[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE REFORMATSKY REACTION WITH 2-TETRALONE

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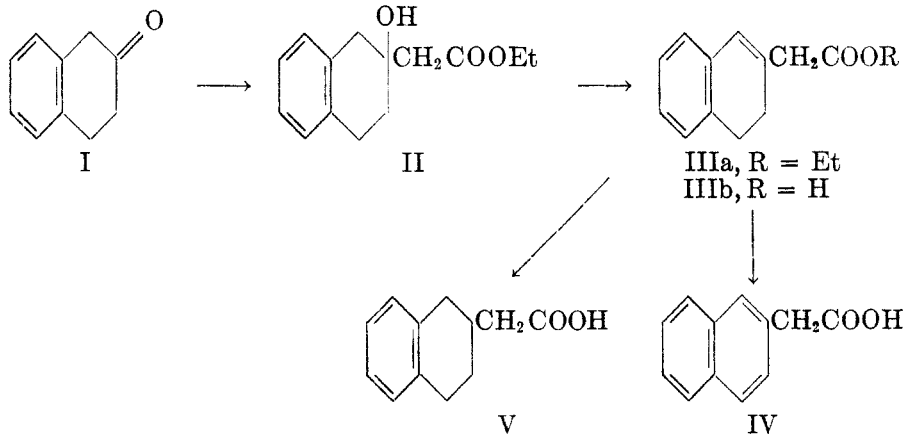
In connection with other studies in this laboratory on the preparation and use of partially hydrogenated derivatives of naphthoic acids and their homologs, the preparation of such compounds related to 2-naphthylacetic acid has been investigated. The 1,2,3,4-tetrahydro acid of this series has been reported previously by two different investigators but the properties of their products differed markedly. In one case, Yokotsuka (1) chloromethylated tetralin, separated the 1- and 2-isomers, and converted the 2-chloride through the cyanide to the acid. The 1,2,3,4-tetrahydro structure was assigned to his product. In view of the well-established fact that chloromethylation always occurs on the aromatic ring (2), such an allocation is of doubtful value. Papa, Schwenk, and Breiger (3), on the other hand, have hydrogenated 2-naphthylacetic acid with Raney nickel alloy in alkali and obtained only one product. Their material melts from 54–55° and has also been assigned the 1,2,3,4-tetrahydro structure since the isomeric 5,6,7,8-tetrahydro acid has been previously prepared by a Willgerodt reaction on *ar*-2-acetotetralin and has been found to melt from 97–98°. The dihydro compound of this series has not been prepared and it is the synthesis of this acid with subsequent conversion to the tetrahydro isomer which we wish to report.

Dihydro- and tetrahydro-1-naphthylacetic acids have been prepared by the Reformatsky reaction with 1-tetralone (4) and a similar scheme employing 2-tetralone has been employed in the present research. The starting ketone (I) was prepared from 2-naphthol by the method of Birch using sodium and liquid ammonia (5).



When 2-tetralone was allowed to react with equal molar amounts of zinc and ethyl bromoacetate in a mixture of benzene and toluene, ethyl 2-hydroxy-1,2,3,4-tetrahydro-2-naphthylacetate (II) was obtained in 38% yield. If large

excesses of zinc and bromo ester were employed (6), the yield was raised to 50%. Activation of the zinc by amalgamation (7) served only to lower the yield by about 20%. The hydroxy ester was most effectively dehydrated to ethyl 3,4-dihydro-2-naphthylacetate (IIIa) with thionyl chloride and pyridine (6). Saponification of the latter ester gave a solid 3,4-dihydro-2-naphthylacetic acid (IIIb). Dehydrogenation of the dihydro acid with sulfur yielded the known 2-naphthylacetic acid (IV) and hydrogenation of the unsaturated acid gave 1,2,3,4-tetrahydro-2-naphthylacetic acid (V). This latter compound was found to melt from 87–88° as compared to a value of 54–55° reported earlier by Papa and collaborators (3). In order to compare the product obtained in this research with a sample

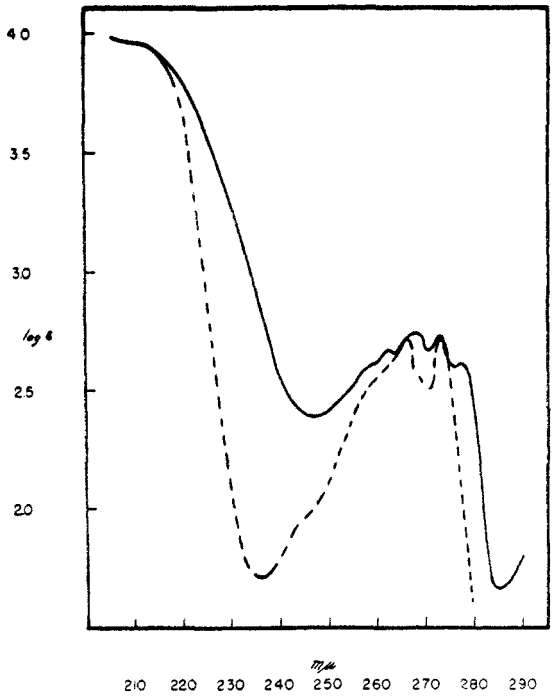


FIGURE 1. ABSORPTION SPECTRUM OF 1,2,3,4-TETRAHYDRO-2-NAPHTHYLACETIC ACID: ————, Papa, Schwenk, and Breiger acid; - - - - - - -, Present work.

of tetrahydro acid prepared by an alternate procedure, 1,2,3,4-tetrahydro-2-naphthoic acid was prepared as described by Newman and Mangham (8) and converted into the homologous acetic acid by an Arndt-Eistert reaction. The acid so prepared was identical in all respects with the product of the Reformatsky sequence.

Dr. Papa kindly supplied a sample of his product and it was found that the difference in melting point was not due to dimorphism. A comparison of spectra of these two compounds (Fig. 1) along with that of 5,6,7,8-tetrahydro-2-naphthoic acid (Fig. 2) suggested that the material of Papa, Schwenk, and Breiger might be a mixture of the two isomeric tetrahydro acids. Accordingly, it was

found that when equal amounts of the authentic compounds were mixed and then recrystallized from petroleum ether, material melting sharply from 53.7–54.8° was obtained and this value remained constant for three recrystallizations. Thus, it seems apparent that Raney nickel alloy reduction of 2-naphthylacetic acid yields a mixture of the two tetrahydro acids which co-crystallize.[1]

When 2-tetralone was allowed to react with methyl γ-bromocrotonate and zinc, methyl γ-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)crotonate (VI) was obtained in 34% yield. Hydrogenation of the hydroxy unsaturated ester followed by dehydration and saponification gave γ-(3,4-dihydro-2-naphthyl)butyric acid (VII) in poor yield. The material melted from 55–65°, whereas a similar

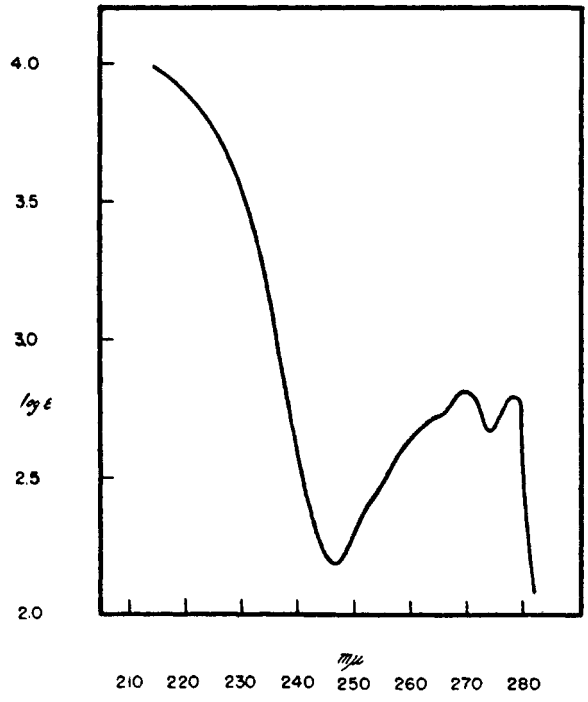
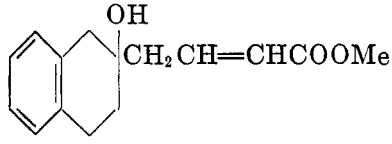
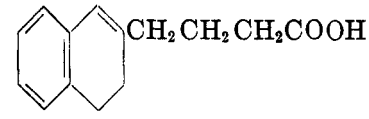


FIGURE 2. ABSORPTION SPECTRUM OF 5,6,7,8-TETRAHYDRO-2-NAPHTHYLACETIC ACID

compound prepared by Bachmann and Wendler (9) from 2-carboethoxy-1-tetralone melted sharply from 70–71°. It would appear that the acid prepared by the Reformatsky pathway is a mixture of isomeric unsaturated acids.



VI



VII

[1] Dr. Papa has informed us that they are in agreement regarding this probable course of the reduction reaction.

The 3,4-dihydro structure has been arbitrarily assigned to the dihydro-2-naphthylacetic acid (IIIb) obtained as described above. An examination of the spectrum (Fig. 3) of this material, however, suggests that such an allocation is probably representative of the majority of the product since the high extinction coefficient is best reconciled with a styrene type of structure (10).

Acknowledgment. We wish to express our appreciation to Mr. Klaus Saegebarth for his assistance in this problem.

EXPERIMENTAL

All melting points are corrected and all boiling points are uncorrected. Spectra were taken in 95% ethanol with a Beckman model DU spectrophotometer.

2-Tetralone. 2-Naphthol (212 g., 1.47 moles) was allowed to react with sodium, *tert*-amyl alcohol, and liquid ammonia as described by Birch (5). The crude reaction product was

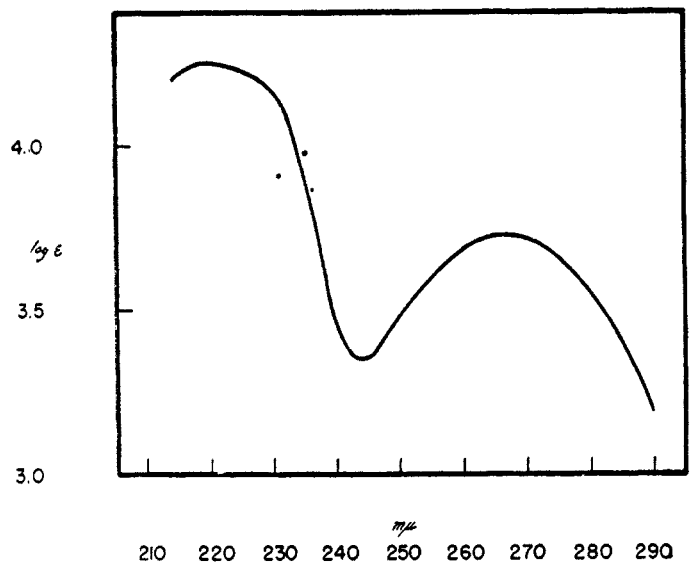


FIGURE 3. ABSORPTION SPECTRUM OF 3,4-DIHYDRO-2-NAPHTHYLACETIC ACID

purified through the bisulfite addition compound; the pure ketone had b.p. 111–115° (5 mm.), n_D^{23} 1.5577, yield 130.5 g. (60.7%).

Ethyl 2-hydroxy-1,2,3,4-tetrahydro-2-naphthylacetate. A solution of 29.7 g. (0.2 mole) of 2-tetralone in 50 ml. of dry benzene and 13 g. (0.2 mole) of freshly sandpapered zinc foil was placed in the usual apparatus. After 10 ml. of benzene had been distilled, a solution of 33.2 g. (0.2 mole) of ethyl bromoacetate in 50 ml. of dry benzene and 100 ml. of dry toluene was added slowly. It was necessary to apply external heat to keep the reaction mixture at reflux temperature.

A second addition of 38 g. (0.23 mole) of ethyl bromoacetate and 33 g. (0.5 mole) of zinc was made after 1½ hours and a third addition of 38 g. (0.23 mole) of bromo ester and 47 g. (0.72 mole) of zinc at the end of three hours. The reaction mixture was heated for two hours after the final addition, cooled, and decomposed with 3 *N* hydrochloric acid. The product had b.p. 160–165° (4 mm.), yield 23.5 g. (50.4%), n_D^{24} 1.5362.

Anal. Calc'd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74.

Found: C, 72.25; H, 7.74.

Ethyl 3,4-dihydro-2-naphthylacetate. A solution of 20 ml. of purified thionyl chloride, 10 ml. of dry pyridine, and 38 ml. of dry benzene was cooled to 0° and 23.0 g. (0.1 mole) of hydroxy ester was added. A strong exothermic reaction ensued and a precipitate formed. The reaction mixture was allowed to stand for 1½ hours at room temperature and then decomposed with ice-water. The dehydrated product distilled from 143–148° (3.5 mm.), n_D^{25} 1.5480, yield 17.9 g. (83%).

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46.

Found: C, 77.48; H, 7.33.

3,4-Dihydro-2-naphthylacetic acid. A solution of 4.96 g. (0.023 mole) of the above unsaturated ester, 5 ml. of 6 *N* aqueous sodium hydroxide, and 75 ml. of methanol was refluxed for four hours under a nitrogen atmosphere. Acidification with dilute acid gave a solid which was recrystallized from petroleum ether, m.p. 88–90°.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43.

Found: C, 76.85; H, 6.43.

1,2,3,4-Tetrahydro-2-naphthylacetic acid. (a) *From a Reformatsky reaction.* The unsaturated acid (0.643 g.) dissolved in 10 ml. of absolute ethanol was hydrogenated over platinum oxide at an initial pressure of 45 lbs. Evaporation of the solvent, recrystallization from petroleum ether, and sublimation gave a pure product, m.p. 87–88°, yield 0.56 g. (87.5%).

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41; Neut. equiv., 190.

Found: C, 75.95; H, 7.07; Neut. equiv., 192.

The *p*-phenylphenacyl ester was prepared, m.p. 104.5–105.5°.

Anal. Calc'd for $C_{26}H_{24}O_3$: C, 81.22; H, 6.29.

Found: C, 81.30; H, 6.40.

(b) *From an Arndt-Eistert reaction.* 1,2,3,4-Tetrahydro-2- naphtnone acid (8), m.p. 95.5–96.5°, was converted into its acid chloride with thionyl chloride and the product distilled, b.p. 102–106° (1 mm.). The acid chloride was reacted with excess diazomethane and the resulting diazoketone rearranged in methanol in the presence of silver oxide to methyl 1,2,3,4-tetrahydro-2-naphthylacetate. The silver was removed, potassium hydroxide was added, and the solution heated for three hours. The acid was isolated and purified as described above, m.p. 87.0–87.5°.

Anal. Found: C, 75.49; H, 7.17; Neut. equiv., 192.

No depression in melting point was noticed upon mixture with acid prepared by the Reformatsky procedure but upon mixing with tetrahydro-2-naphthoic acid, the melting range was 60–70°. The *p*-phenylphenacyl ester also was prepared and was identical with the foregoing ester.

Methyl γ-(2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl)crotonate. The Reformatsky reaction was conducted as described previously except that a mixture of ether and benzene was used as the solvent. A mixture of 42.6 g. (0.29 mole) of 2-tetralone, 139 g. (0.74 mole) of methyl γ-bromocrotonate, and 170 g. (2.6 moles) of zinc foil was used. The reaction mixture was decomposed with dilute acetic acid and then distilled. The ester had to be distilled rapidily to avoid excessive decomposition, b.p. 170–180° (0.2 mm.), yield 23.9 g. (33.4%).

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 74.13; H, 7.41.

Found: C, 72.82; H, 7.19.[2]

γ-(3,4-Dihydro-2-naphthyl)butyric acid. The hydroxycrotonic ester (6.0 g.) was heated in alcohol with Raney nickel, the catalyst filtered, and the product hydrogenated over platinum oxide. One mole equivalent of hydrogen was absorbed. The solvent was removed and the residue dehydrated by heating with potassium acid sulfate at 160–175° for 1½ hours. The product was extracted from the salt with 250 ml. of ethanol, 25 g. of potassium hydroxide was added, and the ester saponified. The acid was isolated in the usual manner and purified by evaporative distillation, yield 2.3 g. A portion of the product was recrystallized from petroleum ether at Dry Ice temperature, m.p. 55–65°; further recrystallization

[2] This analysis, though not entirely satisfactory, is evidence that dehydration had not occurred to a major extent.

did not effect the melting point. Bachmann and Wendler (9) report the value 70–71° for a similar compound.

Anal. Calc'd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46.
Found: C, 77.46; H, 7.32.

SUMMARY

Ethyl 2-hydroxy-1,2,3,4-tetrahydro-2-naphthylacetate has been prepared from 2-tetralone and ethyl bromoacetate by the Reformatsky reaction. The hydroxy ester has been converted to 3,4-dihydro-2-naphthylacetic acid. Hydrogenation of this dihydro acid has yielded 1,2,3,4-tetrahydro-2-naphthylacetic acid. The previously reported preparation of the tetrahydro acid has been shown to be in error in that the product obtained is a mixture of the two isomeric tetrahydro-2-naphthylacetic acids.

Methyl γ-(hydroxy-1,2,3,4-tetrahydro-2-naphthyl)crotonate has been prepared in a like manner using methyl γ-bromocrotonate. Hydrogenation and dehydration of the hydroxy ester yielded a mixture of isomeric γ-dihydro-2-naphthyl butyric acids.

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