

trated *in vacuo*, dissolved in chloroform, washed with dilute hydrochloric acid and with water, and concentrated to dryness *in vacuo*. The residue (170 mg.) was crystallized from benzene by the addition of ether, giving 118 mg. of crude crystalline XXVI. This product was dissolved in 2.5 cc. of hot alcohol and the solution permitted to cool slowly to room temperature. It was then kept at -5° for two days at the end of which time the initial precipitate of long dense needles had become contaminated by a small superficial layer of fluffy crystalline balls, apparently containing the saturated dioltrione (XXIV). The needles were easily separated mechanically and after two further recrystallizations from alcohol melted at $236-238^{\circ}$. A total of 83 mg. was obtained; $[\alpha]_D^{25} +170^{\circ}$. A mixed melting point with an authentic sample of Compound E acetate gave no depression.

Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.61; H, 7.52. Found: C, 68.85; H, 7.34.

Acknowledgment.—The author wishes to thank Dr. K. Folkers and Dr. R. T. Major of these laboratories and Dr. E. S. Wallis of Princeton University for their suggestions in connection with this work. The author is indebted to

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Summary

A new method for the preparation of 17(α)-hydroxy-20-ketopregnanes is described. A 20-ketopregnane is converted to its cyanhydrin which is then dehydrated to give a Δ^{17} -20-cyanopregnene. With osmium tetroxide followed by aqueous sodium sulfite, the unsaturated nitrile is converted to the 17(α)-hydroxy-20-ketopregnane, hydrogen cyanide being spontaneously eliminated from the hypothetical intermediate, 17,20-dihydroxy-20-cyanopregnane. The method is also feasible for introducing a 17(α)-hydroxy group into a 20-keto-21-acetoxypregnane. This permits the synthesis of Kendall's Compound E.

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

The Reaction of Anthracene with Maleic and Fumaric Acid and their Derivatives and with Citraconic Anhydride and Mesaconic Acid

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In the present work the addition of seven dienophiles to anthracene is described, the relative rates of reaction are compared, and the effects of changes in some of the reaction variables are noted. By the addition of both the *cis* and *trans* forms of a dienophile, information on the application of the rule of *cis* addition in the Diels-Alder reaction was obtained.

The reaction of maleic anhydride and anthracene to give *cis*-9,10-dihydroanthracene-9,10-endo- α,β -succinic anhydride³ is well known. We obtained the same anhydride (and not the acid) in high yield from the reaction of maleic acid with anthracene in boiling dioxane. It is not known whether the molecule of water is lost before or after addition, but the latter seems probable in view of the ease with which the *cis*-diacid (I, R = H) is converted to the anhydride (*e.g.*, on recryst-

tallization or on standing in a vacuum desiccator). Diels, Alder and Beckmann⁴ prepared the *cis*-dimethyl ester from the anhydride. We have obtained this ester by the addition of dimethyl maleate to anthracene.

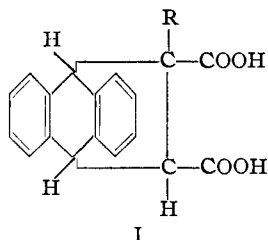
In spite of the impression that fumaric acid does not engage in the Diels-Alder reaction,⁵ we tried its reaction with anthracene and obtained the addition product, the *trans*-acid (I, R = H) in 95% yield. Fumaric acid⁶ reacts more slowly (see Table I) than maleic anhydride, requiring days of refluxing in a given solvent to hours for the anhydride. The reaction of anthracene with maleic acid (or maleic anhydride) to give the *cis* adduct and with fumaric acid to give the *trans* acid offers a simple classroom illustration of the

(4) Diels, Alder and Beckmann, *Ann.*, **486**, 191 (1931).

(5) Alder and Stein, *Ann.*, **514**, 203 (1934) mention that fumaric acid does not add to cyclopentadiene. On page 309 of Richter's "Textbook of Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y. 1943, the following statement appears in the section on the Diels-Alder reaction: "This type of reaction does not occur with the *trans* isomer, fumaric acid."

Dilthey and Henkels, *J. prakt. Chem.*, **149**, 85 (1937), stated that the product obtained from acetylone and fumaric acid was identical with that obtained with maleic acid (or anhydride) and attributed this result to the addition of maleic acid formed by rearrangement of the fumaric acid. After our work had been completed (1942; publication delayed by the war), Bergmann, Eschinazi and Neenam, *J. Org. Chem.*, **8**, 179 (1943), reported the formation of an amorphous acid adduct from 1,1'-bicyclohexenyl and fumaric acid at $190-200^{\circ}$. The nature of the adduct, which was characterized as a dianilide, was not clearly indicated.

(6) In the paper which follows a Diels-Alder reaction is reported in which fumaric acid was superior to maleic anhydride in that it gave a higher yield of adduct and a lower yield of copolymer.



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(3) In this paper the prefixes *cis* and *trans* refer solely to the configuration at the two carbon atoms attached to the carboxyl groups and not to the configuration at the 9,10 positions.

principle of *cis* addition of the diene to the double bond of the dieneophile. We have also prepared the *trans*-dimethyl ester in high yield by the direct addition to anthracene of dimethyl fumarate. Unlike the *cis*-diacid, the *trans*-diacid showed no tendency to lose water and form an anhydride and could be recrystallized unchanged from a mixture of acetic anhydride and acetic acid.

cis-9,10-Dihydroanthracene-9,10-endo- α -methyl- α,β -succinic anhydride (anhydride of I, R = CH₃) had been prepared previously in unspecified yield, by melting together anthracene and citraconic anhydride.⁴ We have prepared it in 96% yield by refluxing the same reactants in either toluene or xylene solution. The *trans*-diacid was obtained directly through the reaction of anthracene and mesaconic acid. Here, too, the *cis*-diacid lost water readily to form the corresponding anhydride whereas the *trans*-diacid did not; in fact, the latter could be sublimed unchanged at 200°. The *cis*-dimethyl ester and the *trans*-dimethyl ester were prepared by treating the corresponding diacids with diazomethane. The *cis*-diester was isomerized to the *trans*-diester by prolonged treatment with methanolic potassium methoxide. The rearrangement of this *cis*-ester with an α -methyl group to the *trans* configuration proceeded much more slowly than the rearrangement of the *cis*-ester without the α -methyl group.

The reaction of bromomaleic anhydride and anthracene yielded *cis*-9,10-dihydroanthracene-9,10-endo- α -bromo- α,β -succinic anhydride. When this anhydride was warmed gently with potassium hydroxide, the bromine group was replaced and the corresponding α -hydroxy diacid was isolated. No attempt was made to determine whether the hydroxy diacid was *cis* or *trans*, but its method of preparation and its stability toward anhydride formation during recrystallization favor the *trans* configuration. These compounds should prove useful for a study of the Walden inversion.

The relative rates of most of the above Diels-Alder reactions were compared in a series of experi-

ments in which homogeneous dioxane solutions of equimolar quantities of the two reactants were refluxed for measured periods of time. The yields of the product are recorded in Table I; the relative accuracy of the results is considered to be $\pm 2-3\%$.

Slower rates resulted when the maleic anhydride was replaced by a *cis*-diacid, a *trans*-diacid or a *trans*-diester, or when a hydrogen on one of the double-bond carbons was replaced by a bromine or a methyl group. It is of interest that bromomaleic anhydride reacts very much more rapidly than does citraconic anhydride although the bromine atom and the methyl group are thought to be similar in size.⁷ The substitution of a hydrogen by a bromine would increase the electron affinity of the dienophile while replacement by a methyl group would not. The rate of addition of chloromaleic and fluoromaleic anhydride would be of interest in this connection as the steric factor should have a lesser magnitude and the electronic factor a greater one.

In another series of runs (Table II) the rate of reaction of citraconic anhydride with anthracene in equal volumes (sufficient for complete solution) of different solvents was determined. As expected, the rate of reaction increased as the reaction temperature was increased. The rate of reaction was greater than expected from the increase in temperature when a mildly polar solvent such as acetic or propionic acid was used instead of low polarity solvents such as toluene and xylene.⁸ An experiment was conducted in 2-nitropropane because of this solvent's somewhat polar nature, but no enhancement of the rate was observed.

TABLE I

RELATIVE RATE OF ADDITION OF DIENOPHILES TO ANTHRACENE

Anthracene, 0.0112 mole; dienophile, 0.0112 mole; dioxane, 50 cc.; reaction temperature, ca. 102°

Dienophile	Reaction time, hr.	Anthracene isolated, %	Yield ^a of product, %
Maleic anhydride	2	31	67
Bromomaleic anhydride	2	62	36
Maleic acid	2	92	6.5
Maleic acid	24	52	47
Dimethyl fumarate	24	58	41 ^b
Fumaric acid	24	70	28
Citraconic anhydride	24	70; 73	28; 26
Mesaconic acid	24	92	7.5

^a High yields of the adducts were obtained by increasing the reaction time, the concentration or the temperature (by means of a higher boiling solvent) (see Experimental).

^b Product isolated as the *trans*-diacid.

TABLE II

EFFECT OF REACTION TEMPERATURE AND SOLVENT ON THE RATE OF REACTION OF ANTHRACENE AND CITRACONIC ANHYDRIDE

Anthracene, 0.0112 mole; citraconic anhydride, 0.0112 mole; solvent, 25 cc. except as noted; reaction time, 24 hours

Solvent	Approx. reaction temperature, °C.	Anthracene isolated, %	Yield of product, %
Benzene	78	91	8
Dioxane	102	59; 58	40; 41
Toluene	111	52; 49	47; 49
2-Nitropropane	122	38	62
Xylene	142	21; 21; 18	78; 78; 80
Acetic acid (50 cc.)	119	40	59
Acetic acid (30 cc.)	119	15	83
Propionic acid	144	13	86

The effect of the concentration of the reactants on the rate of addition of anthracene to citraconic anhydride was studied in still another group of experiments (Table III). Different volumes of dioxane were used for equimolar quantities of the

(7) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1939.

(8) Cf. Fairclough and Hinshelwood, *J. Chem. Soc.*, 236 (1938), and Wasserman, *ibid.*, 1028 (1936).

reactants, and the homogeneous solutions were refluxed for twenty-four hours. The values calculated for a bimolecular reaction rate constant were in fairly close agreement.

TABLE III

EFFECT OF CONCENTRATION OF REACTANTS ON THE RATE OF REACTION OF ANTHRACENE AND CITRACONIC ANHYDRIDE

Anthracene, 0.0112 mole; citraconic anhydride, 0.0112 mole; reaction time, 24 hours; reaction temperature, ca. 102°

Volume of dioxane, cc.	Anthracene isolated, %	Yield of product, %	k^a
12.5	43	57	69
25	58; 59	41; 40	69
50	70; 73	28; 26	71
100	85	14.5	67

^a Bimolecular reaction rate constant (cc./hr. moles) calculated using the higher value for "% anthracene isolated" where there was a choice. The volume of the solution was taken as the volume of the solvent + 1.5 cc.

Experimental

Reactions of Anthracene

With Maleic Acid.—A solution of 2 g. (0.0112 mole) of anthracene and 3.9 g. (0.0336 mole) of maleic acid in 17 cc. of dioxane was refluxed for thirty hours. The dioxane was removed in a current of air on a steam-bath and the residue was shaken for two hours at room temperature with excess, dilute sodium bicarbonate (this treatment had been shown to have no effect on the anhydride). The mixture was filtered and the filtrate was added to an excess of hydrochloric acid; yield of *cis*-9,10-dihydroanthracene-9,10-endo- α,β -succinic acid, 0.035 g. (1%). The bicarbonate-insoluble residue (the anhydride) was warmed gently with 45% potassium hydroxide, water and benzene (in that order) and the clear layers were separated. The benzene layer contained 0.065 g. (3%) of anthracene while the aqueous layer, upon addition to excess hydrochloric acid, yielded 3.10 g. (94%) of *cis*-diacid (I, R = H). As has been reported,⁹ the *cis*-diacid crystallized from ethyl acetate as colorless prisms of the corresponding *cis*-anhydride; m. p. 264–264.5° cor. (reported,⁴ 262–263° for the product prepared directly by the addition of maleic anhydride to anthracene). When a small sample of the diacid in a melting point tube was plunged into a bath at 255° cor., it melted with gassing, solidified after 20–30 seconds and remelted (presumably as the *cis*-anhydride) at 261–263° cor.

With Fumaric Acid.—A solution of 6 g. (0.0336 mole) of anthracene and 1.3 g. (0.0112 mole) of fumaric acid in 50 cc. of dioxane was refluxed for three days, the solvent was removed, and the residue was shaken several hours with dilute sodium bicarbonate and then worked up in the same manner as was the maleic acid mixture; the benzene layer contained 4.08 g. of anthracene. The bicarbonate solution was slowly added with stirring to warm, dilute hydrochloric acid and the mixture was filtered while warm (to keep fumaric acid in solution); yield of *trans*-9,10-dihydroanthracene-9,10-endo- α,β -succinic acid, 3.13 g. (95%); m. p. 240–242° dec. with previous softening at 238° (reported,⁴ 241–242° dec.). A portion of the diacid treated with ethereal diazomethane gave the *trans*-dimethyl ester which crystallized from methanol in colorless, rhombic plates; m. p. 108.4–108.9° cor. (reported,⁴ 106–107° for the product obtained by isomerization of the *cis*-diester by sodium methylate). The *trans*-diacid showed no tendency to form either a *cis* or a *trans*-anhydride when recrystallized from acetic anhydride–glacial acetic acid or when stored for several days in a vacuum desiccator.

With Dimethyl Maleate.—Two grams (0.0112 mole) of anthracene, 2.43 g. (0.0168 mole) of dimethyl maleate¹⁰ and 10 cc. of dioxane were refluxed for eight days. The clear solution was transferred to a sublimation tube, the solvent was removed and the residue was evaporatively distilled at about 0.05 mm. The light-yellow material distilling between 140 and 175° (*cis*-dimethyl ester contaminated with a small amount of anthracene) weighed 3.56 g. and melted at 139–146° with previous softening; estimated yield of diester, 90–95%. After three recrystallizations from methanol, the square, colorless plates of the dimethyl ester of *cis*-9,10-dihydroanthracene-9,10-endo- α,β -succinic acid melted at 150–150.5° cor. This ester (m. p. 150–151°) has been prepared previously by the action of methanolic hydrogen chloride on the *cis*-acid.⁴

In a second experiment a solution of 2 g. (0.0112 mole) of anthracene, 8.1 g. (0.056 mole) of dimethyl maleate and 65 cc. of xylene was refluxed for three days. The xylene was removed and the residue was refluxed for seventeen hours with 50 cc. of methanol and 25 cc. of 45% potassium hydroxide. The methanol was removed, water and benzene were added and the clear layers were separated. The benzene layer contained 0.24 g. (12%) of anthracene and the aqueous layer 2.89 g. (87%) of *trans*-diacid; m. p. 239.5–241° dec. The product was converted to the *trans*-dimethyl ester with diazomethane and was crystallized from methanol; m. p. 108–108.5° cor. alone and when mixed with an authentic sample of the *trans*-diester.

With Dimethyl Fumarate.—A solution of 2 g. (0.0112 mole) of anthracene and 2.43 g. (0.0168 mole) of dimethyl fumarate (prepared by the action of methanolic hydrogen chloride on maleic anhydride; m. p. 101–100.5° after recrystallization from methanol) in 12 cc. of dioxane was refluxed for three days. The solvent was removed and the residue was evaporatively distilled at about 0.05 mm. A total of 3.63 g. of light-yellow *trans*-dimethyl ester contaminated with a small amount of anthracene distilled at 140–175°; estimated yield of diester, 90–95%. Three recrystallizations from methanol raised the melting point of the product from 90–96° to 107–108° cor.

In another experiment a solution of 2 g. (0.0112 mole) of anthracene and 16.2 g. (0.11 mole) of dimethyl fumarate in 150 cc. of xylene was refluxed for three days, and the reaction product was hydrolyzed with methanolic potassium hydroxide and worked up in the manner described in the corresponding dimethyl maleate experiment; anthracene, 0.20 g. (10%); *trans*-diacid, 2.87 g. (87%).

With Citraconic Anhydride.—A solution of 2 g. (0.0112 mole) of anthracene and 2.52 g. (0.0224 mole) of citraconic anhydride¹¹ in 25 cc. of xylene (or toluene) was refluxed for eighty-four hours. Most of the solvent was removed in a current of air, the residue was treated with 45% potassium hydroxide, water and benzene, and the clear layers were worked up in the usual manner; anthracene, 0.06 g. (3%); *cis*-9,10-dihydroanthracene-9,10-endo- α -methyl- α,β -succinic acid (I, R = CH₃), 3.33 g. (96%). When a small sample of the diacid in a melting point tube was plunged into a bath at 173°, it melted with gassing, solidified after 15–20 seconds and remelted (presumably as the *cis*-anhydride) at 181–182°.

The *cis*-diacid was readily converted into the *cis*-anhydride by prolonged drying in a vacuum desiccator or recrystallization from ethyl acetate. The anhydride product evaporatively distilled at 160–190° and ca. 0.05 mm. without appreciable decomposition and crystallized from ethyl acetate in fine, colorless prisms; m. p. 185.1–185.5° cor. (reported,⁴ 182° after repeated recrystallizations). The *cis*-anhydride was formed in about 60% yield by heating 1.8 g. of anthracene with 1.3 g. of citraconic anhydride at 155–165° for two hours according to the procedure of Diels, Alder and Beckmann.⁴

(10) Wolf and Straete, *Bull. classe sci., Acad. roy. Belg.*, **21**, 216 (1935).

(11) Shriner, Ford and Roll, "Organic Syntheses," **11**, 28, 70 (1931).

(9) Bachmann and Kloetzel, *This Journal*, **60**, 481 (1938).

Three grams of recrystallized *cis*-anhydride was hydrolyzed by warm dilute sodium hydroxide, and the clear solution was added to an excess of hydrochloric acid. The damp *cis*-diacid was treated with ethereal diazomethane and the product was triturated with dilute sodium bicarbonate; yield, 3.40 g.; m. p. 133–134.5°. After recrystallization from methanol and evaporative distillation at 135–145° and *ca.* 0.05 mm., the dimethyl ester of *cis*-9,10-dihydroanthracene-9,10-endo- α -methyl- α,β -succinic acid crystallized from methanol in colorless plates; m. p. 140.9–141.2° cor.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.97; H, 5.99. Found: C, 75.00; H, 6.01.

The same compound was prepared in only slightly lower yield by refluxing for eight hours a solution of 5 g. of the anhydride in 250 cc. of methanol which had been saturated with dry hydrogen chloride at 0° and which was treated with hydrogen chloride during the refluxing period.

With Mesoconic Acid.—Two grams (0.0112 mole) of anthracene, 7.3 g. (0.056 mole) of mesaconic acid¹² (m. p. 204–205° cor.) and 40 cc. of propionic acid were refluxed for ninety-six hours at about 144°. The temperature was then held at 90–95° for seventy-two hours more, a total reaction time of seven days. The light-yellow solution gradually darkened but remained clear. The reaction mixture was worked up as before; anthracene, 0.35 g. (17.5%); *trans*-diacid, 2.79 g. (80%). The *trans*-9,10-dihydroanthracene-9,10-endo- α -methyl- α,β -succinic acid (I, R = CH₃), after a treatment with Norit in acetone, crystallized from acetone-ethyl acetate as a colorless powder; m. p. 232.1–232.4° dec. cor.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.02; H, 5.23; neut. equiv., 154. Found: C, 74.04; H, 5.29; neut. equiv., 154.

The *trans*-diacid showed no tendency to form an anhydride. When an unpurified sample (m. p. 214–219° dec.) was heated in a sublimation tube at 200–220° and *ca.* 0.05 mm., some decomposition occurred; but most of the material sublimed as colorless, bicarbonate-soluble, *trans*-diacid.

The *trans*-dimethyl ester, prepared from recrystallized acid and diazomethane, crystallized from methanol in colorless, rhombic prisms; m. p. 119.2–119.7° cor.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 74.97; H, 5.99. Found: C, 75.17; H, 6.05.

The *trans*-diester was also prepared from the *cis*-isomer. A solution of 1 g. of the *cis*-dimethyl ester, 60 cc. of methanol and 30 cc. of 45% potassium hydroxide was refluxed for thirty-two hours. From it 0.78 g. of diacid was isolated, which on treatment with diazomethane and recrystallization of the product from methanol yielded 0.6 g. (60%) of *trans*-dimethyl ester; m. p. 117–118.5°. In another experiment, 1 g. of the *cis*-dimethyl ester and 0.03 g. of

potassium metal were dissolved in 75 cc. of anhydrous methanol, and the solution was refluxed for forty-five hours. The recovered product was shown to be a mixture of about 75% *trans*- and 25% *cis*-diester by fractional crystallization. When a solution of 1.91 g. of the ester in 60 cc. of anhydrous methanol in which 20 mg. of sodium had been dissolved was refluxed for thirty minutes, no change occurred. Under the same conditions the corresponding maleic ester addition product was isomerized to the *trans*-ester.

With Bromomaleic Anhydride.—A mixture of 2 g. (0.0112 mole) of anthracene, 3 g. (0.0169 mole) of bromomaleic anhydride (prepared from dibromosuccinic acid by the method of Walden¹³; b. p. 72–75° at 2–3 mm.) and 15 cc. of toluene was heated on a steam cone for forty-eight hours. The reaction mixture was cooled, a few dark-brown particles were removed by filtration, and the filtrate was concentrated to about one-half of its original volume in a vacuum desiccator. The crystals of *cis*-9,10-dihydroanthracene-9,10-endo- α -bromo- α,β -succinic anhydride which precipitated were filtered and washed with ether; yield, 2.59 g.; m. p. 169–170° cor. A single recrystallization from acetone raised the melting point to 171.5–172.9° cor.

Anal. Calcd. for $C_{18}H_{11}BrO_3$: C, 60.87; H, 3.12. Found: C, 60.81; H, 3.13.

The solvent was removed from the filtrate and the residue was warmed gently with 45% potassium hydroxide, water and benzene. The benzene layer contained 0.06 g. (3%) of anthracene and the acidified and concentrated aqueous layer yielded 1.02 g. (31%) of 9,10-dihydroanthracene-9,10-endo- α -hydroxy- α,β -succinic acid; m. p. 224–230° dec. cor. with previous softening. The hydroxy diacid crystallized from ethyl acetate in colorless prisms; m. p. 232.5–233.2° dec. cor.

*Anal.*¹⁴ Calcd. for $C_{18}H_{14}O_5$: C, 69.66; H, 4.55; neut. equiv., 155. Found: C, 69.63; H, 4.69; neut. equiv., 155.

Summary

The reaction of anthracene with seven dienophiles is described. The order of reactivity with anthracene was found to be: maleic anhydride > bromomaleic anhydride > maleic acid > dimethyl fumarate > fumaric acid, citraconic anhydride > mesaconic acid.

The addition of the *trans*-dienophiles fumaric acid and mesaconic acid yielded *trans*-acids in agreement with the rule of *cis*-addition.

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(13) Walden, *Ber.*, **30**, 2886 (1897).

(14) Semi-microanalysis by Dr. Marjorie Horning.

(12) Shriner, Ford and Roll. "Organic Syntheses" **11**, 74 (1931).