mediately above, was chromatographed on 75 g. of unwashed alumina. Ether–pentane (1:1) eluted needles of what appeared to be 1,2,3,4,4a,5,6,7,8,8a,9,9a-dodecahydro-9-anthracenol (i). After recrystallization from 5 ml. of pentane, it melted at 129–132° (0.15 g., 13% yield), $\lambda_{max}^{CS_2}$ 2.82 and 9.75 μ.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75; O, 7.75. Found: C, 81.5; H, 10.5; O, 7.7.

2,6- and 2,7-Diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa and XIIIb).—A mixture of 50 g. (0.24 mole) of the quinone adduct XII,[17] 150 ml. of benzene and 35.6 g. (0.36 mole) of 2-ethoxy-1,3-butadiene was refluxed for 110 hr., then kept at 0° for 4 hr. The precipitated solid (12.5 g.) was recrystallized from benzene to give 10.2 g. (14% yield) of white, heavy needles, m.p. 169–172° dec., of **2,6-diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa).**

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95; OEt, 29.65. Found: C, 71.2; H, 8.1; OEt, 28.9.

The filtrate from the separation of XIIIa was washed twice with 10% aqueous potassium hydroxide and twice with water. It was dried (K_2CO_3), concentrated to a 75-ml. volume under an inert atmosphere, and diluted with 150 ml. of pentane. The precipitated solid was recrystallized 3 times from ethanol to give 1.42 g. (2% yield) of faintly yellow spherulites, m.p. 148–150°, of **2,7-diethoxy-1,4,4a,-5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIb).**

Anal. Calcd. for $C_{18}H_{24}O_4$: C, 71.02; H, 7.95. Found: C, 71.0; H, 7.7.

Oxidation of 2,6-Diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa).—Air was bubbled through a refluxing solution of 0.30 g. of XIIIa in 10 ml. of 15% alcoholic potassium hydroxide for 30 min. A dark gel formed initially which was soon replaced by a crystalline precipitate. The cooled mixture was filtered and the precipitate washed with cold 95% ethanol. Two recrystallizations of the precipitate (0.28 g.) from benzene gave 0.17 g. of yellow, heavy needles of 2,6-diethoxy-9,10-anthraquinone, m.p. 239.6–240.6° (reported[18] 232°). This material showed no depression in melting point upon admixture with a sample, m.p. 237–239°, prepared from 2,6-dihydroxyanthraquinone as described below.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.9; H, 5.3.

2,6-Diethoxy-9,10-anthraquinone from 2,6-Dihydroxy-9,10-anthraquinone.—To a mixture of 20 g. (0.082 mole) of 2,6-dihydroxyanthraquinone, 6.6 g. (0.166 mole) of sodium hydroxide and 200 ml. of water was added dropwise with stirring at room temperature 25.6 g. (0.166 mole) of diethyl sulfate over a period of 10 min. This mixture was heated for 1 hr. on the steam-bath, cooled, and filtered. The solid was boiled with 1 l. of 95% ethanol and the mixture filtered while hot. After treatment with Darco G-60, the filtrate, on cooling, gave a product which was recrystallized once from pyridine (Darco G-60) and once from benzene to give yellow needles, m.p. 237–239°.[18]

Oxidation of 2,7-Diethoxy-1,4,4a,5,8,8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa).—The oxidation was performed on 0.30 g. of XIIIb in the manner described above for XIIIa. The product was recrystallized twice from absolute ethanol to give 0.15 g. of yellow needles, m.p. 193.8–194.4° (reported[18] m.p. 193–194°).

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.7; H, 5.4.

Perhydro-2,6,9,10-anthracenetetraone (XVa).—A mixture of 1.20 g. of XIIIa, m.p. 169–172° dec., 10 ml. of 95% ethanol and 2 ml. of concentrated hydrochloric acid was refluxed for 30 min., then an additional 5 ml. of ethanol and 2 ml. of acid were introduced, and refluxing was continued for 1 hr. On cooling, 0.61 g. of colorless, powdery material precipitated which was recrystallized from acetone to give 0.23 g. of white plates, m.p. 236.5–238.5°, λ_{max}^{KBr} 5.84 μ (very strong).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.5; H, 6.7.

2,6-Diethoxyperhydro-9,10-anthracenedione (XVb).—A mixture of 1.4 g. (0.0046 mole) of 2,6-diethoxy-1,4,4a,5,8,-8a,9a,10a-octahydro-9,10-anthraquinone (XIIIa), 0.2 g. of 10% palladium-on-charcoal and 250 ml. of absolute alcohol was treated with hydrogen under 45 p.s.i. at room temperature for 2 hr. The filtered mixture was concentrated to a 7-ml. volume whereupon 0.35 g. of crystals separated. Recrystallization once from ethanol and once from Skellysolve C afforded 0.135 g. (10% yield) of XVb, m.p. 177–179°.

Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.10; H, 9.15. Found: C, 70.4; H, 9.1.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

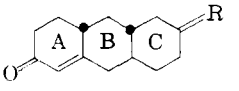
Potential Steroid Substitutes. II.[1] The Formation of a Spiro Compound in the Attempted Preparation of 6-Hydroxy-2,3,4,4aβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-2-anthracenone

BY ROBERT L. CLARKE, WILLIAM T. HUNTER AND SALVADOR J. MARSALA

RECEIVED APRIL 10, 1959

Success in the preparation of the potentially androgenic compounds 6α- and 6β-hydroxy-2,3,4,4aβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-2-anthracenone (Ia and Ib) by the synthetic route shown in Table I depended primarily upon the reaction of ethyl β-anisoyl-β-bromopropionate (IIIa) with sodium diethyl malonate to produce diethyl β-anisoyl-α-carbethoxyglutarate (A). Actually, this bromoester (IIIa) was dehydrohalogenated under the reaction conditions and the ethyl β-anisoylacrylate so produced immediately added diethyl malonate to form diethyl α-(anisoylmethyl)-α′-carbethoxysuccinate (IVa). Performance on compound IVa of the chemical operations planned for compound A produced spiro-[cyclopentanone-3,2′-(1′,2′,3′,4′,4a′,5′,6′,7′-octahydro-7′-naphthalenone)] (XVIII). Several compounds related to the intermediates in this synthetic series are described.

In the first paper of this series[1] certain approaches were described to the synthesis of 6α- and 6β-hydroxy-2,3,4,4aβ,5,6,7,8,8aα,9,10,10aβ-dodecahydro-2-anthracenone (Ia and Ib), potential non-steroidal androgens. These involved the hydrogenation of appropriately substituted anthracenes, and attachment of the A and C rings to the B ring. The present paper presents the details of an attempt



Ia, R = H, α-OH
Ib, R = H, β-OH

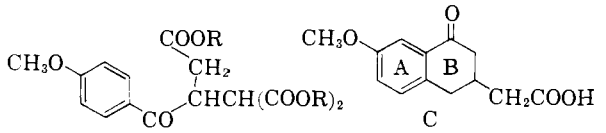
to build the B and C rings consecutively onto the A ring.

The starting material, β-anisoylpropionic acid,[2] was brominated by a modification of a known

(1) Paper I, R. L. Clarke and W. S. Johnson, THIS JOURNAL, **81**, 5706 (1959).

(2) L. F. Fieser and E. B. Hershberg, *ibid.*, **58**, 2314 (1936).

procedure[3] to give β-anisoyl-β-bromopropionic acid (IIa). The ethyl ester of this acid (IIIa) was treated with sodium diethyl malonate with the hope of producing diethyl β-anisoyl-α-carbethoxyglutarate (A). This involved direct replacement



A, R = Et
B, R = H

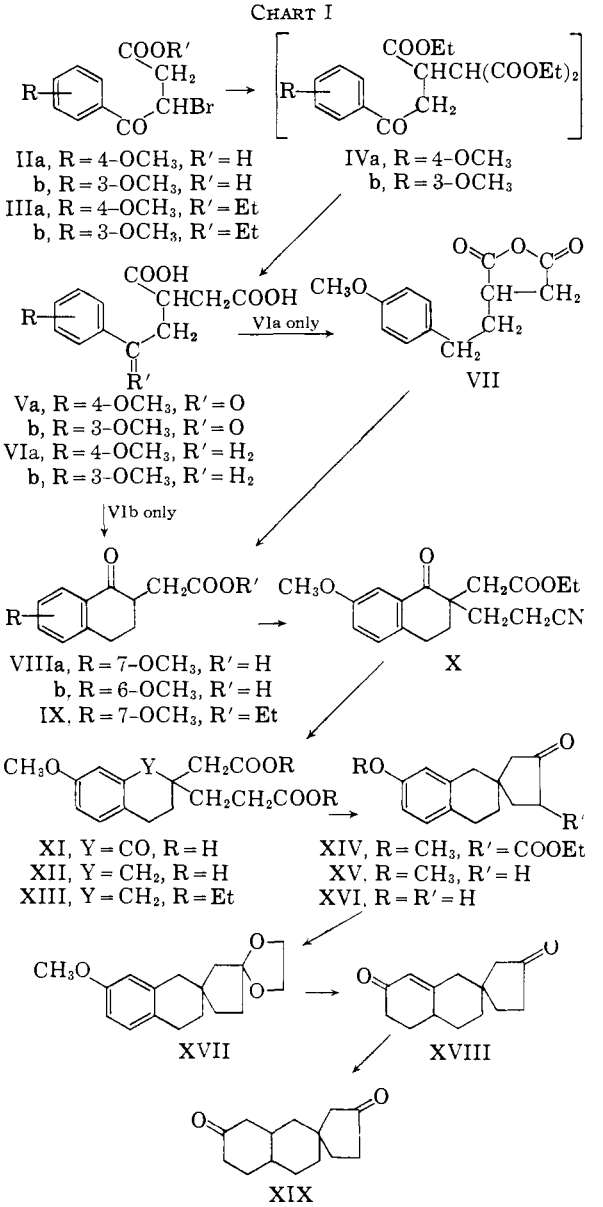
of the bromine atom by the diethyl malonyl group. Hydrolysis of A to give B followed by monodecarboxylation, reduction of the ketone group and cyclization should produce C with two of the rings of I present. The reaction sequence then required building the third ring starting with cyanoethylation alpha to the ketone group and finally producing the α,β-unsaturated ketone structure of I by Birch reduction of the aromatic ring.

The malonic ester reaction above could follow an alternate course (see Chart I) involving dehydrohalogenation of the bromoester IIIa under the strongly basic conditions extant followed by addition of diethyl malonate to the ethyl β-anisoylacrylate so produced. The product from this sequence of reactions would be diethyl α-(anisoylmethyl)-α′-carbethoxysuccinate (IVa).

The synthesis was carried forward several steps before a point was reached where the actual course of this malonic ester reaction was determined. As will be shown below, the reaction involved dehydrohalogenation followed by addition of diethyl malonate and compound IVa was formed. Compound IVa was hydrolyzed and decarboxylated to produce α-(anisoylmethyl)-succinic acid (Va). Reduction of the ketone group of compound Va gave α-[β-(4-methoxyphenyl)-ethyl]-succinic acid (VIa) which lost water upon distillation and yielded α-[β-(4-methoxyphenyl)-ethyl]-succinic anhydride (VII). Cyclization of compound VII in the presence of aluminum chloride was accomplished in 98% yield to give 7-methoxy-1-oxo-1,2,3,4 - tetrahydro - 2 - naphthaleneacetic acid (VIIIa).

7-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid (VIIIa) is reported by Paranjape, *et al.*,[4] to melt at 88° (prepared by two different methods). The compound at hand melted at 124.2–125°. Either the sequence of reactions described above had gone in the desired direction to form A or perhaps compound VIIIa had actually been formed but in a different crystal form with a melting point different from that reported. One of the synthetic procedures of Paranjape, *et al.*, was repeated. 2-Bromo-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenone was treated with sodio diethyl malonate[5] to give compound VIIIa in low yield. It melted at 125–127° and showed no melting point depression upon admixture with compound VIIIa prepared from compound II. The infrared spectra of the samples were identical. Thus, formal proof for the structure of the compound at hand was obtained.

CHART I



The series of reactions initially planned to be run on 7-methoxy-1-oxo-1,2,3,4-tetrahydro-3-naphthaleneacetic acid (C) was effected with compound VIIIa. The spiro products XVI and XVIII ultimately to be formed were considered worthy of physiological examination because of the rigidity of the ring system and the appropriate distribution of substituent groups. The spiro ring perhaps would serve to give the thickness to the structure which is furnished by the C-13 methyl group in natural steroids.

Cyanoethylation of the ethyl ester (IX) of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid produced ethyl 2-(2′-cyanoethyl)-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthalene-

(3) M. J. Bougault, *Ann. chim. phys.*, [8] **15**, 512 (1908).

(4) K. Paranjape, N. L. Phalnikar and K. S. Nargund, *J. Univ. Bombay*, **12A**, pt. 3, 61 (1943).

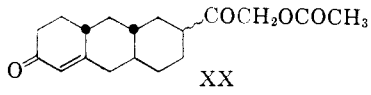
(5) If dehydrohalogenation occurred here, the product would aromatize immediately so that no Michael-type addition could occur to produce a 3-naphthaleneacetic acid.

acetate (X). This compound was hydrolyzed to form 2-(2′-carboxyethyl)-7-methoxy-1-oxo-1,2,-3,4 - tetrahydro - 2 - naphthaleneacetic acid (XI). Compound XI was reduced smoothly in the presence of palladium-on-charcoal to 2-(2′-carboxyethyl) - 7 - methoxy - 1,2,3,4 - tetrahydro-2-naphthaleneacetic acid (XII), which was converted to its diethyl ester XIII. Cyclization of compound XIII under Dieckmann conditions produced spiro-[(5-carbethoxycyclopentanone)-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XIV). Hydrolysis and decarboxylation of compound XIV gave spiro-[cyclopentanone-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XV).

It was necessary to protect the carbonyl group in compound XV by preparing its ethylenedioxy derivative XVII before performing a Birch-type reduction on the methoxy-aromatic moiety. Reduction of compound XVII with sodium and alcohol in liquid ammonia followed by hydrolysis of the protecting group produced spiro-[cyclopentanone - 3,2′ - (1′,2′,3′,4′,4a′,5′,6′,7′ - octahydro-7′ - naphthalenone)] (XVIII). A trace of spiro-[cyclopentanol - 3, 2′ - (7′ - methoxy - 1′, 2′, 3′,4′-tetrahydronaphthalene)] was also isolated. Compound XVIII failed to show any androgenic activity.

Catalytic hydrogenation of XVIII in the presence of palladium-on-calcium carbonate produced spiro - [cyclopentanone - 3,2′ - (7′ - decalone)] (XIX). The methoxy group of compound XV was cleaved to produce spiro-[cyclopentanone-3,2′-(7′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XVI). Compound XVI proved devoid of estrogenic activity.

Just as the anthracene derivative I is related to testosterone,[1] so is 6-acetoxyacetyl-2,3,4,4aβ,-5,6,7,8,8aα,9,10,10aβ - dodecahydro - 2 - anthracenone (XX) related to desoxycorticosterone acetate. Synthetic work directed toward compounds XX and I was conducted simultaneously. β-Bromo-β-(3-methoxybenzoyl)-propionic acid (IIb), prepared from β - (3 - methoxybenzoyl) - propionic acid,[6] was converted to its ethyl ester IIIb and



XX

this ester treated with sodium diethyl malonate. Here, as in the similar reaction with compound IIIa, a dehydrohalogenation occurred followed by Michael addition to produce diethyl α-carbethoxy-α′ - (3 - methoxybenzoylmethyl) - succinate (IVb). Hydrolysis and decarboxylation of the triester IVb produced α-(3-methoxybenzoylmethyl)-succinic acid (Vb). Catalytic reduction of the carbonyl function of compound Vb furnished α-[β-(3-methoxyphenyl)-ethyl]-succinic acid (VIb).

Cyclization of the acid VIb occurred readily in the presence of hydrogen fluoride. The product, 6-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid (VIIIb), corresponded in its properties to those reported[7] since completion of this work. At this point it was realized (from results obtained in the first synthetic sequence described above) that this 6-methoxy series also was destined to result in a spiro compound and not the desired anthracene derivative. No further transformations were performed on compound VIIIb.

Several further attempts were made to produce β-anisoylglutaric acid (B). There was some possibility that tricarballylic anhydride would react with anisole in the presence of aluminum chloride to produce the acid B. This required that anisole react with the hindered carbonyl of the anhydride. Only α-(anisoylmethyl)-succinic acid (Va) was isolated (78% yield).

Both 3- and 4-methoxybenzoylpropionic acids and their ethyl esters failed to undergo cyanoethylation or Mannich-type reactions. Yet acetoanisone gives a tricyanoethylation product.[8] The methylene group to be attacked here is beta to the carboxy or carbethoxy functional group, a factor evidently responsible for its inactivity. Further evidence of the inactivity of this methylene group is furnished by the failure of ethyl β-anisoylpropionate to react with chloroacetonitrile in the presence of sodium hydride.

Ethyl anisoylacetate reacted with one mole of chloroacetonitrile to form ethyl α-anisoyl-β-cyanopropionate, but the latter compound failed to react further with a second mole of chloroacetonitrile to form β-anisoyl-β-carbethoxyglutaronitrile. This glutaronitrile could have been hydrolyzed and decarboxylated to give B.

A few additional reactions were carried out with intermediates at hand. 7-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid (VIIIa) was cleaved with hydrobromic acid to produce 7-hydroxy - 1 - oxo - 1,2,3,4 - tetrahydro - 2 - naphthaleneacetic acid. The acid VIIIa was reduced catalytically to 7-methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetic acid. This reduced compound was converted to its ethyl ester and to 7-methoxy-1,2,3,4 - tetrahydro - 2 - naphthaleneacetyl chloride. Reaction of this acid chloride with diazomethane, followed by treatment with acetic acid, furnished 2-acetoxyacetylmethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene

Experimental[9]

β-Anisoyl-β-bromopropionic acid (IIa) was prepared by a modification of the procedure of Bougault.[3] To a stirred solution of 439 g. (2.11 moles) of β-anisoylpropionic acid[2] in 4.4 l. of acetic acid held at 50–60° was added a solution of 355 g. (2.22 moles) of bromine in 1.1 l. of acetic acid in 3 hr. The acetic acid was distilled from the mixture *in vacuo* at <60°. The residual oil solidified when stirred with 2 l. of cold water. It was filtered (582 g.), dissolved in 1.7 l. of hot benzene, and the solution treated with Darco G-60. The filtered solution, upon treatment with an equal volume of pentane and cooling, deposited 510 g. (84% yield) of brominated acid[10] IIa, m.p. 110–113°.

(6) E. L. Martin, THIS JOURNAL, **58**, 1438 (1936).

(7) E. Buckta, M. Klisch, S. Maier and H. Bayer, *Ann.*, **576**, 7 (1952).

(8) H. A. Bruson and T. W. Riener, THIS JOURNAL, **64**, 2850 (1942).

(9) All melting points are corrected unless otherwise noted. The infrared spectra were determined with a Perkin–Elmer model 21 double beam recording spectrophotometer equipped with a sodium chloride prism. Chromatograms were run on 100–200 mesh silica gel, the Davison Chemical Corp., Baltimore, Md. The authors wish to express their appreciation to Mr. K. D. Fleischer and his associates for the analytical data reported, to Dr. F. C. Nachod and Miss Catherine M. Martini for the spectral data reported, and to Dr. A. L. Beyler for the biological testing.

(10) Contact with this compound caused a case of severe eye irritation.

When chloroform was used as the solvent for bromination, concentration of the mother liquors caused separation of what is presumed to be **β-anisoyl-β,β-dibromopropionic acid**. Two recrystallizations of this acid from chloroform gave colorless, massive prisms, m.p. 159–161° (2.3% yield).

Anal. Calcd. for $C_{11}H_{10}O_4Br_2$: C, 36.09; H, 2.75; Br, 43.67. Found: C, 36.3; H, 3.0; Br, 43.6.

α-(Anisoylmethyl)-succinic Acid (Va).—A mixture of 500 g. (1.77 moles) of β-anisoyl-β-bromopropionic acid (IIa), 1.3 l. of absolute ethanol, 1 l. of benzene and 7 ml. of concentrated sulfuric acid was refluxed for 4 hr. Solvent (500 ml.) was distilled from the mixture and 500 ml. of fresh benzene was added. The mixture was refluxed for 2 hr. and this replacement process followed by a reflux period was repeated twice. The resulting mixture was diluted with 1 l. of ether, washed twice with water, twice with 10% potassium carbonate, once with water, and dried ($CaCl_2$). The solvent was removed at <60° *in vacuo* and the residual oil (521 g.), **ethyl β-anisoyl-β-bromopropionate (IIIa)**, alkylated without further purification.

Sodium diethyl malonate was prepared from 266 g. (1.66 moles) of diethyl malonate and 65 g. (1.66 moles) of sodium amide in 4 l. of dry benzene. The 521 g. (1.66 moles) of crude ethyl β-anisoyl-β-bromopropionate above in 1 l. of benzene was added dropwise at <40°. The reaction mixture was then refluxed for 2 hr., cooled, washed twice with water, dried ($CaCl_2$), and freed from solvent *in vacuo* at 100°. The resulting crude **diethyl α-(anisoylmethyl)-α'-carbethoxysuccinate (IVa)** was saponified without purification.

This crude triester was refluxed for 3 hr. with 220 g. (5.5 moles) of sodium hydroxide, 1.1 l. of water and 1.1 l. of 95% ethanol. The cooled solution was treated with 450 ml. of concentrated hydrochloric acid and the ethanol removed by warming *in vacuo*. The slushy residue of **α-(anisoylmethyl)-α'-carboxysuccinic acid** was decarboxylated by adding to it 800 ml. of concentrated hydrochloric acid and 1.7 l. of acetic acid and then refluxing the mixture for 6 hr. The solvents were removed, the solid residue boiled with 1.2 l. of acetic acid for 30 min., the insoluble salts removed, and the filtrate diluted with 4 l. of water. Crude **α-(anisoylmethyl)-succinic acid (Va)** separated on cooling (370 g.) which, after recrystallization from ethyl acetate using Darco G-60, amounted to 275 g. (57% over-all yield from IIa), m.p. 165–168° (uncor.). An analytical sample, after a second recrystallization from ethyl acetate, melted at 161–162.5°.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.29. Found: C, 58.6; H, 5.5.

α-[β-(4-Methoxyphenyl)-ethyl]-succinic Acid (VIa).—A mixture of 240 g. (0.90 mole) of α-(anisoylmethyl)-succinic acid, 1.6 l. of glacial acetic acid and 13 g. of 7% palladium chloride-on-charcoal catalyst was treated with hydrogen under 500 p.s.i. at 40° for 3 hr. The catalyst was separated and the solvent removed from the filtrate by warming *in vacuo*. The dark residue was recrystallized from water using Darco G-60 to give 162 g. (71% yield) of α-[β-(4-methoxyphenyl)-ethyl]-succinic acid, m.p. 133–136°. An analytical sample, after a second recrystallization from water, melted at 138–139°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.1; H, 6.5.

α-[β-(4-Methoxyphenyl)-ethyl]-succinic Anhydride (VII).—α-[β-(4-Methoxyphenyl)-ethyl]-succinic acid (109 g., 0.43 mole), in a flask fitted with a distillation head, was heated at 200° under 10 mm. pressure for 1 hr. The pressure was then lowered to 0.2 mm. and the temperature of the flask raised until the "head" temperature reached 190° and the anhydride started to distil. The distillation was stopped at this point. The flask contents solidified upon cooling and the 100 g. of product (99% yield) so obtained melted at 63–65°. An analytical sample, recrystallized from ether, melted at 68–69°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.67; H, 6.02. Found: C, 66.6; H, 6.2.

7-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid (VIIIa).—To a solution of 100 g. (0.75 mole) of α-[β-(4-methoxyphenyl)-ethyl]-succinic anhydride in 300 ml. of nitrobenzene was added in 15 min. a solution of 105 g. of aluminum chloride in 1 l. of nitrobenzene and the mixture allowed to stand at room temperature for 2 days. The nitrobenzene was removed by steam distillation and the still-pot residue cooled and filtered. The filter cake was recrystallized from benzene to give 98.3 g. (98% yield) of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid, m.p. 123–125°. An analytical sample, recrystallized a second time from benzene, melted at 124–125°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.67; H, 6.02; neut. equiv., 234. Found: C, 66.8; H, 6.2; neut. equiv., 237.

7-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid (VIIIa) from 2-Bromo-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenone.—To sodium diethyl malonate prepared from 3.85 g. (0.024 mole) of diethyl malonate and 0.6 g. (0.025 mole) of sodium hydride in 100 ml. of benzene was added a solution of 5.5 g. (0.022 mole) of 2-bromo-7-methoxy-1,2,3,4-tetrahydro-1-naphthalenone[4,11] in 50 ml. of benzene in 4 min. The resulting solution was refluxed for 90 min. and allowed to stand for 65 hr. Water was added and the layers were separated. The organic layer was washed twice with water and then freed from solvent by warming *in vacuo*. The oily residue was refluxed for 30 min. with a mixture of 4 g. (0.1 mole) of sodium hydroxide, 25 ml. of 95% ethanol and 50 ml. of water. The solvents were removed as before and the residue boiled for 3 hr. with a mixture of 20 ml. of acetic acid and 20 ml. of concentrated hydrochloric acid. These reagents were removed by warming *in vacuo*, the residue was dissolved in 2 *N* aqueous sodium hydroxide, and the solution washed with ether. The solution was acidified and the product extracted with ether. Evaporation of the ether from the solution left an oily residue which failed to solidify.

Chromatography of this oil in 1:4 ether–pentane on 100 g. of silica gel gave 0.65 g. (13% yield) of white needles which, after one recrystallization from water, melted at 125–127°. The product showed no depression in melting point upon admixture with a sample prepared from α-[β-(4-methoxyphenyl)-ethyl]-succinic acid and their infrared spectra were identical.

Ethyl 7-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetate (IX).—A mixture of 147 g. (0.63 mole) of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid, 250 ml. of absolute ethanol, 500 ml. of benzene and 1 ml. of concentrated sulfuric acid was refluxed for 1 hr. Solvent (200 ml.) was distilled out and replaced by 200 ml. of absolute ethanol. After another hour reflux period the replacement was repeated. After a 2-hr. reflux period the solvent was completely removed and 300 ml. of water added. The mixture was extracted twice with ether and the extracts washed with dilute sodium hydroxide and dried (Na_2SO_4). Removal of the ether gave the desired ester which, after two recrystallizations from methanol, afforded 116 g. (70% yield), m.p. 75–78° (uncor.).

The analytical sample, m.p. 74.7–75.3°, was purified by chromatography on silica gel using pentane and absolute ether as eluting solvents followed by recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.6; H, 7.2.

Ethyl 2-(2'-Cyanoethyl)-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetate (X).—To a solution of 115 g. (0.44 mole) of ethyl 7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetate in 750 ml. of dry benzene was added 23.6 g. (0.44 mole) of acrylonitrile and then 1 ml. of a saturated solution of sodium ethoxide in absolute ethanol. The solution was allowed to stand at room temperature for 15 hr., was refluxed for 2 hr., and then freed from solvent by warming *in vacuo*. Water (300 ml.) was added, the mixture made acid with dilute hydrochloric acid, and the product extracted with ether. The ether was removed from the dried (Na_2SO_4) extracts and the residual oily product dissolved in 3:7 ether–pentane and poured onto 1.2 kg. of silica gel. This same solvent mixture (12 l.) eluted 22 g. (19% recovery) of starting material. A 1:1 mixture of these solvents eluted 68.5 g. (50% yield) of the desired cyanoethylated product, m.p. 68–73° (uncor.). The analytical sample, recrystallized from methanol, melted at 69.5–71°.

Anal. Calcd. for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.7; H, 6.8; N, 4.3.

2-(2'-Carboxyethyl)-7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid (XI).—A mixture of 23 g. (0.073 mole) of X, 90 ml. of acetic acid and 90 ml. of concentrated hydrochloric acid was refluxed for 12 hr. and the reagents were then removed by warming *in vacuo*. The residue, re-

(11) E. Mosettig and E. L. May, *J. Org. Chem.*, **5**, 528 (1940).

crystallized from 1.2 l. of water, afforded 20 g. (89% yield) of the desired dicarboxylic acid, m.p. 158–160°. The analytical sample, after a second recrystallization from water, melted at 160–161°.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92; neut. equiv., 306. Found: C, 62.9; H, 6.0; neut. equiv., 316.

2-(2′-Carboxyethyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid (XII).—A mixture of 15 g. (0.049 mole) of XI, 150 ml. of acetic acid and 7.5 g. of 7% palladium chloride-on-charcoal catalyst[12] was treated with hydrogen under 60 p.s.i. at 50°. The reduction was complete in 20 min. The catalyst was separated, the solvent removed by warming *in vacuo*, and water added. The product solidified, (13.5 g., 94% yield) and melted at 172–175° dec. An analytical sample recrystallized from aqueous ethanol, melted at 175–177° dec.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.9; H, 7.0.

Ethyl 2-(2′-Carbethoxyethyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetate (XIII).—A mixture of 54 g. (0.18 mole) of XII, m.p. 172–175°, 250 ml. of absolute ethanol, 500 ml. of benzene and 5 ml. of concentrated sulfuric acid was refluxed for 2 hr. Solvent (250 ml.) was distilled out of the mixture and replaced by 250 ml. of absolute ethanol. After an additional 4-hr. reflux period all of the solvent was removed by warming *in vacuo*. The residual oil was taken up in ether, this solution was washed with dilute sodium hydroxide, with water, and then dried (Na_2SO_4). The ether was removed and the residue distilled, the product boiling at 207–214° (0.6 mm.), 51.1 g. (77% yield), $n^{25}D$ 1.5142. This diester was used without further purification.

Spiro-[cyclopentanone-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XV).—A solution of sodium ethoxide in 300 ml. of dry toluene was prepared using 4.14 g. (0.18 mole) of sodium and 10 ml. of absolute ethanol. Compound XIII (55.4 g., 0.159 mole) in 250 ml. of dry toluene was added and the mixture refluxed for 90 min. Solvent (75 ml.) was distilled from the mixture and reflux continued for 1 hr. A further 40-ml. portion was distilled from the mixture and reflux continued for another hour. Addition of dilute hydrochloric acid to the cooled solution caused precipitation of a solid which turned to an oil and redissolved. The toluene layer was separated, washed with water, and dried (Na_2SO_4). Distillation of the toluene *in vacuo* left an oily residue of crude **spiro-[(5-carbethoxycyclopentanone)-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XIV)** which was hydrolyzed and decarboxylated without purification.

The crude spiro compound was refluxed with 250 ml. of concentrated hydrochloric acid and 250 ml. of acetic acid for 3 hr. These reagents were then distilled *in vacuo*, 100 ml. of water added, the mixture made alkaline with dilute sodium hydroxide, and the product extracted with ether. The dried (Na_2SO_4) extracts were freed from ether whereupon the residual oil slowly solidified; 31 g., m.p. 42–51°.

Chromatography of this crude compound (XV) in a 1:4 mixture of ether–pentane on 500 g. of silica gel gave 25.8 g. (70% yield) of the spiro ketone, m.p. 53–55°. An analytical sample, recrystallized once from hexane and once from ether, melted at 56–57.5°.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.5; H, 7.6.

Spiro-[ethylenedioxycyclopentane-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XVII).—A mixture of 5 g. (0.022 mole) of spiro-[cyclopentanone-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)], 1.5 g. (0.024 mole) of ethylene glycol, 0.1 g. of *p*-toluenesulfonic acid and 100 ml. of toluene was refluxed in a system containing a water separator. When separation of water was complete (1 hr.) the mixture was cooled, washed once with dilute potassium carbonate solution, once with water, and dried (Na_2SO_4). The toluene was distilled and the oil residue fractionated. The somewhat impure product (3.1 g., 52% yield) was collected at 156–158° (0.37 mm.)

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.09. Found: C, 74.9; H, 7.5.

Spiro-[cyclopentanone-3,2′-(1′,2′,3′,4′,4a′,5′,6′,7′-octahydro-7′-naphthalenone)] (XVIII).—To a mixture of 4.7 g. (0.017 mole) of spiro-[ethylenedioxycyclopentane-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)], 30 ml. of absolute ether, 10 ml. of absolute ethanol and 150 ml. of liquid ammonia was added 4.7 g. (0.2 mole) of sodium in small pieces over a period of 15 min. The ammonia was allowed to evaporate, 100 ml. of cold water was added, and the product extracted with ether. The ether was evaporated and the residual oil refluxed for 30 min. in a mixture of 10 ml. of 95% ethanol and 10 ml. of 10% aqueous sulfuric acid. The alcohol was removed by distillation, the aqueous residue made alkaline with 10% sodium hydroxide, and the oil extracted with ether. The extract was dried (Na_2SO_4) and the ether distilled.

The residual oil was chromatographed on 100 g. of silica gel. A 1:1 ether–pentane mixture eluted a trace of **spiro-[cyclopentanol-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)]**, which, upon recrystallization from hexane, melted at 49–51°; λ_{max}^{EtOH} 287 mμ (log *E* 3.33), 279 mμ (log *E* 3.36) and 219 mμ (log *E* 3.86); $\lambda_{max}^{CS_2}$ 2.82 μ with no maxima in the carbonyl region.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.4; H, 8.6.

Elution of the column with 3:1 ether–pentane gave 1.5 g. of crude spiro-[cyclopentanone-3,2′-(1′,2′,3′,4′,4a′,5′,6′,7′-octahydro-7′-naphthalenone)], m.p. 62–85°. One recrystallization from ether gave 0.5 g., m.p. 100–103°. A second recrystallization gave 0.37 g., m.p. 102–103°; λ_{max}^{EtOH} 237 mμ (log *E* 4.19); $\lambda_{max}^{CS_2}$ 5.76 and 5.97 μ.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.2; H, 8.5.

Spiro-[cyclopentanone-3,2′-(7′-decalone)] (XIX).—A mixture of 0.44 g. (0.002 mole) of spiro-[cyclopentanone-3,2′-(1′,2′,3′,4′,4a′,5′,6′,7′-octahydro-7′-naphthalenone)], 20 ml. of absolute ethanol and 0.5 g. of 2% palladium chloride-on-calcium carbonate catalyst was treated with hydrogen under 40 p.s.i. at 25°. Hydrogenation of the double bond was complete in 20 min. The filtered mixture was freed from alcohol by warming *in vacuo*. The residual oil solidified, m.p. 102–112°. Two recrystallizations from ether afforded 125 mg., m.p. 114–117°. Chromatography on 50 g. of silica gel using ether–pentane mixtures for elution failed to sharpen the melting point. The compound showed no ultraviolet maximum in the 237 mμ range, but showed infrared maxima at 5.76 and 5.84 μ.

Spiro-[cyclopentanone-3,2′-(7′-hydroxy-1′,2′,3′,4′-tetrahydronaphthalene)] (XVI).—A mixture of 1.0 g. of spiro-[cyclopentanone-3,2′-(7′-methoxy-1′,2′,3′,4′-tetrahydronaphthalene)], 25 ml. of glacial acetic acid and 3 ml. of 47% aqueous hydrobromic acid was refluxed for 7 hr. The acids were removed by warming *in vacuo* and the residual oil partioned between water and ether. The ether layer was extracted with 2 *N* sodium hydroxide solution and the phenolic product precipitated from this extract with dilute hydrochloric acid. This product was chromatographed on 15 g. of silica gel. Ether–pentane (2:3) eluted XVI which was recrystallized from 5:8 pentane–benzene to give 0.39 g. (42% yield) of m.p. 147–148.5°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.5; H, 7.5.

β-Bromo-β-(3-methoxybenzoyl)-propionic Acid (IIb).—To a solution of 32 g. (0.154 mole) of β-(3-methoxybenzoyl)-propionic acid[6] at 45° was added one-third of a solution of 24.7 g. (0.154 mole) of bromine in 100 ml. of chloroform. After the bromine color disappeared, the temperature of the reaction mixture was lowered to 30° and the bromine addition completed. The solvent was boiled off on the steam-bath *in vacuo* and the oily residue of bromo acid used without further purification.

Ethyl β-Bromo-β-(3-methoxybenzoyl)-propionate (IIIb). A mixture of crude β-bromo-β-(3-methoxybenzoyl)-propionic acid as described above (assumed 0.15 mole), 120 ml. of absolute ethanol, 300 ml. of benzene and 1 ml. of concentrated sulfuric acid was refluxed for 20 hr. in a system containing a water separator. The solvents were removed by warming *in vacuo*, the residual oil was dissolved in ether, and this solution washed once with water and twice with 10% potassium carbonate solution. The dried ($CaCl_2$) ether solution was freed from solvent and the crude oily residue of bromoester used without further purification.

α-(3-Methoxybenzoylmethyl)-succinic Acid (Vb).—Sodium diethyl malonate was prepared from 29 g. (0.18 mole) of diethyl malonate and 7 g. (0.18 mole) of sodamide in 200 ml. of benzene. The crude ethyl β-bromo-β-(3-methoxybenzoyl)-propionate described above (assumed 0.15 mole) in

(12) The use of less catalyst or a higher temperature gave poorer yields.

75 ml. of benzene was added to the refluxing sodium diethyl malonate mixture with stirring in 30 min. The resulting mixture was refluxed for 2 hr., cooled, washed twice with water, dried (Na_2SO_4), and freed from solvent by warming *in vacuo*.

The residual oil, crude **diethyl α-carbethoxy-α'-(3-methoxybenzoylmethyl)-succinate (IVb)**, was saponified by refluxing a mixture of it, 30 g. (0.75 mole) of sodium hydroxide, 150 ml. of 95% ethanol and 150 ml. of water for 2 hr.

After the mixture had stood overnight, it was freed from solvent by warming *in vacuo* and the residual oil treated with 75 ml. of concentrated hydrochloric acid, 10 ml. of water and 125 ml. of acetic acid. Reflux of this mixture for 2.5 hr. caused monodecarboxylation of the **α-carboxy-α'-(3-methoxybenzoylmethyl)-succinic acid** present at this point. All solvent was removed by warming *in vacuo* and the residue extracted with four 100-ml. portions of hot ethyl acetate. The combined extracts were treated with Darco G-60 and then reduced to a 75-ml. volume. Cooling gave 18.5 g. of solid which was recrystallized from 185 ml. of water (charcoal treatment) to furnish 15.7 g. (38% over-all yield from III) of **α-(3-methoxybenzoylmethyl)-succinic acid (Vb)**, m.p. 131–135° (uncor.). An analytical sample, recrystallized again from water, melted at 131.5–132.5°.

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.29. Found: C, 58.9; H, 5.5.

α-[β-(3-Methoxyphenyl)-ethyl]-succinic Acid (VIb).—A mixture of 13.3 g. (0.05 mole) of α-(3-methoxybenzoylmethyl)-succinic acid, 150 ml. of acetic acid and 3 g. of 7% palladium-on-charcoal catalyst was treated with hydrogen under 55 p.s.i. at 45° for 28 hr. The catalyst was separated and the solvent removed by warming *in vacuo*. The residual oil was dissolved in dilute sodium hydroxide, the solution treated with charcoal, and the filtrate acidified. The 11.4 g. of poorly formed solid which precipitated was distilled at 0.35 mm. pressure using a bath temperature of 230°.[13] The distillate was dissolved in dilute sodium hydroxide with the aid of heat and the solution acidified. The precipitated solid was recrystallized from water with charcoal treatment to give 7.85 g. (62% yield) of the desired acid VIb, m.p. 110.5–113°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.1; H, 6.5.

6-Methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid[7] **(VIIIb).**—α-[β-(3-Methoxyphenyl)-ethyl]succinic acid (6.1 g., 0.024 mole) was dissolved in 100 ml. of 100% hydrogen fluoride and the latter allowed to evaporate overnight. The residue was dissolved in dilute sodium hydroxide and the filtered solution acidified. The precipitated solid was recrystallized twice from ethyl acetate to give 3.6 g. (64% yield) of VIIIb, m.p. 167.5–168.5° [reported[7] 171–172° (cor. ?)].

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.67; H, 6.02. Found: C, 66.9; H, 6.3.

α-(Anisoylmethyl)-succinic Acid (Va) from Tricarballylic Anhydride.—To a mixture of 2.46 g. (0.023 mole) of anisole, 3.6 g. (0.023 mole) of tricarballylic anhydride,[14] 8 ml. of nitrobenzene and 32 ml. of ethylene dichloride was added at 0° with stirring 9.15 g. (0.069 mole) of aluminum chloride in three increments. The mixture was then kept at 0° for 1 hr. and overnight at 25°. It was poured onto a mixture of ice and 15 ml. of concentrated hydrochloric acid and the organic solvents were removed by steam distillation. Chilling the still-pot contents caused precipitation of the product. Recrystallization of this material from 35 ml. of water with charcoal treatment gave 4.7 g. (78% yield) of compound Va, m.p. 159–162°. It showed no depression in melting point upon admixture with a sample prepared from compound IIa as described above.

Anal. Calcd. for $C_{13}H_{14}O_6$: neut. equiv., 133.1. Found: neut. equiv., 132.

Ethyl α-Anisoyl-β-cyanopropionate.—To a solution of 22.2 g. (0.1 mole) of ethyl anisoylacetate in 200 ml. of dry benzene was added 2.6 g. (0.11 mole) of sodium hydride. The mixture was refluxed for 1 hr., 8.0 g. (0.11 mole) of chloroacetonitrile added in 10 min., and reflux continued for 5 hr. Water was added to the cooled mixture and the layers were separated. The organic layer was washed twice with water and dried (K_2CO_3). Following removal of the solvent, the residual oil was distilled, the portion boiling at 159–185° (0.8 mm.) being saved (10.5 g.). This was redistilled to give 7.1 g. (27% yield) of ethyl α-anisoyl-β-cyanopropionate, b.p. 172–179° (0.44 mm.), $n^{25}D$ 1.5390.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36. Found: C, 64.4; H, 5.6; N, 5.4.

7-Hydroxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid.—A mixture of 4.0 g. (0.017 mole) of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid, 12 ml. of 47% aqueous hydrobromic acid, and 100 ml. of acetic acid was refluxed under nitrogen for 24 hr. Removal of the acids by distillation at reduced pressure left an oil residue which solidified. Trituration of the solid with water, filtration, and air drying gave 3.2 g. (85% yield) of the desired product, m.p. 190–191° dec. Two recrystallizations of the sample from water with charcoal treatment gave 1.1 g. of pale pink plates, m.p. 193.5–194.5° dec.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.1; H, 5.3.

7-Methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid.—A solution of 5 g. (0.021 mole) of 7-methoxy-1-oxo-1,2,3,4-tetrahydro-2-naphthaleneacetic acid (VIIIa) in 150 ml. of acetic acid was treated with hydrogen under 60 p.s.i. at 40° in the presence of 2.5 g. of 7.5% palladium-on-charcoal as a catalyst. Reduction of the ketone group was complete in 3.5 hr. The catalyst was removed and the solvent distilled. The residual oil, which solidified, was triturated with water and air-dried to give 4.5 g. (96% yield) of crude product, m.p. 93–96°. An analytical sample, recrystallized from benzene–pentane mixture, melted at 98–99°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32; neut. equiv., 220.3. Found: C, 71.1; H, 7.1; neut. equiv., 220.5.

Ethyl 7-Methoxy-1,2,3,4-tetrahydro-2-napththaleneacetate.—A mixture of 5 g. (0.023 mole) of 7-methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetic acid, 100 ml. of benzene, 20 ml. of absolute ethanol and 1 ml. of concentrated sulfuric acid was refluxed for 1 hr. Then 50 ml. of solvent was distilled from the mixture and replaced by 50 ml. of absolute ethanol. After a 2-hr. reflux period the process was repeated. Then all solvent was distilled, the residue made alkaline with dilute sodium hydroxide, and the product extracted with ether. Removal of the ether from the extracts and distillation of the residual oil gave 3.3 g. (59% yield) of colorless oil, b.p. 140–142° (approx. 0.5 mm.), $n^{25}D$ 1.5208.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.6; H, 8.2.

7-Methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetyl Chloride.—A mixture of 4.0 g. (0.018 mole) of 7-methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetic acid, 3 ml. (4.9 g., 0.041 mole) of thionyl chloride and 100 ml. of chloroform was refluxed for 2 hr., allowed to stand overnight, and then refluxed for 1 hr. The solvent and the residual oil were distilled. Crude product (1.6 g.) was collected at 140–143° (0.7 mm.). It was used without further purification.

Anal. Calcd. for $C_{13}H_{15}O_2Cl$: Cl, 14.85. Found: Cl, 13.8.

2-Acetoxyacetylmethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene.—A solution of 1.5 g. (0.0063 mole) of 7-methoxy-1,2,3,4-tetrahydro-2-naphthaleneacetyl chloride in 40 ml. of dry ether was added to a stirred solution of approximately 5 g. (0.12 mole) of diazomethane in 50 ml. of ether which was cooled by ice-water. The ether was then evaporated at below 45°, 25 ml. of acetic acid was added, and the mixture heated at 100° for 90 min. The acetic acid was removed by distillation, the residue was extracted with ether, and the extracts dried (Na_2SO_4). Removal of the ether gave an oil which solidified (1.5 g., m.p. 57–65°).

The solid was chromatographed on 50 g. of silica gel. Elution with 3:7 ether–pentane gave 0.9 g. of the desired product which, after recrystallization from hexane, melted at 70–72°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.4; H, 7.3.

RENSSELAER, N. Y.

(13) The solid effervesced as it melted and the material which distilled was probably the acid anhydride.

(14) W. A. Bone and C. H. G. Sprankling, *J. Chem. Soc.*, **81**, 29 (1902).