tion of the solution and addition of 100 ml. of water gave 8.5 g. (93%) of triphenylmethane, m.p. 90–93°, after one recrystallization from ethanol. Mixed melting points with an authentic sample were not depressed. Sublimation of the acid fraction for one hour at 100° and 1 mm. pressure gave 0.3 g. of benzoic acid, m.p. 118–120° (no depression with an authentic sample). Crystallization of the residue from water gave 6.6 g. (88% yield) of benzilic acid, m.p. 148–150°. Mixed melting points with an authentic sample showed no depression.

A similar reaction carried out for only five minutes gave a yield of 26% of triphenylmethane, m.p. 85–91° and 33% of benzilic acid, m.p. 149–151°, as well as 64% recovered VI, m.p. 125–128°.

New York 27, N. Y. Received November 25, 1950

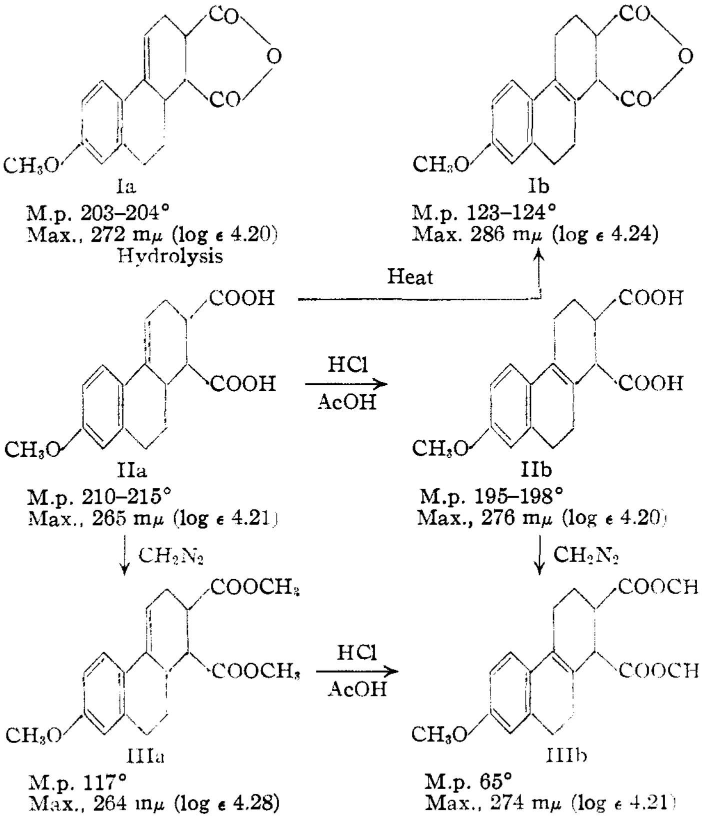
[Contribution from the Chemistry Laboratory of the University of Michigan]

Synthesis of Isoequilenin via the Diels–Alder Reaction. The Configuration of the C/D Ring Juncture of the Estrogenic Hormones

By W. E. Bachmann and John Controulis[1]

The Diels–Alder reaction of 1-vinyl-6-methoxy-3,4-dihydronaphthalene with mesaconic acid yielded two structurally isomeric adducts, the structures and configurations of which were established. The anhydride adduct formed from maleic anhydride and the diene, the corresponding acid and the dimethyl ester, all of which have a 1,2,3,9,10,10a-hexahydrophenanthrene structure, were isomerized to 1,2,3,4,9,10-hexahydrophenanthrene derivatives. A number of hexahydrophenanthrene compounds were dehydrogenated to tetrahydrophenanthrene compounds at 80°. Several *cis* to *trans* isomerizations and a *trans* to *cis* epimerization were carried out. By dehydrogenation and an Arndt–Eistert reaction one of the adducts was converted into an intermediate in the synthesis of isoequilenin.

Dane and co-workers[2] obtained *cis*-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic anhydride (Ia) by the reaction of 1-vinyl-6-methoxy-3,4-dihydronaphthalene with maleic anhydride and prepared the dimethyl ester IIIa of the corresponding acid. By hydrolysis of the anhydride and of the ester we have now prepared the dicarboxylic acid IIa. When the acid was kept at its melting point (215°) a new anhydride was produced. The ultraviolet absorption spectra (Figs. 1 and 2) showed that the double bond had shifted to a new position of conjugation with the aromatic ring and the new anhydride must be *cis*-7-methoxy-1,2,3,4,9,10-hexahydro-1,2-dicarboxylic anhydride (Ib). The new location of the double bond would account for the increase in the position of the absorption maximum. When the acid IIa and its dimethyl ester IIIa were warmed with hydrogen chloride in acetic acid the isomeric acid IIb and ester IIc, respectively, were produced. The correspondence of the new acid and new ester was shown by the formation of the ester from the acid and diazomethane. As shown in Chart I, which shows the interrelationships, the melting points of the members of the "b" series were lower than those of the "a" series and the position of the maxima were shifted to the regions of higher wave length. The curves of the "a" series (Fig. 1) show an inflection or second maximum at 285–290 mμ which is not present in the members of the "b" series (Fig. 2).[3]



Bachmann and Scott[4] showed unequivocally that a *trans* unsaturated acid could add to a diene in the Diels–Alder reaction. We have found that 1-vinyl-6-methoxy-3,4-dihydronaphthalene reacts with mesaconic acid (methylfumaric acid) in boiling propionic acid to give a mixture of the two structurally isomeric adducts, *trans*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (IV) and *trans*-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (VI). The reaction is slow (four to five days) and the yield of products is low (presumably on account of polymerization or de-

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(1) From the Ph.D. dissertation of John Controulis, June, 1950.

(2) E. Dane, O. Höss, A. W. Bindseil and J. Schmidt, *Ann.*, **532**, 39 (1937).

(3) These results are in agreement with those of J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948), on related compounds.

(4) W. E. Bachmann and L. B. Scott, This Journal, **70**, 1458 (1948).

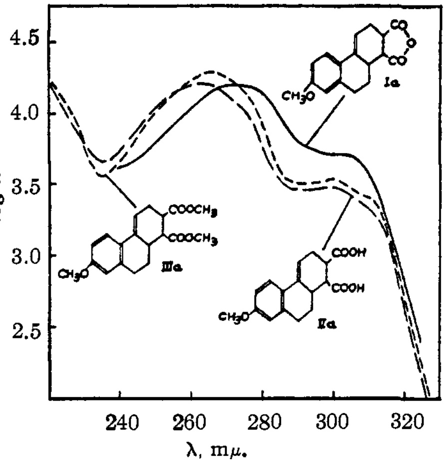

Fig. 1.

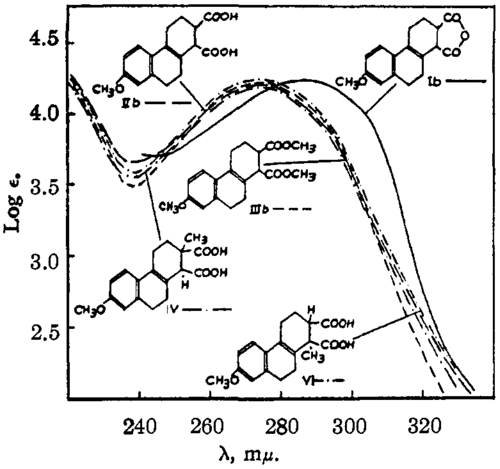

Fig. 2.

composition of the diene). The close correspondence of the absorption curves (Fig. 2) of IV and V with the curves of IIb and IIIb indicated that the original adducts had isomerized in the acidic medium to the compounds with the double bond between B and C rings. The general structures of the adducts were proved by dehydrogenation and decarboxylation in the presence of palladium at 315°; IV yielded 2-methyl-7-methoxyphenanthrene and VI gave 1-methyl-7-methoxyphenanthrene.

The two adducts differed from the corresponding adducts formed with citraconic anhydride,[5] an indication that the carboxyl groups were oriented in a *trans* configuration in IV and VI. Confirmation of the *trans* configuration in the 1-methyl adduct was obtained by dehydrogenation of the dimethyl ester of VI by palladium in boiling ethanol to the known dimethyl ester of *trans*-1-methyl-7-methoxy - 1,2,3,4 - tetrahydrophenanthrene - 1,2-dicarboxylic acid.[4] The facile dehydrogenation of VI (and of other 1,2,3,4,9,10-hexahydrophenanthrene compounds) is similar to the easy dehydrogenation of equilin to equilenin and of isoequilin to isoequilenin.[6] A similar dehydrogenation of the dimethyl ester of IV yielded the new dimethyl ester of *trans*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V). It is of interest that the configurations were not affected during the dehydrogenation; likewise corresponding *cis*-hexahydro compounds yielded *cis*-tetrahydro compounds.

The adducts obtained from mesaconic acid were of importance in interpreting some of the reactions of the adducts formed from 1-vinyl-6-methoxy-3,4-dihydronaphthalene and citraconic anhydride. Bachmann and Chemerda had obtained two adducts in the Diels–Alder reaction, one (m.p. 163°) with the methyl group in the 2-position and the other (m.p. 128°) with a 1-methyl group. At the time, judgment was reserved concerning the location of the double bond. Since then Heer and Miescher[3] have shown by absorption spectra that the 2-methyl adduct has the double bond between the B and C rings. They reported a 1-methyl adduct with m.p. 124–125° in which the double bond was placed wholly in the C ring. In the present work the absorption spectra indicated that the double bond in the 1-methyl anhydride with m.p. 128° and its acid and methyl ester is situated at the B/C ring juncture, for the maxima are located in nearly the same positions as the maxima of the isomerized maleic anhydride adduct and its derivatives; the curves for the dicarboxylic acid (max. 274 mμ, log ε 4.19 in ethanol) and the dimethyl ester (max. 276 mμ, log ε 4.24 in ethanol) derived from the 128° anhydride were practically identical with those of IV and VI in Fig. 2; the curve for the anhydride (max. 290 mμ, log ε 4.26 in chloroform) was similar to that of Ib. The 163° anhydride is *cis*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene - 1,2 - dicarboxylic anhydride and the 128° anhydride is *cis*-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic anhydride.

When the dimethyl ester of *cis*-2-methyl-7-methoxy - 1,2,3,4,9,10 - hexahydrophenanthrene-1,2-dicarboxylic acid was hydrolyzed with strong methanolic potassium hydroxide some epimerization occurred (undoubtedly at the 1-position) and the *trans* diacid (IV) was produced. This result clearly shows the relationship between the adducts obtained from citraconic and mesaconic acid. The epimerization of the dimethyl ester of *cis*-2-methyl - 7 - methoxy - 1,2,3,4 - tetrahydrophenanthrene-1,2-dicarboxylic acid to the *trans* isomer (V) was effected by means of triphenylmethylsodium, and epimerization in the opposite direction, namely, *trans* to *cis*, resulted during the attempted half-hydrolysis of the dimethyl ester of *trans*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V) by dilute alkali.

The anhydride of *cis*-2-methyl-7-methoxy-1,2,3,4,9,10 - hexahydrophenanthrene - 1,2 - dicarboxylic acid was smoothly dehydrogenated to the anhydride of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (VII) in boiling benzene in the presence of palladium. Similarly the dimethyl ester of the *cis*-hexahydro compound yielded the dimethyl ester of the *cis*-tetrahydro compound. Again no epimerization took place during the dehydrogenation.

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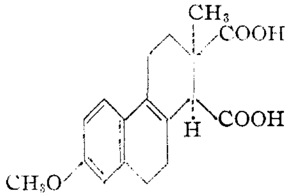
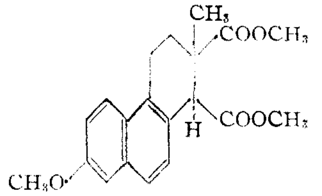
[5] W. E. Bachmann and J. M. Chemerda, This Journal, **70**, 1468 (1948).

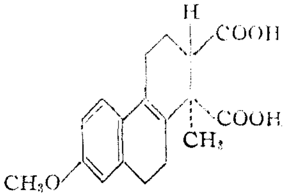
[6] H. Hirschmann and O. Wintersteiner, *J. Biol. Chem.*, **126**, 737 (1938).



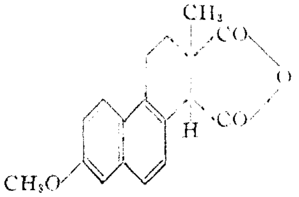
IV
M.p. 206–208°
Max. 274 mμ (log ε 4.22)



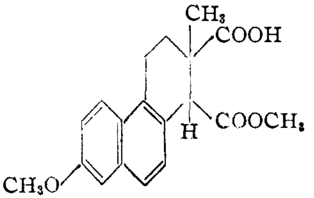
V



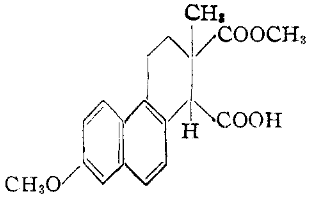
VI
M.p. 248–250°
Max., 275 mμ (log ε 4.21)



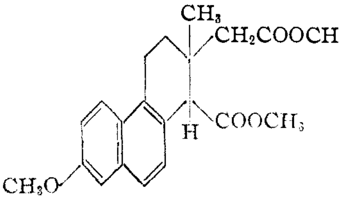
VII



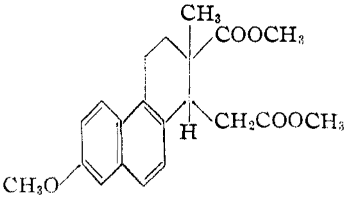
VIII
M.p. 187–189°
Max., 238 mμ (log ε 4.72)



IX
M.p. 156–158°
Max., 238 mμ (log ε 4.75)



X



XI

Hydrolysis of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid by potassium carbonate in aqueous methanol yielded a separable mixture of the two possible acid esters *cis*-1-carbomethoxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (VIII, m.p. 187–189°) and *cis*-1-carboxy-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (IX, m.p. 156–158°). That no epimerization had occurred during the half-hydrolysis was shown by re-formation of the original *cis* diester from both acid esters by treatment with diazomethane. The acid ester with the carboxyl group attached to the tertiary carbon atom was the chief product when *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (VII) was heated with methanol, while the acid ester with the acid group attached to the secondary carbon atom was the major product of the reaction of the anhydride with sodium methoxide. The structures of the acid esters followed from the products formed in the Arndt–Eistert reaction. The ultraviolet absorption spectra (Fig. 3) of the isomers were practically identical.

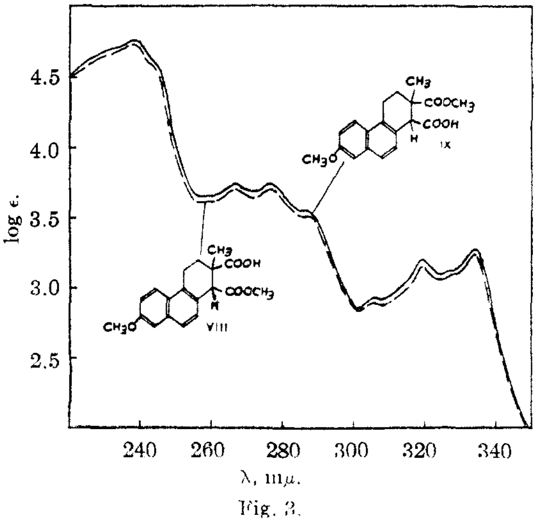


Fig. 3.

An Arndt–Eistert synthesis was carried out on both acid esters. From the higher melting acid ester (VIII) a single product was obtained which was not identical with either of the two diastereoisomeric forms of the dimethyl ester of 2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (XI) and hence must be the dimethyl ester of 1-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-2-acetic acid (X). The lower-melting isomer (IX) yielded the α-form of the dimethyl ester of 2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (XI),[7] which is a precursor of isoequilenin.

This result constitutes a synthesis of isoequilenin *via* the Diels–Alder reaction and furnishes evidence concerning the configuration of the estrogenic hormones at the C/D ring juncture.[8] In the absence of epimerization,[9] the *cis* configuration in IX is retained in XI and isoequilenin possesses a *cis* configuration at the C/D ring juncture, while the natural hormones equilenin, estrone and estradiol have the C and D rings fused in a *trans* configuration. This result is in agreement with the conclusions which were tentatively suggested earlier by others and for which considerable evidence has been obtained recently in this Laboratory.[10]

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(7) W. E. Bachmann, W. Cole and A. L. Wilds, This Journal, **62**, 824 (1940).

(8) Compare G. Stork and G. Singh, *Nature*, **165**, 816 (1950).

(9) The formation of the acid chloride was carried out under conditions which did not lead to epimerization in the case of 2-phenylcyclohexanecarboxylic acid [C. D. Gutsche, This Journal, **70**, 4150 (1948)]. Moreover, it has been shown that no epimerization occurred in the Arndt–Eistert reaction on the somewhat similar compounds, *cis*- and *trans*-2-carbomethoxycyclohexanecarboxylic acid, *cis*- and *trans*-2-carbomethoxy-2-methylcyclohexanecarboxylic acid [Davis, Ph.D. dissertation (1942) in "Summaries of Theses," Harvard Graduate School, 1946] and *cis*- and *trans*-2-phenylcyclohexanecarboxylic acid.

(10) W. E. Bachmann and F. Ramirez, This Journal, **71**, 2273 (1949); **72**, 2527 (1950); W. E. Bachmann and A. Dreiding, *ibid.*, **72**, 1323 (1950).

In addition to XI, the Arndt–Eistert reaction on the acid ester IX yielded the same product X as was obtained from the isomeric acid ester; indeed under the conditions of the experiment X was the chief product of the reaction. This may be the result of an interchange of the ester grouping and acid chloride grouping as has been observed by Cason[11] on simpler aliphatic analogs.

Grateful acknowledgment is extended to Dr. J. M. Vandenbelt, Denise Lundquest, Jere Saladonis and Patricia Welch for the ultraviolet absorption spectra data and to Mr. Charles E. Childs, Mrs. Patricia Ramey and Jere Saladonis of Parke, Davis and Company for the microanalyses.

Experimental

Preparation of 6-Methoxy-1-tetralone.—A solution of 380 g. of β-methoxynaphthalene in one liter of acetic acid and 6 g. of Adams catalyst was shaken under four atmospheres of hydrogen at 70–80°; the calculated amount of hydrogen was absorbed in two to three hours. The 6-methoxytetralin was collected at 120–128° and 8–12 mm.; yield 335 g. The ultraviolet spectrum (max. at 228 mμ, log ε 3.96 and 281 mμ, log ε 3.31, in methanol), the practically complete solubility in alkali of a sample which had been demethylated and the formation of 6-methoxy-1-tetralone on oxidation were evidence of the structure of the product.

A solution of 243 g. of chromic anhydride in 100 ml. of water and 700 ml. of acetic acid was added dropwise in five hours to a stirred, cold (5–10°) solution of 248 g. of 6-methoxytetralin in 250 ml. of propionic acid and 1127 ml. of acetic acid. Stirring was continued for 16 hours more as the temperature rose gradually to 25°. The dark viscous residue which remained after removal of the solvents under reduced pressure was heated with 2.5 liters of water for one-half hour and extracted into a total of 3.5 liters of ether. The ether solution was washed with saturated sodium carbonate solution and with water, dried and concentrated. A solution of the residue in one liter of benzene was passed through a 70 × 2.5 cm. column of Brockmann alumina. Concentration under reduced pressure of the effluent solution yielded 167 g. of 6-methoxy-1-tetralone, m.p. 78–79°.

The reaction between the ketone and the Grignard reagent from acetylene was carried out by the procedure described[5] with slight modifications. Acetylene, purified by passage through water, concentrated sulfuric acid, and a calcium sulfate drying tower, was passed into a chilled stirred solution of ethylmagnesium iodide, which had been prepared from 28 g. of magnesium and 110 ml. of ethyl iodide in 250 ml. of dibutyl ether and then diluted with 500 ml. of benzene. Acetylene was introduced for one hour at 5°, one hour at 25° and three hours at 50–60°. Analysis of an aliquot (titration of the base and measurement of the acetylene liberated on hydrolysis; the acetylene was absorbed in alkaline mercuric cyanide) indicated that the solution contained 85% of the bis-Grignard reagent and 15% of the mono compound. After the addition of a solution of 20 g. of 6-methoxy-1-tetralone in 50 ml. of benzene, addition of acetylene to the stirred mixture was continued for two hours; during this time the temperature was raised to 50–60°. After 16 hours at room temperature the mixture was hydrolyzed with ice and aqueous ammonium chloride, and the moist solution was concentrated under reduced pressure. The eneyne obtained by dehydration at 100–110° and 0.5 mm. for one-half hour distilled at 115–120° and 0.5 mm.; yield 9–10 g. Catalytic reduction of the eneyne in 50 ml. of ethanol was carried out at room temperature in the presence of 0.5 g. of 5% palladium-on-charcoal until a test portion gave no precipitate with ammoniacal silver nitrate solution; yield of crude 1-vinyl-6-methoxy-3,4-dihydronaphthalene, 9 g.

Some bis-(6-methoxy-3,4-dihydronaphthyl)-acetylene (inadvertently called the diol in reference 5) (m.p. 175–176°) was isolated as a by-product in some runs. The ultraviolet absorption spectrum of this compound in methanol had the following maxima: 232 mμ (log ε 4.46), 271 (4.39), 292 (4.36).

Compounds Derived from the Adducts Formed by Addition of Maleic Anhydride to 1-Vinyl-6-methoxy-3,4-dihydronaphthalene. (a) **1,2,3,9,10,10a - Hexahydrophenanthrene Compounds.**—The *cis*-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene-1,2-dicarboxylic anhydride (Ia), which formed in a few minutes when 1 g. of the diene was added to a solution of 1 g. of maleic anhydride in 10 ml. of benzene, was recrystallized from dioxane and then from aqueous acetone; weight of colorless needles, 0.4 g.; m.p. 203–204° cor.

The clear solution which was obtained by warming 300 mg. of the anhydride (Ia) with 5% aqueous potassium hydroxide was poured into excess dilute hydrochloric acid. Partial evaporation of a dioxane solution of the solid yielded 210 mg. of microcrystalline ***cis*-7-methoxy-1,2,3 9,10,10a-hexahydrophenanthrenedicarboxylic acid (IIa)**, m.p. 210–215° cor.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0. Found: C, 66.9; H, 6.2.

The dimethyl ester (IIIa) of the acid, prepared in methanol with diazomethane, crystallized from methanol in colorless prisms; m.p. 115–117° cor. (reported[2] 117°).

(b) **1,2,3,4,9,10-Hexahydrophenanthrene Compounds** — The diacid IIa (50 mg.) was heated in a nitrogen atmosphere at 210–220° for 15 minutes. The resulting ***cis*-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrenedicarboxylic anhydride (Ib)** crystallized from benzene in colorless prisms; weight, 20 mg.; m.p. 123–124° cor.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.5. Found: C, 71.4; H, 5.6.

The solution which was obtained by heating 40 mg. of the diacid IIa with 0.5 ml. of acetic acid containing 9% of dry hydrogen chloride deposited 38 mg. of colorless needles of ***cis*-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrenedicarboxylic acid (IIb)**; m.p. 195–198°, depressed to 170–190° by admixture with IIa.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0. Found: C, 67.3; H, 5.7.

A solution of 40 mg. of the diester IIIa in 0.2 ml. of a 9% solution of hydrogen chloride in acetic acid was allowed to stand at room temperature for 45 minutes, diluted with water and extracted with ether. The ethereal extract was washed with aqueous potassium carbonate and with water, dried and evaporated. The resulting **dimethyl ester of *cis*-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (IIIb)** crystallized from methanol in colorless needles; weight 25 mg., m.p. 65° cor. The same diester (m.p. and mixed m.p.) was obtained by treatment of the diacid IIb with diazomethane.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.0; H, 6.7. Found: C, 68.5; H, 7.0.

Reaction of the Diene with Mesaconic Acid.—A solution of 9 g. of 1-vinyl-6-methoxy-3,4-dihydronaphthalene and 16 g. of mesaconic acid in 100 ml. of propionic acid was refluxed for four days. After the removal of most of the propionic acid under reduced pressure, 50 ml. of benzene was added and the solution was filtered from insoluble mesaconic acid; the latter was washed with benzene and the washings were added to the main solution. The crystalline product which was obtained by extraction of the benzene extract with 2 *N* potassium hydroxide followed by acidification was recrystallized twice from methanol and then from ethyl acetate-benzene; m.p. 205–210°. By another recrystallization from ethyl acetate the ***trans*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (IV)** was obtained in clusters of colorless needles; weight 110 mg., m.p. 206–208° cor.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3; H, 6.4. Found: C, 68.2; H, 6.4.

The dimethyl ester, prepared from 20 mg. of the acid in methanol with diazomethane, crystallized from aqueous methanol in slender colorless needles; weight 18 mg., m.p. 67–68°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.8; H, 6.6.

The residue obtained by evaporation of the combined filtrates from the first three recrystallizations of IV was recrystallized from 90% methanol. Three crops of crystals (m.p. 240–250°) were collected, combined and the whole recrystallized from methanol; weight 300 mg. of thick

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(11) J. Cason, THIS JOURNAL, **69**, 1548 (1947).

colorless plates of **_trans_-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (VI)**; m.p. 248–250° cor.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3; H, 6.4. Found: C, 68.2; H, 6.4.

The dimethyl ester, prepared from 80 mg. of the acid in methanol with diazomethane, crystallized from aqueous methanol in stout colorless needles; weight 68 mg., m.p. 83–84°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.7; H, 7.0. Found: C, 69.9; H, 6.9.

Degradation of the Adducts.—A mixture of *trans*-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (m.p. 248–250°) and half its weight of palladium–charcoal catalyst was heated in a current of nitrogen at 300–315° for 15 minutes. The product isolated by extraction with acetone was digested with *N* sodium hydroxide and recrystallized from methanol. The colorless plates of 1-methyl-7-methoxyphenanthrene melted at 131–132° alone and when mixed with an authentic specimen.

By a similar procedure colorless needles of 2-methyl-7-methoxyphenanthrene were obtained from *trans*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid; m.p. 142–144° alone and when mixed with an authentic specimen.

Dehydrogenation of the Esters.—A solution of 30 mg. of the dimethyl ester of *trans*-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid in 10 ml. of absolute ethanol was refluxed with 30 mg. of 5% palladium-on-charcoal for 30 hours, filtered and evaporated. After two recrystallizations from methanol the product formed colorless plates; m.p. 134–135°, not depressed by admixture with authentic dimethyl ester of *trans*-1-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid.[4]

By a similar procedure 15 mg. of the dimethyl ester of *trans*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid and 15 mg. of the catalyst yielded the **dimethyl ester of _trans_-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (V)**, which crystallized from methanol in colorless cubes; weight 12 mg., m.p. 157–158°.

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.2; H, 6.5. Found: C, 69.6; H, 6.7.

Compounds Derived from the Adducts Formed by Addition of Citraconic Anhydride to 1-Vinyl-6-methoxy-3,4-dihydronaphthalene.—The mixture of adducts was prepared as described by Bachmann and Chemerda[5] and recrystallized from acetone and ethyl acetate. Addition of petroleum ether to the solution from which the *cis*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic anhydride had been removed resulted in precipitation of colorless needles of *cis*-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic anhydride, which after recrystallization from ethyl acetate–petroleum ether melted at 126–128° (reported[5] 127–128°). By warming 50 mg. of this anhydride with 150 mg. of potassium hydroxide in 5 ml. of water until solution resulted, acidifying, and recrystallizing from methanol, 30 mg. of colorless plates of **_cis_-1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid** was obtained, m.p. 135–137°.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.3; H, 6.3. Found: C, 68.2; H, 6.4.

Dehydrogenation of the Adducts.—By refluxing a mixture of 2.1 g. of *cis*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic anhydride and 1 g. of 5% palladium-on-charcoal in 50 ml. of benzene for 42 hours and recrystallizing the product from benzene, 1.2 g. of colorless prisms of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic anhydride (VII) was obtained; m.p. 180–182° (reported[5] 185–186° for the product obtained by dehydrogenation at 315–320°).

Dehydrogenation of 50 mg. of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid[5] (m.p. 90–92°) with palladium in boiling ethanol (27 hours) yielded 45 mg. of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid after recrystallization from methanol; m.p. 99–100° (reported[5] 100–101°).

Epimerization Experiments.—A mixture of 800 mg. of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (m.p. 90–92°), 11.2 g. of potassium hydroxide and 14 ml. of water in 36 ml. of methanol was refluxed for 20 hours; a colorless precipitate appeared during the first hour. The precipitate, which was collected by filtration of the cooled mixture, yielded 600 mg. of the *cis*-diacid (m.p. 176–178, m.p. of dimethyl ester 90–92°) on acidification. Evaporation of the methanolic filtrate, acidification of an aqueous solution of the residue and recrystallization of the precipitate from methanol yielded 85 mg. of *trans*-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-1,2-dicarboxylic acid (IV); m.p. 206–208°, alone and when mixed with the adduct obtained from mesaconic acid.

A benzene solution of 450 mg. of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid was treated with 18 ml. of an ethereal 0.0001 *M* solution of triphenylmethylsodium. After 30 minutes, dilute hydrochloric acid was added and the product which was isolated from the ether–benzene solution was heated with excess 4 *N* potassium hydroxide on a steam-bath for one-half hour. The acidic product (200 mg.) which was obtained by acidification of the clarified aqueous solution was treated with diazomethane, and the resulting ester was recrystallized from methanol. The first crop of crystals which separated melted at 145–155°; after a second recrystallization the crystals of the dimethyl ester of *trans*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid melted at 155–156°, alone and when mixed with the product described previously. When a mixture of 100 mg. of this *trans*-diester, 10 ml. of methanol and 3 ml. of 0.1 *N* sodium hydroxide was refluxed on a steam-bath for 22 hours, and the acidic product, which was formed as the sodium salt, was isolated and treated with diazomethane, 73 mg. of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid with m.p. 96–99° was obtained.

Isomeric Acid Esters of _cis_-2-Methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic Acid.—Following Heer and Miescher[12] for a similar case, 600 mg. of the anhydride of the acid was added to a solution of sodium methoxide prepared from 1 g. of sodium and 100 ml. of anhydrous methanol. After a few minutes the clear solution was poured into 75 ml. of dilute hydrochloric acid, the precipitated acid ester was extracted into benzene, and the dried benzene solution was evaporated. On slow evaporation (two days) a methanolic solution of the solid (420 mg., m.p. 150–170°) deposited large thick prisms and clusters of needles, which were separated mechanically. By recrystallization of the prisms from ethyl acetate, 150 mg. of **_cis_-1-carboxy-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene (IX)** was obtained, m.p. 156–157°.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.5; H, 6.1. Found: C, 69.4; H, 6.3.

By recrystallization of the clusters of needles from ethyl acetate 50 mg. of *cis*-1-carbomethoxy-2-carboxy-2-methyl-7 methoxy-1,2,3,4-tetrahydrophenanthrene (VIII) with m.p. 187–189° (mixed m.p. with IX 150–183°) was obtained, which was identical with the product of the reaction of the anhydride with methanol.[5]

Both acid esters were formed when 300 mg. of the dimethyl ester of *cis*-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene-1,2-dicarboxylic acid (m.p. 99–100°) was refluxed with 300 mg. of potassium carbonate, 5 ml. of water and 12 ml. of methanol for 20 hours. The chief product was ester VIII; 50 mg. of IX was isolated.

The original dimethyl ester of the *cis*-dicarboxylic acid (m.p. 98–100°) resulted on treatment of each isomeric acid ester with diazomethane.

Arndt–Eistert Reactions on the Acid Esters. (a) On _cis_-1-Carbomethoxy-2-carboxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene.—To a solution of 1.2 ml. of oxalyl chloride in 1.2 ml. of benzene was added 175 mg. of the acid-ester (VIII, m.p. 187–189°); in a few minutes a clear yellow solution resulted. After two hours the liquids were removed at room temperature under reduced pressure; 1 ml. of dry benzene was added and then removed under reduced pressure. A solution of the acid chloride in benzene was added to an ethereal solution containing an excess of diazomethane (prepared from 2.5 ml. of 4-methyl-4-(methylnitrosoamino)-2-butanone). Evolution of gas was observed. After two days at room temperature the solution was fil-

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(12) J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 229 (1948).

tered and evaporated under reduced pressure. The residue, presumably the diazoketone, was a pale yellow viscous liquid.

A suspension of 50 mg. of silver oxide in 5 ml. of anhydrous methanol was refluxed on a steam-bath until a silver mirror was formed (15 minutes). Then a solution of the diazoketone in a few ml. of methanol and an additional 50 mg. of silver oxide were added and the whole was refluxed for eight hours. Evaporation of the filtered solution yielded a viscous yellow liquid which could not be made to crystallize.

A solution of the product in 10 ml. of benzene was passed through a column (150 × 7 mm.) of aluminum oxide (Fisher Scientific Co.). A yellow band appeared near the top of the column. Six 10-ml. portions of benzene (eluates collected in separate flasks) served to wash through 100 mg. of colorless liquid. The yellow material on the column was finally eluted by benzene–methanol and methanol.

The colorless liquid (100 mg.), which did not crystallize when seeded with the alpha (m.p. 126°) or beta (m.p. 114°) forms of the dimethyl ester of 7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (XI), was hydrolyzed by refluxing with a solution of 0.28 ml. of *N* sodium hydroxide (sufficient for one ester group) in 2.5 ml. of methanol for three hours. The methanol was removed by evaporation in a current of air, and water and a little alkali were added to dissolve the sodium salt of the acid ester. A small quantity of insoluble material was extracted into ether, the clear aqueous solution was acidified with hydrochloric acid and the precipitated acid ester was extracted with ether. Evaporation of the ether left a colorless liquid which crystallized readily when scratched under ether–petroleum ether. The colorless solid was collected on a filter; weight 50 mg., m.p. 143–145°. The acid ester crystallized from ether–petroleum ether in colorless needles, m.p. 147–148°. The neutral ester, presumably the **dimethyl ester of *cis*-1-carboxy-2-methyl-2-carboxymethyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene** (X), prepared by means of diazomethane crystallized from petroleum ether (60–75°) in colorless needles, m.p. 74–75°.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.7. Found: C, 70.7; H, 6.7.

(b) On ***cis*-1-Carboxy-2-carbomethoxy-2-methyl-7-methoxy-1,2,3,4-tetrahydrophenanthrene.**—When 180 mg. of the acid ester (IX, m.p. 156–157°) was added to a solution of 1.2 ml. of oxalyl chloride in 1.2 ml. of benzene a crust of solid formed on the bottom and adhered to the glass. By tapping and swirling, the solid was dislodged and finally (15 minutes) went into solution. After two hours the yellow solution was evaporated under reduced pressure, and the residue treated with 1 ml. of dry benzene, which was then removed under reduced pressure. The residual acid chloride was added to ethereal diazomethane and the diazoketone was rearranged exactly in the manner described for its isomer in the preceding section.

A solution of the product, a viscous yellow liquid, in 5 ml. of benzene and 40 ml. of petroleum ether (60–75°) was passed through a column of alumina (150 × 7 mm.) which had been wet with petroleum ether. The following fractions were collected: (1) 40 ml. p.e. + 5 ml. benzene (nothing on evaporation); (2) 8 ml. p.e. + 2 ml. benzene (nothing); (3) 5 ml. p.e. + 5 ml. benzene (nothing); (4) 5 ml. p.e. + 5 ml. benzene (trace of colorless liquid); (5) 10 ml. benzene (45 mg. colorless liquid); (6) 10 ml. benzene (30 mg. colorless liquid); (7) 10 ml. benzene + 1 ml. methanol (30 mg. viscous yellow liquid); (8) 10 ml. benzene (viscous yellow liquid). Small amounts of methanol were added to each fraction after evaporation and the solutions allowed to evaporate slowly but no crystals appeared except in (7).

The colorless liquids in fractions 4, 5 and 6 were combined and hydrolyzed by boiling with a solution of 0.22 ml. of *N* sodium hydroxide in 2 ml. of methanol for three hours. The acid ester was isolated as described in the preceding preparation; yield 45 mg. of colorless solid, m.p. 144–147°. From ether–petroleum ether it crystallized in needles; m.p. 146–148° alone and when mixed with the product (m.p. 146–148°) obtained from the isomeric acid ester.

Fractions 7 and 8 were combined and dissolved in 10 ml. of benzene and passed through a 25 × 7 mm. column of alumina and washed with two 10-ml. portions of benzene, one of 1:1 benzene–chloroform and finally chloroform. The first 10-ml. fraction contained colorless liquid which crystallized readily on scratching under methanol; the second and third fractions contained nothing and the last ones contained viscous yellow gum. The crystals from the first fraction were collected on a filter; yield 10 mg., m.p. 124–126°. From methanol the product crystallized in clusters of thick colorless plates; m.p. 126–127° alone and when mixed with authentic alpha form (m.p. 126–127°, precursor of isoequilenin) of the dimethyl ester of *cis*-7-methoxy-2-methyl-2-carboxy-1,2,3,4-tetrahydrophenanthrene-1-acetic acid (XI); the melt solidified readily on cooling and on reheating melted at 126–127°.

Ultraviolet Absorption Spectra.—Ethanol was used as the solvent for all of the compounds in the figures with the exception of the anhydrides Ia and Ib for which chloroform was employed.

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[Contribution from the Converse Memorial Laboratory of Harvard University and the National Heart Institute]

Ring Effects in Autoxidation. A New Type of Camps Reaction[1,2]

By Bernhard Witkop,[3] James B. Patrick[3,4] and Myron Rosenblum

2,3-Cyclopentenoindole (I), by catalytic oxidation as well as autoxidation, is readily converted to 1-aza-7,8-benzcyclooctanedi-2,6-one (VII), opened by base (and acid) to yield δ-*o*-aminobenzoylbutyric acid (IX). The homologous lactam (VIII) with base undergoes a new type of Camps reaction to yield 2,3-cyclopenteno-4-quinolone (X), while the homologous 10-membered lactam undergoes intramolecular angular condensation to tetrahydrophenanthridone (XI). 2,3-Cycloöctenoindole (IV) is easily converted to the 2-keto derivative VI by autoxidation. VI was synthesized by applying the Japp-Klingemann reaction to 2-hydroxymethylenecycloöctanone. Attention is directed to the diagnostic value of the infrared and ultraviolet absorption spectra of α- and γ-quinolones, permitting an easy distinction between the two types of compounds.

It has been shown that catalytic oxygenation,[5,6] as well as autoxidation,[7] converts tetrahydrocarbazole (II) into the hydroperoxide V ($n = 6$) which easily rearranges to the lactam (VIII). We have now extended these reactions to homologous tricyclic indole derivatives in which the size of the isocyclic ring C varied from 5 to 8 members. The results are summarized in the chart.[8]

Whilst tetrahydrocarbazole (II) is stable in various solvents (ethyl acetate, chloroform, alcohol, etc.), 2,3-cyclopentenoindole (I)[9] in solution (*e.g.*,

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[1] On the Mechanism of Oxidation. II. First paper in this series, This Journal, **73**, 2196 (1951).

[2] Presented in part before the Summer Symposium on Natural Products, University of New Brunswick, Fredericton, N. B., August 22–26, 1950.

[3] National Heart Institute, Washington 14, D. C.

[4] Research Corporation Fellow 1950.

[5] B. Witkop and J. B. Patrick, This Journal, **72**, 633, 1428 (1950).

[6] B. Witkop and J. B. Patrick, *ibid.*, **73**, 2188 (1951).

[7] R. J. S. Beer, L. McGrath and A. Robertson, *J. Chem. Soc.*, 2118 (1950).

[8] *Cf.* J. B. Patrick, M. Rosenblum and B. Witkop, *Experientia*, **6**, 461 (1950).

[9] W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, **123**, 3244 (1923).