyric acid in 22% yield from naphthalene and α-bromobutyric acid, 1-naphthaleneacetonitrile in 42% yield from naphthalene and chloroacetonitrile, *p*-xenylacetic acid from biphenyl and chloroacetic acid, and 1-methyl-4- and 1-methyl-5-naphthaleneacetic acids from 1-methylnaphthalene and chloroacetic acid.

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