[Contribution from the Chemical Research Laboratories of the
Schering Corporation]

SELECTIVE RANEY NICKEL HYDROGENATION OF METHYL γ-(6-METHOXY-1,2,3,4-TETRAHYDRO-1-NAPHTHYLIDENE)-CROTONATE. SYNTHESIS OF 1-KETO-7-METHOXY-1,2,3,4,9,10-HEXAHYDROPHENANTHRENE[1]

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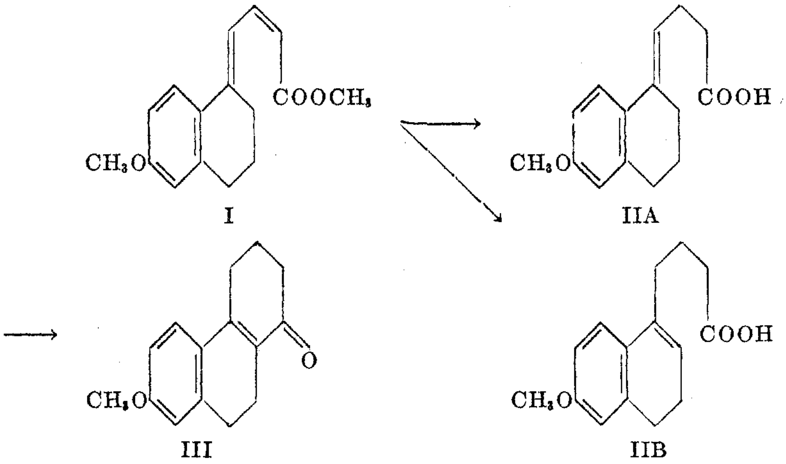
The recently described (1) synthesis of the compound 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (III) utilizes the Reformatsky reaction of 6-methoxy-1-tetralone and methyl γ-bromocrotonate to construct the appropriately substituted tetralin derivative, methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate (I). Catalytic reduction of I with Raney nickel catalyst at room temperature and pressure preferentially reduces the α,β-double bond and the resulting butyric acid II, obtained after saponification, is then cyclized to the tricyclic ketone III. The obvious simplicity of this approach to ketone III is even more striking in view of the accessibility of 6-methoxy-1-tetralone (2).



As part of a program on the synthesis of 6-methoxy-1-tetralone (2b, 2c) and extensions of this ring system, we have had an opportunity to investigate this synthesis of I. From a practical standpoint, it appeared to us that the transformations I → II → III had not been fully realized since the reactions were performed on a milligram scale, the ketone III was isolated only as the semicarbazone or dinitrophenylhydrazone, and no evidence was presented as to whether the double bond in II was exocyclic or endocyclic, (IIA and IIB). The latter factor could materially influence the yield in the cyclization reaction should the reagent and/or reaction conditions not promote the isomerization IIA → IIB. In addition, the preferential reduction of the α,β-double bond of the dienoic

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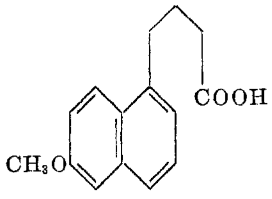
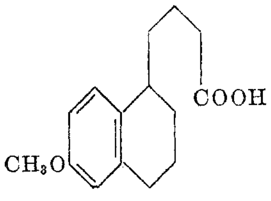
ester I appears to be a critical step in this synthesis in view of the known variable catalytic activity of Raney nickel (3).

The Reformatsky reaction to the dienoic ester I proceeded as described, although in somewhat lower yield. However, our results in the transformations I → II and II → III are at variance with those reported (1) and form the basis of this paper.

The initial experiments on the preferential reduction of the Reformatsky ester I did not yield any of the acid II (Table I, experiments 1–4). In these experiments strict adherence to the described quantity of reagents and reaction conditions was observed. In only one of these experiments was the theoretical amount of hydrogen absorbed, whereas in the other three experiments hydrogen uptake ceased far short of theory. From hydrogenations 1–4 and from subsequent experiments under identical conditions, 6 and 14, there was obtained a mixture of two acids unequivocally identified as γ-(6-methoxy-1-naphthyl)butyric acid (IV) and γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid (V). The amounts of these two acids obtained were approximately equal except in experiments 2, 6, and 14 in which the theoretical amount of hydrogen was absorbed. Separation of acids IV and V was effected readily by extraction of the mixture with petroleum ether in which the former acid is insoluble.


IV


V

From these experiments it is apparent that two competing reactions occur in the hydrogenation of I, to give rise to acids IV and V, the former resulting from a shift of the two double bonds of the ester I into the hydroamatic ring, whereas V is the direct result of the hydrogenation of both the α,β and γ,δ double bonds. The ratio of acids IV and V formed in experiments 1–4, 6, and 14 is consistent with this interpretation of the reaction since only in the experiments in which the theoretical amount of hydrogen was absorbed (2, 6, and 14) was a predominate amount of acid V formed.[2]

To test this hypothesis and to determine the effect of Raney nickel catalyst on the Reformatsky ester an alcoholic solution of I was refluxed with a Raney nickel catalyst. Three products were isolated and identified in this experiment; compound IV, compound IIB, and γ-(6-methoxy-1,2,3,4 tetrahydro-1-naphthylidene)crotonic acid, the latter resulting from the saponification of the ester I. It is probable that in an atmosphere of hydrogen acid IIB would be converted to V.

[2] It has been postulated by one of the referees that initial hydrogenation of I to IIA and/or IIB followed by disproportionation of two molecules of IIA and/or IIB into IV and V, the one acting as a hydrogen donor and the other as an acceptor, is a more plausible explanation of the experimental results.

The course of the hydrogenation of I was favorably altered by the simple expedient of pre-aging or deactivating the nickel catalyst. The identical catalyst employed in experiments 1–4, after standing for two weeks in ethanol at about 5°, converted ester I into a mixture of two acids, 7.6% of IV and 53% of IIA (#7, Table I).

TABLE I

HYDROGENATION OF METHYL γ-(6-METHOXY-1,2,3,4-TETRAHYDRO-1-NAPHTHYLIDENE)CROTONATE

No.	MOLES OF ESTER	CATALYST[a]	H_2 UPTAKE, %	TIME (*min.*)	YIELD ACIDS, %			
					V	IV	IIA	IIB
1	0.09	A	85	24.0	43	32	0	0
2	.09	A	100	15.0	59	29	0	0
3	.09	A	68	35.0	41	43	0	0
4	.09	A	85	25.0	42	37	0	0
5	.045	B	100	5.5	0	23	55	0
6	.045	A	100	5.5	55	37	0	0
7	.038	C	100	7.2	0	7.6	53	0
8	.033	D	100	4.0	50	18.7	0	0
9	.025	E	100	6.5	0	16.0	66	0
10	.019	F	100	5.5	0	0	74	0
11	.019	G	100	3.2	0	21.0	53	0
12	.019	F	100	7.5	0	0	53[b]	0
13	.019	F	100	5.5	0	0	84	0
14	.019	A	100	4.0	63	21	0	0
15	.023	H	100	8.5	0	0	96	0
16	.074	F	100	16.0	0	0	74.5	0
17	.097	H	100	28.5	0	0	97.5	0
18	.1	I	100	15.5	0	0	73	21.5
19	.1	I	100	19.0	0	0	55	39
20	.19	I	100	32.5	0	0	38	54.8
21	.2	I	100	38.0	0	0	49.5	47.4
22	.05	J	100	6.5	0	0	47.5	43.
23	.05	J	100	7.0	0	0	44.5	48.5

[a] The catalysts are Raney nickel [*Org. Syntheses*, **21**, 15 (1941)] and aged for the period indicated in absolute ethanol at about 5°. A, freshly prepared; B, one month; C, 14 days; D, three weeks; E, six weeks; F, catalyst E plus acetic acid; G, seven weeks; H, catalyst A plus acetic acid; I, eight weeks plus acetic acid; J, Raney nickel obtained as follows: One half mole of acetone dissolved in 200 ml. of absolute ethanol was reduced in a Parr hydrogenator with 10 g. of catalyst A. After the theoretical quantity of hydrogen was absorbed the solution was decanted and the catalyst was used directly. [b] The yield reported is the material recovered after accidental loss of about 35% of the product.

Separation of this mixture of acids was effected by the use of petroleum ether in which IIA was readily soluble. Further aging of this and similarly prepared catalysts up to seven weeks, did not appreciably alter the course of the reaction (experiments 5, 9, and 11), the yields of IV averaging 20% and IIA 58%. An anomalous result was obtained in experiment 8 from which only acids IV and V were isolated.

It was often been reported that Raney nickel catalyst loses much of its activity on long storage (3, 4). Assuming that this factor is essentially the basis for the change in the course of the hydrogenation, we investigated the effect of deactivating both freshly prepared and aged Raney nickel catalyst with acetic acid. These experiments are summarized in Table I. In none of these experiments was any acid IV and V formed. In experiments 10, 12, 13, 15, 16, and 17 in which acetic acid was added, freshly prepared nickel catalyst and nickel catalyst aged for six weeks gave only acid IIA in yields of 75–97.5%. However, nickel catalyst aged for at least eight weeks plus acetic acid gave approximately equal amounts of the two isomeric acids IIA and IIB, the combined yield exceeding 90% in each of four experiments 18–21.

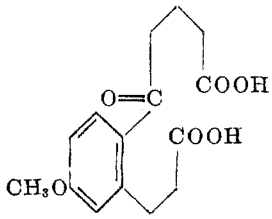
Fortuitously, these acids have an appreciable difference in solubility in petroleum ether, the latter being the least soluble. There is also an appreciable difference in the melting points of these acids, IIA melting at 75.5–76° and IIB at 83–84°. The melting point of acid IIB is somewhat higher than that reported (79–80°) by Chuang Tien and Huang (5) and Robinson and Thompson (6) who obtained IIB by the cyclodehydration of methyl 5-keto-8-(*m*-methoxyphenyl)-octanoate.

With Raney nickel catalyst deactivated by prior reduction of acetone, ester I gave about equal amounts of acids IIA and IIB (experiments 22 and 23). These findings parallel the results obtained with aged nickel (eight weeks) plus acetic acid.

The ultraviolet absorption spectrum of acids IIA and IIB exhibited a maximum at 265 mμ and a minimum at 240 mμ in agreement with the literature (1). Since in both acids the double bond is conjugated with the aromatic ring it is impossible to differentiate these two structural isomers.

Indirect evidence for the structures assigned IIA and IIB was afforded by cyclization of the acids to the tricyclic ketone III. The endocyclic isomer IIB gave 96% of III whereas IIA gave only 63% of the ketone. In both cases the ketone was readily isolated as a crystalline solid in contrast with the previously reported difficulties in obtaining this product in crystalline form (7, 8). It may be inferred that a higher yield of III would be expected from the endocyclic isomer since cyclization can occur without the prior rearrangement of the double bond as would be required for isomer IIA.

Proof of the structure of isomers IIA and IIB was obtained by ozonolysis of the acids. As expected IIA gave 6-methoxy-1-tetralone identified as the 2,4 dinitrophenylhydrazone and IIB gave the keto diacid VI characterized as the dinitrophenylhydrazone.



VI

EXPERIMENTAL

All melting points are corrected. The hydrogenations were carried out in a low pressure apparatus. The petroleum ether used in this work had a boiling range of 35–60°. Methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate was prepared as described (1).

I. Preparation and separation of a mixture of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl) butyric acid and γ-(6-methoxy-1-naphthyl)butyric acid. Methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate (11.5 g., 0.045 mole) dissolved in 200 ml. of absolute ethanol was hydrogenated at atmospheric pressure and room temperature in the presence of 10 g. of catalyst A, the theoretical amount of hydrogen being absorbed rapidly (runs 2, 6, and 14). In three other experiments under the same conditions (runs 1, 3, and 4), the hydrogen absorption stopped after 70–85% of the theoretical uptake. The catalyst was removed and the colorless filtrate was added to 10 g. of potassium hydroxide dissolved in 750 ml. of water. The mixture was refluxed under nitrogen for three hours and the alcohol was removed by distillation. The aqueous alkaline solution was extracted several times with ether, made strongly acid with concentrated hydrochloric acid, and then extracted with three 150-ml. portions of ether. The ether extracts were washed with water, dried over sodium sulfate, and the ether was removed on the steam-bath. The residue, a light tan solid, m.p. 70–105°, was transferred to a Soxhlet extractor and was extracted with petroleum ether for 12 hours. The petroleum ether solution was treated with Norit, concentrated to about 250 ml. and, after cooling in an ice-bath, γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid separated, yield 6 g. (55%), m.p. 74–75°. The analytical sample after recrystallization from petroleum ether melted at 76–77°, previously reported m.p. 79° (1). A mixture melting point with an authentic sample of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid[3] melted at 76–77°.

Anal. Calc'd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12.
Found: C, 72.84, 72.79; H, 8.05, 7.90.

The petroleum ether-insoluble fraction (4 g., 37%) was a light tan, crystalline solid, m.p. 141–147°. Recrystallized from methanol, it had m.p. 151–152°; m.p. previously reported for γ-(6-methoxy-1-naphthyl)butyric acid, 149–150° (9a), 150–151° (9b).

Anal. Calc'd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60.
Found: C, 73.63, 73.57; H, 6.45, 6.35.

This acid was cyclized to the known 7-methoxy-1-keto-1,2,3,4-tetrahydrophenanthrene. From 10 g. of γ-(6-methoxy-1-napthyl)butyric acid, there was obtained 8.5 g. (90.5%) of the ketone, m.p. 99.5–100°, literature (7b) m.p. 98–100°.

II. Preparation and separation of a mixture of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid and γ-(6-methoxy-1-naphthyl)butyric acid. Compound I (11.5 g., 0.045 mole) dissolved in 200 ml. of absolute ethanol was reduced in the presence of 10 g. of catalyst B. The catalyst was removed and the light yellow-colored alcoholic filtrate was worked up as described under I.

The petroleum ether-soluble fraction was recrystallized from petroleum ether and 6 g. (55%) of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid, m.p. 74–76°, was obtained. The analytical sample was recrystallized three times from petroleum ether, m.p. 75.5–76°.

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37.
Found: C, 72.80, 73.08; H, 7.14, 7.16.

The melting point of a mixture of this acid, with a sample of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid was 64–68.5°.

The petroleum ether-insoluble residue from the Soxhlet extraction was recrystallized from methanol, yield 2.5 g. (23%), m.p. 150–151°, mixture melting point with γ-(6-methoxy-1-naphthyl)butyric acid, 150–151°.

III. Preparation and separation of a mixture of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naph-

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[3] Kindly supplied by Dr. Gilbert Stork, Department of Chemistry, Columbia University, N. Y.

thylidene)butyric acid and γ-(6-methoxy-3,4-dihydronaphthyl)butyric acid. Compound I (25.8 g., 0.097 mole) dissolved in a mixture of 250 ml. of absolute ethanol and 5 ml. of glacial acetic acid was hydrogenated in the presence of catalyst I in the manner described in the preceding experiments. The reduced ester was hydrolyzed and the crude reduced acid, yield 23.5 g. (97%), was placed in a Soxhlet extractor and extracted with 1,500 ml. of petroleum ether for 17 hours. At this stage there was no residue in the Soxhlet thimble. On cooling the petroleum ether extract overnight, a crystalline material (crop I) precipitated, yield 11.5 g., m.p. 80–81°. The petroleum ether filtrate was evaporated to about 100–150 cc. and on cooling gave crop II, yield 7.5 g., m.p. 67–69°.

After several recrystallizations from petroleum ether, crop I melted at 83–84°, previously reported for γ-(6-methoxy-3,4-dihydro-1-naphthyl)butyric acid, m.p. 79.5° (5, 6).

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37.
Found: C, 73.13; H, 7.02.

Crop II, on recrystallization from a small volume of petroleum ether melted at 73–74°. Mixed with an authentic sample of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)-butyric acid, m.p. 73–74°.

Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37.
Found: C, 73.27; H, 7.27.

IV. Preparation of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid. A solution of 6 g. (0.023 mole) of I dissolved in 100 ml. of absolute ethanol containing 1 ml. of glacial acetic acid was reduced as in the previous examples employing catalyst H. The reduced acid, after saponification, was transferred to a Soxhlet extractor and was extracted for 12 hours with petroleum ether. From the petroleum ether there was obtained 5.5 g. (96%), m.p. 74.5–75.5°. There was no residue in the Soxhlet cup. A mixture of this product with an authentic sample of the naphthylidene acid melted at 74–76°. Melting point of a mixture with a sample of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid, 64–67°.

Cyclization of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid to 7-methoxy-1-keto-1,2,3,4,9,10-hexahydrophenanthrene. To a solution of 18 g. of γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)butyric acid in 180 ml. of glacial acetic acid and 360 ml. of acetic anhydride, there was added 180 ml. of glacial acetic acid containing 2 g. of freshly fused zinc chloride. The mixture was warmed on the steam-bath under nitrogen for five hours, 300 ml. of absolute methanol was cautiously added, and the resulting mixture was vacuum-concentrated under nitrogen on the steam-bath. To the dark red residue was added a solution of 1,500 ml. of 10% potassium hydroxide and the mixture was warmed on the steam-bath for one hour. The basic reaction mixture was extracted several times with ether, and the ether extracts were washed with water until free of alkali and then dried over sodium sulfate. The ether was removed on the steam-bath and the residue, which at first was an orange oil, soon crystallized. The crude product was recrystallized from methanol using charcoal, yield 10.5 g. (63%), m.p. 76–76.5°; previously reported m.p. 75–76° (8).

Cyclization of γ-(6-methoxy-3,4-dihydro-1-naphthyl)butyric acid to 1-keto-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene. The 3,4-dihydro acid (22 g., 0.09 mole) was cyclized and the product was isolated as in the preceding example. The yield of ketone was 19.5 g. (96%), m.p. 75.5–76°. The characteristic iodine-colored *2,4-dinitrophenylhydrazone* was obtained melting at 256–257°, previously reported m.p. 256° (8), 253–255° (10), 250–252° (1). The *semicarbazone* melted at 249–250°, previously reported m.p. 248–249° (1), 238–240° (11).

Action of Raney nickel catalyst on ester I. Compound I (5 g.) in 100 ml. of absolute ethanol and 5 g. of freshly prepared neutral Raney nickel catalyst were refluxed for five hours on the steam-bath. The mixture was kept overnight at room temperature, the catalyst was filtered off, and an equal volume of water containing 5 g. of potassium hydroxide was added. The resulting mixture was refluxed under nitrogen for three hours, excess ethanol was removed by vacuum-distillation, and the residue was extracted with ether. The aqueous alkaline solution was acidified with hydrochloric acid, and the precipitate (4.5 g.) was filtered, air-dried, and then extracted for seven hours with petroleum ether in a Soxhlet extractor. The petroleum ether solution was evaporated to a small volume and cooled, yield 1.9 g., (21%) m.p. 80–83°. Mixture melting point with an authentic sample of γ-(6-methoxy-3,4-dihydro-

1-naphthyl)butyric acid, 81–83°. Mixture melting point of this product with γ-(6-methoxy-1,2,3,4-tetrahydronaphthyl)butyric acid was 60–65°. The petroleum ether-insoluble (3.5 g., 72.5%), m.p. 117–122°, was recrystallized from absolute methanol. The first crop of crystals was yellow in color, m.p. 138–141°. After concentrating the methanol filtrate there was obtained acid IV as white needles melting at 151.5–152°. The yellow crystalline solid, m.p. 138–141°, after four recrystallizations from absolute methanol melted at 144–146°. This product is probably a mixture of the naphthylbutyric acid IV and the acid derived from the starting ester I.

Ozonolysis of IIA. Ozone was bubbled into a solution of 2.5 g. of IIA in 50 ml. of C.P. chloroform at −60° until the solution retained the characteristic blue color indicating an excess of ozone. The solution, on attaining room temperature, was decomposed with dilute acetic acid and evaporated to dryness on the steam-bath *in vacuo*. The residue was triturated with a 5% sodium bicarbonate solution and was extracted with ether. The ether extracts were washed with sodium bicarbonate solution, dried over sodium sulfate, and the ether was removed. The residue was treated with an alcoholic solution of 2,4-dinitrophenylhydrazine and the red *2,4-dinitrophenylhydrazone*, after two recrystallizations from chloroform, melted at 236–238°. Mixture melting point with an authentic sample of 6-methoxy-1-tetralone dinitrophenylhydrazone, 236–238°.

Ozonolysis of IIB. A chloroform solution of 2.15 g. of the acid IIB was ozonized in the manner described for IIA. After trituration with 5% sodium bicarbonate the resulting solution was extracted with ether. The aqueous solution was neutralized with dilute hydrochloric acid and extracted with chloroform. The chloroform extracts were concentrated and the residue (1.6 g.) was converted to the 2,4-dinitrophenylhydrazone, m.p. 183.5–185.5° after two recrystallizations from a mixture of chloroform-alcohol.

Anal. Calc'd for $C_{21}H_{22}N_4O_9$: N, 11.81. Found: N, 11.64.

SUMMARY

The preferential reduction of the α,β double bond of methyl γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthylidene)crotonate has been shown to be dependent on the activity of the Raney nickel catalyst. With freshly prepared catalyst two competitive reactions occur to give rise to γ-(6-methoxy-1-naphthyl)butyric acid and γ-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)butyric acid. Raney nickel deactivated by aging, by acetic acid, or by prior reduction reduces preferentially the α,β double bond in yields exceeding 90%. The identity of the two isomeric acids obtained by this reduction procedure has been determined.

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