lene gave a higher yield of monomeric adduct than did maleic anhydride.

Citraconic anhydride and mesaconic acid add to 1-vinylnaphthalene and to 1-vinyl-6-methoxynaphthalene to give the *cis* and *trans* forms of adducts in which the methyl group is in the 1-position of the hydrophenanthrene nucleus.

cis–trans Interconversions of the products are described.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 1, 1947

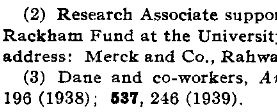
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Diels–Alder Reaction of 1-Vinyl-6-methoxy-3,4-dihydronaphthalene with Citraconic Anhydride[1]

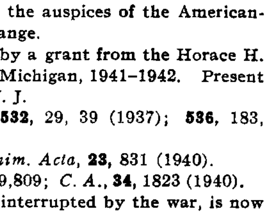
BY W. E. BACHMANN AND J. M. CHEMERDA[2]

1-Vinyl-6-methoxy-3,4-dihydronaphthalene has been allowed to react with a number of dienophiles in order to obtain estrogens or suitable intermediates for the synthesis of estrone.[3,4,5] In 1941 we began an investigation[6] of the reaction of this diene with citraconic anhydride.[7] Theoretically, two sets of products were possible: I, with the methyl group in the 1-position, and II, with the methyl group in the 2-position. In virtue of the three asymmetric carbon atoms, each of the structures can exist in eight stereoisomeric forms (four racemic mixtures). However, the principle of *cis* addition reduces the number to two racemic mixtures for each structure; and, if the rule of the "maximum accumulation of double bonds" prior to addition is applicable, only one racemic mixture for each structural isomer should be obtained. The configuration of the 2-methyl derivative should be IIa; similarly, the single racemic mixture of I would have the H's on C_2 and C_{10a} and the methyl group on C_1 *cis* to each other.

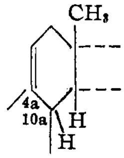
Citraconic anhydride reacted with 1-vinyl-6-methoxy-3,4-dihydronaphthalene in boiling benzene to give a mixture of adducts in 70% yield, from which two pure, crystalline anhydrides were isolated. The anhydrides, m. p. 128° (one part) and m. p. 163° (two parts), comprised at least 60% of the mixture.[8] These results illustrate the pronounced steric selectivity of the Diels–Alder addition. For convenience in isolation, the crude product was hydrolyzed, and the acid portion was separated from neutral material and reconverted to anhydrides by fusion at 190–200°. It was not determined whether the original compounds were regenerated or whether this treatment shifted the double bond (for example, to the 4a-10a position).[9]



I



II



IIa

The 128° anhydride is *cis*-1-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride (I), since treatment of it or the corresponding acid with palladium on charcoal[10] at 315° for a short time yielded 1-methyl-7-methoxyphenanthrene and (after hydrolysis) the *cis*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V) of Bachmann and Scott.[7] The 163° anhydride is *cis*-2-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride (II); it and the acid (IV) derived from it were transformed smoothly into 2-methyl-7-methoxyphenanthrene[11] and the anhydride of

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[1] Presented by W. E. Bachmann in Basel, Zürich, and Geneva, Switzerland, May 9–16, 1947, under the auspices of the American-Swiss Foundation for Scientific Exchange.

[2] Research Associate supported by a grant from the Horace H. Rackham Fund at the University of Michigan, 1941–1942. Present address: Merck and Co., Rahway, N. J.

[3] Dane and co-workers, *Ann.*, **532**, 29, 39 (1937); **536**, 183, 196 (1938); **537**, 246 (1939).

[4] Goldberg and Müller, *Helv. Chim. Acta*, **23**, 831 (1940).

[5] Bockemuller, U. S. Patent 2,179,809; *C. A.*, **34**, 1823 (1940).

[6] This investigation, which was interrupted by the war, is now being resumed. Further work on the reaction of the diene with citraconic anhydride and a study of the reaction with mesaconic acid are in progress.

[7] See Bachmann and Scott, THIS JOURNAL, **70**, 1458 (1948), for the addition of citraconic anhydride and of mesaconic acid to 1-vinyl-6-methoxynaphthalene.

[8] *Cf.* Breitner, *Med. u. Chem.*, **4**, 317 (1942); *Chem. Zentr.*, **114**, I, 2688 (1943); *C. A.*, **38**, 4953 (1944). The German abstract appeared after most of our experimental work had been completed. Breitner obtained a potent estrogen from an anhydride adduct (m. p. 210°) prepared from the diene and citraconic anhydride. Later the Government Intelligence Team (Report No. 248, Pharmaceuticals at the I. G. Farbenindustrie Plant, Elberfeld, Germany, Office of the Publication Board, Department of Commerce, Washington, D. C.) reported that Breitner's product was prepared from an adduct melting at about 125° and at 160° after several recrystallizations.

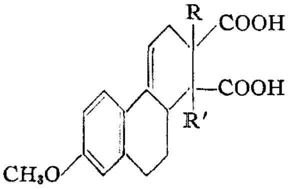
[9] The structures I, II, III, and IV are written with the double bond in the 4–4a position until more information is available.

[10] Hartung, THIS JOURNAL, **50**, 3370 (1928); **66**, 888 (1944).

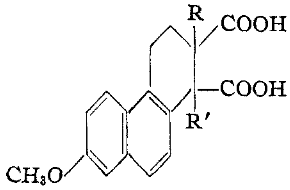
[11] Heer and Miescher, *Experientia*, **3**, 322 (1947), recently reported the formation of 1-methyl- and 2-methyl-7-methoxyphenanthrene from the adducts which they obtained from the diene and citraconic anhydride. An example of a 1-methyl-1-carboxyhydrophenanthrene derivative which has been decarboxylated and dehydrogenated is abietic acid (Ruzicka, *et al.*, *Helv. Chim. Acta*, **6**, 692 (1923); **16**, 842 (1933)) and of a 2-methyl-2-carboxy derivative is estric acid (Butenandt, Weidlich and Thompson, *Ber.*, **66**, 601 (1933)).

cis-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (anhydride of VI).[12] The formation of the 2-methyl- as well as the 1-methylhydrophenanthrene adduct is in contrast to the behavior of 1-vinylnaphthalene and 1-vinyl-6-methoxynaphthalene, which yielded only the 1-methyl derivatives with citraconic anhydride and with mesaconic acid.[7]

The 1-methylhexahydro acid III, derived from the 128° anhydride, was hydrogenated smoothly in the presence of palladium-charcoal to a mixture of stereoisomeric octahydro acids (VIIa) from which a single pure compound was isolated in 70–80% yield *via* the dimethyl ester or more efficiently through the anhydride. It is of interest that a single compound was formed in such a high yield on reduction.

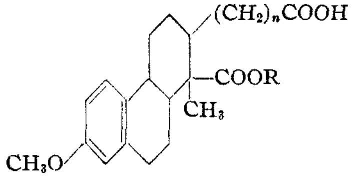


III, $R' = CH_3$; $R = H$
IV, $R = CH_3$; $R' = H$

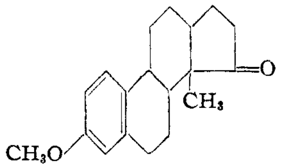


V, $R' = CH_3$; $R = H$
VI, $R = CH_3$; $R' = H$

Two Arndt–Eistert reactions were carried out on the acid ester (presumably VIIb) obtained by half hydrolysis of the dimethyl ester of VIIa. Pyrolysis of the lead salt of the product (presumably VIId) yielded a neutral product, m. p. 100–101°, whose analysis was in fair agreement with that of the methyl ether of an isomer of estrone (VIII). The small amount of material available prevented us from fully characterizing the compound.

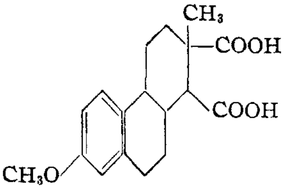


VIIa, $n = 0, R = H$
VIIb, $n = 0, R = CH_3$
VIIc, $n = 1, R = CH_3$
VIId, $n = 2, R = H$
VIIe, $n = 2, R = CH_3$



VIII

The 2-methylhexahydro acid IV, derived from the 163° anhydride, absorbed hydrogen rapidly in acetic acid only when a large proportion of Adams catalyst was employed. Whether this is indicative of the double bond lying in the 4a-10a position is left undecided at this time. From the mixture of products a crystalline octahydro acid IX could be isolated but only in low yield. After conversion of the non-crystallizable acids to anhydrides by distillation, a crystalline anhydride of the octahydro acid was isolated readily. Crystalline derivatives of the same octahydro acid were obtained by reduction of the hexahydro acid ester and the dimethyl ester. Various methods suggest themselves for converting these compounds to estrone or its stereoisomers and these are now under investigation.



IX

Experimental

Preparation of 1-Vinyl-6-methoxy-3,4-dihydronaphthalene.—Purified acetylene was bubbled at the rate of 2–3 bubbles per second for twenty-four hours through an ice-cold, ethereal solution of ethylmagnesium iodide (the iodide was used instead of the bromide[3] because of the greater solubility of the acetylene Grignard reagent in ether–benzene) prepared from 28 g. of magnesium and 110 cc. of ethyl iodide in 500 cc. of ether. The ether layer was decanted from the heavy, viscous purple layer of the acetylene-bis-magnesium iodide, which was then dissolved in 300 cc. of dry thiophene-free benzene. To the filtered Grignard solution, 20 g. of 6-methoxy-1-tetralone[13] was added in one portion. After eight hours at room temperature, the reaction mixture was hydrolyzed with ice-cold ammonium chloride solution, and the filtered organic layer was evaporated under reduced pressure at 35–40°. The partly solid residue was filtered and the solid diol, $-C(OH)C\equiv C(OH)C-$, on the filter was washed with small amounts of ether; after a second evaporation, a second crop of diol was removed. The filtrate was evaporated in a modified Claisen flask with an 8-inch Vigreux column, and the apparatus was filled with nitrogen and then evacuated before the dehydration was carried out. At 100–110° (0.5–0.6 mm.) the liquid bubbled vigorously as water was evolved; the eneyne, 1-ethynyl-6-methoxy-3,4-dihydronaphthalene, distilled smoothly at 118–123° (0.5–0.6 mm.) (reported, 124–130° at 0.5 mm.[3] and 120° at 0.1 mm.[4] for a purer sample); yield, 10.9 g. (52%). The eneyne reacted instantly with ammoniacal silver nitrate solution and with an alcoholic mercuric chloride solution in the presence of sodium ethoxide.[14]

For best results exposure of the carbinol to air should be avoided throughout. Midway in the distillation of a batch of acetylenic carbinol which had been kept overnight in a refrigerator, a sudden violent reaction set in with the formation of a green tar in the flask and the receiver. This danger can be partially averted by storage of the carbinol in an atmosphere of nitrogen at 0°, but it is better to carry out the entire sequence of steps from the hydrolysis of the Grignard reaction mixture to the distillation without interruption. Because the eneyne oxidized rapidly in the presence of air even at 0°, the partial hydrogenation to the diene was carried out immediately after the distillation.

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[12] This compound should prove useful in a project now in progress concerned with the determination of the configuration at C/D ring fusion of equilenin, estrone and other steroids.

[13] Burnop, Elliot and Linstead, *J. Chem. Soc.*, 727 (1940). In place of steam distillation, we distilled under reduced pressure the crude 6-methoxy-1-tetralone obtained by chromic acid oxidation of 6-methoxytetralin.

[14] Shriner and Fuson, "The Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd edition, 1940, p. 59.

The eneyne (10.9 g.) in 30–40 cc. of absolute alcohol with 0.5 g. of palladium-charcoal absorbed the equivalent of one mole of hydrogen at slightly more than one atmosphere pressure in one to three hours. After filtration from the catalyst and concentration *in vacuo* at 35–40°, 1-vinyl-6-methoxy-3,4-dihydronaphthalene was obtained as a practically colorless liquid. Since the product gave no test for an ethynyl group, it was used in the Diels-Alder reaction without further purification. A sample reacted instantly with maleic anhydride in benzene to give an adduct melting at 201–202° (reported,[3] 201°) after one recrystallization.

Reaction of the Diene with Citraconic Anhydride.—A solution of 31 cc. of citraconic anhydride and 10.9 g. of the diene in 150 cc. of dry thiophene-free benzene was refluxed for forty-eight hours, the solvent was removed from the mixture in a current of air, and the residual citraconic anhydride was distilled at 100° (0.5 mm.). The sticky, semi-crystalline residue was warmed gently on a steam-bath with 10 cc. of 45% aqueous potassium hydroxide solution and 40 cc. of water until the anhydrides were hydrolyzed (fifteen minutes). After the removal of 1.5 g. of alkali-insoluble material by extraction with ether, the aqueous solution was added with stirring to a solution of 15 cc. of concentrated hydrochloric acid and 15 cc. of water. The precipitated acid, after it had crystallized (on standing or when seeded and scratched) was filtered and washed thoroughly with water. A solution of the product in ethyl acetate deposited crystalline acid (m. p. 174–179°) which on continued recrystallization was transformed to an anhydride (m. p. 161.5–165°). The product was separated more efficiently by recrystallization of the anhydrides (12.3 g. or 70%) which were prepared by fusion of the above mixture of dicarboxylic acids at 190–200° in an atmosphere of nitrogen. Breitner[8] obtained about the same yield of adduct by heating the diene with citraconic anhydride at 50–60° and allowing the temperature to rise to 160–190°.

A hot solution of the anhydrides in 25 cc. of ethyl acetate and 10 cc. of acetone was concentrated and then seeded with the high melting isomer. After one to two hours at room temperature, 4.6 g. of ***cis*-2-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride** (II) was obtained as square yellowish tablets, m. p. 158–162°. A colorless, constant-melting product was obtained after evaporative distillation at 160–200° (0.01 mm.) and one recrystallization from ethyl acetate, m. p. 163–163.5°.

Anal.[m,15] Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 73.1; H, 6.2.

The anhydride reacted readily with a dilute solution of potassium permanganate in acetone.

The mother liquor from the first crop of high melting anhydride was concentrated to a volume of about 10 cc. and allowed to cool undisturbed. A mixture of crystals was obtained consisting of small yellow tablets (m. p. *ca.* 160°) and large, jagged, rectangular, colorless masses, m. p. 125–150°. The two forms were separated mechanically and 2.6 g. of fairly pure ***cis*-1-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic anhydride** (I) was obtained. After one recrystallization from ethyl acetate the anhydride melted at 125–128°; yield 2.1 g. After evaporative distillation at 0.01 mm. and recrystallization from ethyl acetate–ligroin, the anhydride melted at 127–128°.

Anal.[m] Calcd. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1. Found: C, 72.8; H, 6.2.

Additional crops of material were obtained from the mother liquor after removal of the second crop. These usually were rich in the lower melting anhydride. In one experiment there appeared to be some indication of the presence of an additional isomer but complete characterization of this substance has not been accomplished.

Derivatives and Reactions of 1-Methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic Acid

Proof of Structure of the 128° Anhydride.—Three hundred milligrams of the 128° anhydride (I) and 150 mg. of palladium charcoal[10] were heated in an atmosphere of nitrogen at 310–315° for fifteen minutes when gas evolution ceased. The product after separation from the catalyst was digested with *N* sodium hydroxide. The insoluble portion (10 mg.) gave a yellow trinitrobenzene derivative in alcohol; m. p. 136–138°. Mixed melting point determinations with samples of the trinitrobenzene derivatives of synthetic 1-methyl and 2-methyl-7-methoxyphenanthrene proved conclusively that the neutral material was 1-methyl-7-methoxyphenanthrene.

Acidification of the alkaline filtrate followed by recrystallization of the product from aqueous acetone yielded 150 mg. of an acid as colorless needles, m. p. 196–198° dec. (bath pre-heated to 185°). The dimethyl ester, prepared by means of diazomethane crystallized from methanol in colorless needles, m. p. 168–169° alone and when mixed with dimethyl ester of *cis*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V).[7]

1-Methyl-7-methoxyphenanthrene was prepared in the following manner. One gram of 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene was added to a solution of methylmagnesium iodide prepared from 0.3 g. of magnesium. After forty-eight hours at 0°, the reaction mixture was hydrolyzed with ice-cold ammonium chloride solution and the desired carbinol, 1-methyl-1-hydroxy-7-methoxy-1,2,3,4-tetrahydrophenanthrene, was isolated by evaporation of the filtered organic layer; yield of product after trituration with ethyl acetate–ligroin, 0.48 g., m. p. 78–92°. More material was isolated from the mother liquor.

A mixture of 480 mg. of the carbinol and 100 mg. of palladium charcoal[10] was heated at 300–320° in an atmosphere of nitrogen for thirty minutes. An acetone extract of the reaction mixture was filtered, concentrated and diluted with alcohol. The 1-methyl-7-methoxyphenanthrene which crystallized in nacreous colorless leaflets (200 mg., m. p. 131–132.5°) was recrystallized from alcohol, purified through the picrate and recrystallized from absolute alcohol; m. p. 135–136° (reported,[16] 133.5–134°).

The **trinitrobenzene derivative** crystallized from hot alcohol–benzene in bright yellow needles, m. p. 143–143.5°.

Anal.[k] Calcd. for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.94 Found: C, 60.59; H, 3.93.

Dimethyl Ester of the Acid III.—The **dimethyl ester of *cis*-1-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic acid**, obtained from the crude diacid and diazomethane, crystallized from aqueous methanol in rectangular prisms; m. p. 83.5–85°.

Anal.[m] Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.6; H, 6.8.

Reduction of the Hexahydro Acid.—The crude diacid from 4.3 g. of the 128° anhydride (I) in 75 cc. of acetic acid with 1.5 g. of palladium-charcoal absorbed one mole equivalent of hydrogen in one to two hours at slightly more than one atmosphere pressure. When 10 to 20% of catalyst by weight was used, about twenty-four hours was required for the hydrogenation. The filtered solution was evaporated to dryness and the solid diacid mixture was converted either to the anhydrides or to the dimethyl esters for purification. The anhydrides were obtained by refluxing the diacid with 40 cc. of acetic anhydride and 25 cc. of acetyl chloride for three hours. After removal of the solvents under reduced pressure, 2.85 g. of an anhydride crystallized from ethyl acetate as glistening thick prisms; m. p. 161–163.5°. From the filtrate an additional 0.7 g. of anhydride, m. p. 162–164°, was obtained; total yield, 83%. After one more recrystalliza-

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[15] Analyses marked "m" are by Dr. T. S. Ma and those marked "k" are by Mr. Fred Kaufmann.

[16] Short and Stromberg, *J. Chem. Soc.*, 319 (1936); *ibid.*, 516 (1937).

tion, ***cis*-1-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic anhydride (anhydride of VIIa)** was pure and melted at 163–164°.

Anal.[k] Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 72.0; H, 7.0.

The same dimethyl ester was obtained by diazomethane treatment of the diacid mixture and of the hydrolysis or methanolysis product of the pure anhydride. The **dimethyl ester of *cis*-1-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic acid** crystallized from methyl alcohol in colorless needles, m. p. 126–127.5°.

Anal.[m] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.5; H, 7.4.

Hydrolysis of the Dimethyl Ester of VIIa to the Acid Ester.—A solution of 3.7 g. of the above *cis*-dimethyl ester in 50 cc. of methanol and 10.5 cc. of 1.04 *N* sodium hydroxide solution was refluxed for thirty-eight hours. After removal of methanol in a current of air, the residue was treated with water and ether. The ethereal solution contained 0.7 g. of a mixture of *cis* and *trans* esters. Acidification of the aqueous layer gave the acid ester (2.7 g.; m. p. 169–183°) which crystallized from ethyl acetate in colorless prisms; yield, 2.56 g. (85%); m. p. 184–188°. After a few recrystallizations from ethyl acetate the acid ester, presumably ***trans*-1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-carboxylic acid (VIIb)** melted at 186–187° dec.

Anal.[m] Calcd. for $C_{19}H_{24}O_5$: C, 68.7; H, 7.3. Found: C, 69.0; H, 7.3.

The acid ester is assigned the *trans* configuration because on treatment with diazomethane it gave a practically quantitative yield of a **dimethyl ester** (different from the original diester) which crystallized from methanol in colorless rhombs; m. p. 134–135°. A mixture of this ester and the original diester melted at 107°.

Anal.[m] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.7; H, 7.4.

Partial hydrolysis of the *trans*-dimethyl ester gave the same acid ester in 85% yield.

Arndt–Eistert Synthesis on the Acid Ester VIIb.—Oxalyl chloride was found to be superior to thionyl chloride and phosphorus pentachloride for preparing the ester acid chloride. The acid ester (50 mg.) was added to 0.25 cc. of oxalyl chloride in 1 cc. of dry thiophene-free benzene and after two hours at room temperature the solution was evaporated. Treatment of the residual yellow gum with methanol gave 40 mg. of pure *trans*-dimethyl ester; no acidic products were isolated.

After many failures the following procedure was found to be successful for the Arndt–Eistert synthesis. The acid chloride solution, prepared as above from 500 mg. of pure *trans*-acid ester, was evaporated under reduced pressure at room temperature. Twice, the residue was redissolved in benzene and the solution evaporated. A solution of the colorless acid chloride in 15 cc. of dry benzene was added slowly to an ice-cold distilled, ethereal solution of diazomethane (prepared from 4.5 cc. of nitrosomethylurethan). The reaction appeared to be slow. After one day at 0° and another day at room temperature, the reaction mixture was filtered and evaporated to dryness under reduced pressure. The semicrystalline mass yielded 390 mg. (72%) of crystalline diazoketone upon trituration with ether–ligroin, m. p. 131–133° dec.

For the rearrangement, a silver mirror was prepared by refluxing a suspension of 0.1 g. of silver oxide in 15 cc. of methanol for one and one-half hours. To the hot mixture, the diazoketone was added in one portion. After one-half hour of refluxing another portion of silver oxide was added and refluxing was continued for another half-hour. After filtration of the suspension and evaporation of the solvent, the yellow oil was evaporatively distilled at 180–230° (0.03 mm.) and saponified by refluxing with 0.9 cc. of 1.04 *N* sodium hydroxide solution for three hours; weight of acid ester, 270 mg. The acid ester, presumably **1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-acetic acid (VIIc)**, crystallized from ethyl acetate in glistening prisms; yield 180 mg. (57%), m. p. 182–186°; after several recrystallizations of the compound the m. p. was 186–187°.

Anal.[k] Calcd. for $C_{20}H_{26}O_5$: C, 69.33; H, 7.56. Found: C, 69.95; H, 7.76.

A portion of the pure acid ester with diazomethane gave the **dimethyl ester** which crystallized from methanol in tiny colorless prisms; m. p. 78–79°.

Anal.[k] Calcd. for $C_{21}H_{28}O_5$: C, 70.0; H, 7.8. Found: C, 69.9; H, 8.0.

For the next Arndt–Eistert synthesis, 500 mg. of the acid ester (VIIc) was allowed to react with 3 cc. of oxalyl chloride in 2 cc. of dry benzene for three hours at room temperature. The reaction of the acid chloride with diazomethane at 0° was rapid; after twelve hours at 0°, the suspension of crystalline diazoketone in ether was evaporated to dryness. In this manner 570 mg. of a light cream-colored diazoketone was obtained, m. p. 138–140°.

The crude diazoketone was submitted to a rearrangement in methanol as described, and the product was hydrolyzed by refluxing with 1.45 cc. of 1.03 *N* sodium hydroxide solution in 10 cc. of methanol for one and one-half hours; weight of acid ester, 530 mg.; m. p. 171–180°. The acid ester, presumably **1-methyl-1-carbomethoxy-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-2-propionic acid (VIIe)**, crystallized from ethyl acetate in small thin plates, yield 380 mg. (70%), m. p. 183–184° with previous sintering; after one more recrystallization the m. p. was 184.5–186°.

Anal.[k] Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.52; H, 7.78.

Cyclization of the Diacid VIId.—A mixture of 130 mg. of the acid ester (VIIe), 3 cc. of 45% aqueous potassium hydroxide and 6 cc. of methanol was refluxed for twenty-one hours. Acidification of the alkaline solution gave a crystalline diacid (presumably VIId), m. p. 214–215°, which was used without further purification. In our best experiment, 61 mg. of the diacid was heated in methanol with 60 mg. of lead acetate and the white suspension was evaporated to dryness.[17] The solid was **heated at 290–310°** at 0.01 mm. until distillation stopped. The distillate was digested with 5% sodium hydroxide solution and the neutral product isolated by extraction with benzene. The compound, presumably **7-methoxy-1′-keto-1-methyl-1,2,3,4,4a,9,10,10a-octahydro-1,2-cyclopentenophenanthrene (VIII)** crystallized from methanol in small prisms, yield 10 mg., m. p. 99–100.5°, unchanged by another recrystallization. In another run, less well-defined crystals were obtained by recrystallization from aqueous methanol, m. p. 100–101°. Both samples were analyzed.

Anal.[k] Calcd. for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 79.47, 79.93; H, 8.42, 8.54.

Derivatives and Reactions of 2-Methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic Acid

Proof of Structure of 163° Anhydride.—A mixture of 1 g. of the 163° anhydride (or the corresponding acid) and 500 mg. of palladium–charcoal was heated in an atmosphere of nitrogen at 315–320° for fifteen minutes. The filtered acetone extract of the product was treated with Norit, concentrated and diluted with ethyl acetate. Practically colorless rectangular prisms of the **anhydride of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (VI)** crystallized; yield 610 mg.; m. p. 183–186°. After several recrystallizations from ethyl acetate and benzene the pure anhydride melted at 185–186°.

Anal.[k] Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 73.0; H, 5.5

A mixture of 1.08 g. of the 185–186° anhydride and 50 cc. of methanol was refluxed for twenty-two hours.

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[17] Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).

Upon concentration of the solution chalky prisms of an **acid ester** crystallized; yield, 650 mg., m. p. 186–188°.

Anal.[k] Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.56; H, 6.02.

Additional crystalline material could be obtained from the mother liquor, but it was not pure. Both the material from the mother liquor and the pure acid ester above reacted with diazomethane to give the ***cis*-dimethyl ester**, m. p. 100–101°, which crystallized from aqueous methanol in chalky white needles.

Anal.[k] Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.22; H, 6.44.

The same dimethyl ester was obtained by the dehydrogenation of the hexahydro dimethyl ester and the octahydro dimethyl ester. The yield of ester was inferior to the yield of the aromatic anhydride because of its less favorable solubility in organic solvents.

Digestion with *N* sodium hydroxide of the material in the filtrate after removal of the anhydride left 47 mg. of solid (m. p. 105–135°), which after two recrystallizations from methanol gave 10 mg. of 2-methyl-7-methoxyphenanthrene, m. p. 141–144° alone and when mixed with a synthetic specimen. The m. p. (141–143.5°) of the trinitrobenzene derivative was not depressed by a sample of known structure.

2-Methyl-7-methoxyphenanthrene was synthesized by reducing 1.2 g. of 1-keto-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene[18] to the corresponding 1-hydroxy derivative by means of a ten-fold excess of aluminum isopropoxide. The reaction mixture was hydrolyzed with ice-cold dilute sulfuric acid solution, the product extracted with benzene and the benzene extract washed with dilute ammonia. Evaporation of the extract gave 1.2 g. of a stereoisomeric mixture of carbinols, m. p. 102–115°; after one recrystallization from benzene–petroleum ether, the m. p. was 109.5–117°.

A mixture of 500 mg. of the recrystallized carbinols and 100 mg. of palladium–charcoal[19] was heated at 315° in an atmosphere of nitrogen for fifteen minutes. A filtered acetone extract of the product was concentrated, diluted with alcohol. After a few recrystallizations of the plate-like crystals (310 mg., m. p. 142–143.5°) and purification through the picrate, the melting point was not changed significantly but the analysis was low in carbon. The following treatment with alkali removed the impurity and led to an analytically pure sample. The crude product was dissolved in methyl alcoholic potassium hydroxide with the aid of warm acetone and water was added until crystallization began. The **2-methyl-7-methoxyphenanthrene** crystallized from alcohol-acetone in slender rectangular prisms, m. p. 144.5–145.5° (reported,[3] 143–144°).

Anal.[k] Calcd. for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.57; H, 6.26.

The **trinitrobenzene derivative** crystallized from hot alcohol–benzene in fine orange needles, m. p. 146–147°.

Anal.[k] Calcd. for $C_{22}H_{17}N_3O_7$: C, 60.69; H, 3.94. Found: C, 60.62; H, 3.96.

Dimethyl Ester of the Acid IV.—The 163° anhydride did not appear to react with warm dilute sodium bicarbonate solution but was hydrolyzed rapidly by hot *N* sodium hydroxide solution. Upon acidification of the alkaline solution, the dicarboxylic acid (IV) was obtained which melted at 179–180° after one recrystallization from ethyl acetate.

The **dimethyl ester of 2-methyl-7-methoxyhexahydrophenanthrene-1,2-dicarboxylic acid** prepared from the crude dicarboxylic acid by means of diazomethane, crystallized from aqueous methanol as hexagonal plates, m. p. 90–93°. After two more recrystallizations from aqueous methanol, the pure ester melted at 91–92°.

Anal.[m] Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.9; H, 7.0.

Preparation of the Acid Ester.—A solution of 2.57 g. of the aforementioned dimethyl ester in 30 cc. of methanol containing 7.1 cc. of 1.1 *N* sodium hydroxide was refluxed for forty-six hours. After evaporation of the methanol, addition of water and extraction of the insoluble material (0.08 g.) with benzene, dilute hydrochloric acid was added to the aqueous layer. The product crystallized when stirred with ether and after evaporation of the ether, 2.45 g. of solid was filtered and washed with water, m. p. 117–170° dec. The **acid ester** crystallized from ethyl acetate in silken colorless needles, yield 730 mg., m. p. 185–187° dec. At the melting point the acid ester gave the anhydride (II), m. p. 163°.

Anal.[m] Calcd. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7. Found: C, 69.1; H, 6.7.

When a solution of 5 g. of the 163° anhydride in methanol was refluxed for twelve hours and concentrated, 2.16 g. of needles was obtained; m. p. 182.5–184° dec. alone and when mixed with the acid ester obtained by alkaline hydrolysis. Both acid esters were converted to the dimethyl ester, m. p. 91°, obtained from the anhydride in the manner described.

Hydrogenation of Derivatives of the 163° Anhydride. (a) Dicarboxylic Acid.—Attempts to hydrogenate derivatives of the hexahydro anhydride to octahydro derivatives using 5–10% by weight of Adams catalyst were unsuccessful. When 40–50% by weight of the catalyst was used, hydrogenation was rapid. A mixture of 850 mg. of the diacid IV, 35 cc. of acetic acid, and 300 mg. of pre-reduced Adams catalyst absorbed one mole equivalent of hydrogen at slightly more than one atmosphere pressure in forty-five minutes. On concentration of the filtered solution in a current of air, 56 mg. of the octahydro dicarboxylic acid IX crystallized in colorless prisms, m. p. 202–203° dec. Since it was difficult to obtain more crystalline material from the mother liquor, the residual material was evaporatively distilled at 200–250° (0.01 mm.) to convert the diacids into the corresponding anhydrides. The solution of the distillate in ethyl acetate yielded 335 mg. of anhydrides in two crops, m. p. 165–166° and m. p. 150–155°. ***cis*-2-Methyl-7-methoxy - 1,2,3,4,4a,9,10,10a - octahydrophenanthrene-1,2-dicarboxylic anhydride,** the material from the first crop, was recrystallized from ethyl acetate without any change in melting point.

Anal.[k] Calcd. for $C_{19}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.23; H, 6.74.

(b) **Acid Ester.**—Hydrogenation of 1.3 g. of the acid ester of IV was accomplished with 0.45 g. of pre-reduced Adams catalyst in 50 cc. of acetic acid in three hours. The filtered solution was concentrated and the residue crystallized from ethyl acetate, yield 420 mg., m. p. 194–204° dec. The pure **octahydro acid ester** crystallized from ethyl acetate in small cubes, m. p. 206–208° dec. (bath preheated to 180°). The melting point varied markedly with the rate of heating.

Anal.[m] Calcd. for $C_{19}H_{24}O_5$: C, 68.7; H, 7.3. Found: C, 68.8; H, 7.2.

(c) **Dimethyl Ester.**—A mixture of 1.15 g. of the dimethyl ester of IV and 0.4 g. of pre-reduced Adams catalyst in 35 cc. of acetic acid absorbed one mole equivalent of hydrogen at slightly more than one atmosphere pressure in forty-five minutes. A methanol solution of the product deposited colorless needles of the **dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic acid**, yield 470 mg., m. p. 104.5–108.5°; after several recrystallizations the m. p. was 108.5–109.5°.

Anal.[k] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.3; H, 7.6.

The configurations of the derivatives isolated from the three hydrogenations were the same. Both the anhydride and the acid ester were converted to the 109.5° dimethyl ester.

Hydrolysis of the Dimethyl Ester.—Alkaline hydrolysis of the dimethyl ester gave **2-methyl-7-methoxy-1,2,3,4,-**

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(18) Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

4a,9,10,10a-octahydrophenanthrene-1,2-dicarboxylic acid (IX) which crystallized from ethyl acetate in colorless prisms, m. p. 211–213° dec.

Anal.[m] Calcd. for $C_{18}H_{22}O_5$: C, 68.0; H, 7.0. Found: C, 68.0; H, 7.1.

Summary

Two structurally isomeric adducts are formed in the reaction of citraconic anhydride with 1-vinyl-6 methoxy-3,4-dihydronaphthalene. One is a derivative of 1-methylhexahydrophenanthrene; the other has the methyl group in the 2-position of the hexahydrophenanthrene nucleus. From one a compound was synthesized whose analysis agreed with that of the methyl ether of an isomer of estrone. Preliminary studies have been carried out on the conversion of the other isomeric Diels–Alder adduct to estrone.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF INDIANA UNIVERSITY AND YALE UNIVERSITY]

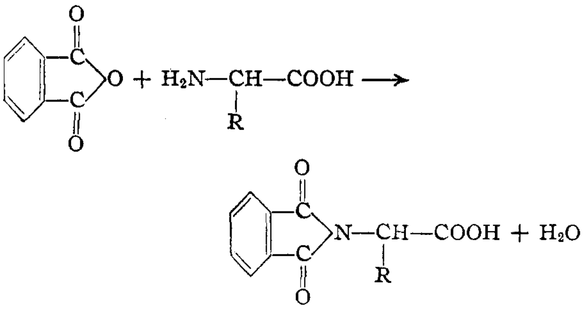
Amino Acids. V.[1] Phthalyl Derivatives

BY JOHN H. BILLMAN[2] AND WILLIAM F. HARTING[3]

Interest in amino acids has increased enormously during recent years mainly because of the many new uses which have been found for these compounds in the nutritional and medicinal fields. Additional reagents for the characterization of amino acids are accordingly useful.

Succinic anhydride and maleic anhydride were investigated as reagents but proved to be unsatisfactory. However phthalic anhydride gives compounds of excellent properties with a large number of amino acids.

Table I contains a list of the phthalyl derivative prepared in these laboratories. Phthalic anhydride condenses with amino acids according to the following general equation, the reaction being complete in fifteen minutes at 180–185°.



The recorded yields are those obtained from 0.2 to 0.5 g. of the amino acid. Much smaller amounts of the amino acid can be used with equal success. Large amounts, such as 5 g. of several of the amino acids were tried and in most cases the yields were considerably higher than those reported in the table. All of the derivatives were easily and

TABLE I

PHTHALYL DERIVATIVES OF AMINO ACIDS

Amino acid used	M. p. of derivative °C. (uncor.)	Yield, %	Analyses, % Calcd.	Analyses, % Found	Neutral equivalents Calcd.	Neutral equivalents Found
Glycine[a]	191–192	90	C 58.54	58.57	205	205
			H 3.41	3.56		
DL-Alanine[b]	160–161	92	N 6.39	6.45	219	218
DL-α-Amino-*n*-butyric acid[c]	95.5–96.5	65			233	231
DL-α-Amino-isobutyric acid[d]	152–153	79			233	231
DL-α-Amino-*n*-valeric acid	103–104	53	N 5.66	5.84	247	244
DL-Valine	101.5–102	54	N 5.66	5.82	247	249
DL-α-Amino-α-methylbutyric acid[e]	139–140	53	C 63.16	62.97	247	248
			H 5.26	5.44		
DL-Norleucine	111.5–112.5	38	N 5.36	5.25	261	259
DL-Leucine[f]	140–141	41			261	260
L-Leucine[5,6,g]	115–116	70	N 5.36	5.22	261	264
DL-Isoleucine	120–121	66	N 5.36	5.34	261	264
L-Glutamic acid	188–189	45	N 5.05	4.93	277	275
DL-α-Aminophenylacetic acid[h]	167–168	64	C 68.3	68.5	281	280
			H 3.9	4.0		
DL-Phenylalanine	174–175	79	N 4.74	4.81	295	300
DL-Threonine	102–103	30	N 5.62	5.81	243	246

[a] Reese, *Ann.*, **242**, 1 (1887). [b] Gabriel, *Ber.*, **38**, 634 (1905). [c] Hildesheimer, *Ber.*, **43**, 279 (1910). [d] Gabriel, *Ber.*, **44**, 59 (1911). [e] Freytog and Gabriel, *Ber.*, **48**, 648 (1915). [f] Ulrich, *Ber.*, **37**, 1695 (1904). [g] Fling, Minard and Fox report the m. p. of 118–119°. [h] McKenzie and Barrow, *J. Chem. Soc.*, **103**, 1332 (1913) (m. p. 170.5–171.5°).

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(1) Paper IV, Billman and Parker, THIS JOURNAL, **67**, 1069 (1945).

(2) On leave at Yale University, September, 1946–June, 1947.

(3) Present address: Coca-Cola Company, Linton, Indiana.