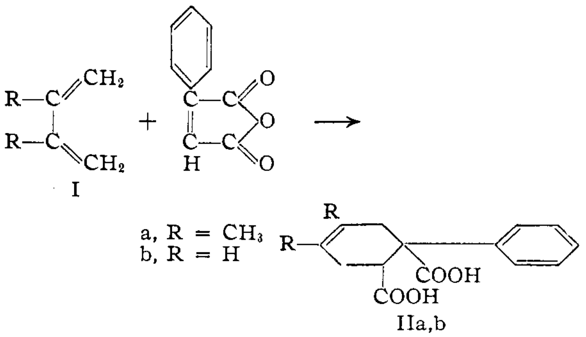
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

# Phenylmaleic Anhydride as a Dienophile

BY LEONARD E. MILLER AND D. J. MANN

The reaction of phenylmaleic anhydride[1] (I) with cyclic or open-chain dienes has not been reported previously. That this compound does indeed participate in a Diels–Alder reaction as a dienophile is demonstrated by its adduct formation with anthracene, 1,3-butadiene, 2,3-dimethyl-1,3-butadiene, cyclopentadiene, isoprene, 2-ethyl-1,3-butadiene and 2-isopropyl-1,3-butadiene.

In the cases of the open chain symmetrical dienes, 1,3-butadiene and 2,3-dimethyl-1,3-butadiene, a single product was isolated as might be expected from the Alder rules.[2] Since the adducts were actually isolated not as anhydrides but as dibasic acids which recrystallized as such, as shown by their solubility in aqueous 5% sodium bicarbonate and elementary analyses, the structural formulas below are written in the diacid form.

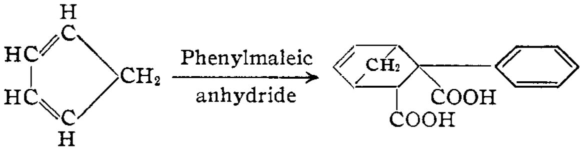


I

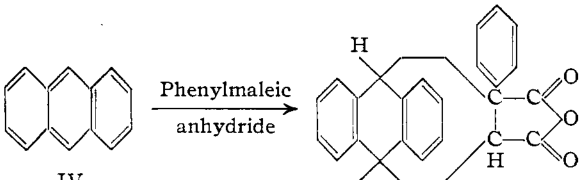
a, R = $CH_3$
b, R = H

IIa,b

A single adduct was obtained similarly with cyclopentadiene III and with anthracene IV. The anthracene adduct in the form of the dibasic acid, however, was converted to the corresponding anhydride on purification by recrystallization from toluene–petroleum ether (high boiling).

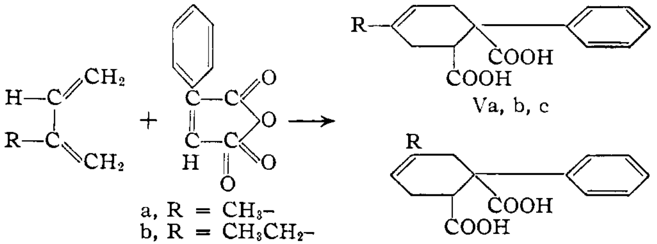


III



IV

When the unsymmetrically substituted butadienes were employed, two structurally isomeric adducts (V and VI) were formed; the latter in only small quantities.



Va, b, c

a, R = $CH_3$–
b, R = $CH_3CH_2$–
c, R = $(CH_3)_2CH$–

VIa, b, c

That the isoprene adducts Va and VIa were truly structural isomers rather than the several possible stereoisomers was established by the pyrolysis of their calcium salts[3] to form 3- and 4-methylbiphenyls which in turn were oxidized with aqueous alkaline potassium permanganate to give *m*-phenylbenzoic acid and *p*-phenylbenzoic acid. These benzoic acids showed no melting point depression when mixed with authentic samples.[4]

In a similar manner, the 2-ethyl-1,3-butadiene adducts Vb and VIb were degraded to *m*- and *p*-phenylbenzoic acids to establish them as structural rather than as stereoisomers.

The degradation of the 2-isopropyl-1,3-butadiene adducts Vc and VIc to the corresponding phenylbenzoic acids was unsuccessful, but Bucher[5] has shown that the oxidation of 4-isopropylbiphenyl to *p*-phenylbenzoic acids proceeds with difficulty. However, on the basis of the structural similarity of the starting dienes it may be assumed tentatively that Vc and VIc are structural isomers as well.

The methyl esters of the adducts (except anthracene) were prepared using an ethereal solution of diazomethane.

These dibasic acid adducts melted with the evolution of gas (not carbon dioxide) to give oils which did not resolidify on being cooled and which were insoluble in aqueous 5% sodium bicarbonate in contrast to the solubility of the dibasic acids. Presumably anhydrides were formed from the dibasic acids on melting. A similar oil was also obtained when Va was heated under reflux with acetic anhydride. In the case of the isoprene adducts, the oil obtained by either method was reconverted to the original diacid by solution in aqueous 5% sodium hydroxide and reprecipitation with concentrated hydrochloric acid.

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(1) L. E. Miller, H. B. Staley and D. J. Mann, THIS JOURNAL, **71**, 374 (1949).

(2) Alder and Stein, *Angew. Chem.*, **50**, 510 (1937); Bergmann and Eschinazi, THIS JOURNAL, **65**, 1405 (1943).

(3) Bachmann and Kloetzel, *ibid.*, **60**, 2204 (1938).

(4) Jacobsen, *Ber.*, **28**, 2546 (1895); Carnelly, *J. Chem. Soc.*, **29**, 18 (1876).

(5) Bucher, THIS JOURNAL, **32**, 374 (1910).

TABLE I

| Diene | Yield, % | M. p., °C. diacid adduct | Neut. equiv. | | Anal. diacid adduct | | | | M. p., °C. Dimethyl ester | Anal. dimethyl ester | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Carbon | | Hydrogen | | | Carbon | | Hydrogen | |
| | | | Calcd. | Found | Calcd. | Found | Calcd. | Found | | Calcd. | Found | Calcd. | Found |
| 2,3-Dimethyl-1,3-butadiene | IIa 91[b] | 217–218.5 | 137 | 139 | 70.05 | 69.96 | 6.61 | 6.78 | 94–94.5 | 71.49 | 71.69 | 7.33 | 7.47 |
| 1,3-Butadiene | IIb 83.1[c,d,f] | 196–197 | 123 | 123.5 | 68.28 | 68.04 | 5.73 | 5.98 | 103–104 | 70.05 | 70.16 | 6.61 | 6.72 |
| Cyclopentadiene | 51.5[c,f] | 172–174 | 129 | 127.5 | 69.75 | 69.84 | 5.46 | 5.68 | 97–97.5 | 71.31 | 71.53 | 6.33 | 6.45 |
| | Va 73.1 | 172–174 | | 131.5 | | 69.27 | | 6.42 | 62–63 | | 70.97 | | 7.21 |
| Isoprene[e,f,g,h] | | | 130 | | 69.21 | | 6.20 | | | 70.81 | | 6.99 | |
| | VIa 5.9 | 192–194 | | 131.7 | | 69.12 | | 6.45 | 104–105[a] | | 71.02 | | 7.12 |
| | Vb 52.7 | 163–165 | | 139.5 | | 70.04 | | 6.84 | 76–77[a] | | 71.55 | | 7.39 |
| 2-Ethyl-1,3-butadiene[7][c,d,f,i] | | | 137 | | 70.05 | | 6.61 | | | 71.49 | | 7.33 | |
| | VIb 8.8 | 165–166 | | 136 | | 70.08 | | 6.73 | 89–90 | | 71.41 | | 7.48 |
| | Vc 52.6 | 162–164 | | 144.0 | | 71.09 | | 7.22 | 81–82 | | 72.18 | | 7.76 |
| 2-Isopropyl-1,3-butadiene[7][c,d,f,j] | | | 144 | | 70.81 | | 6.99 | | | 72.12 | | 7.64 | |
| | VIc 6.1 | 175–177 | | 145.2 | | 70.90 | | 7.03 | 88–89 | | 72.08 | | 7.79 |

[a] Colorless needles. [b] Reaction carried out in 15 ml. of boiling toluene for seventy hours, or in an excess of refluxing diene for ten hours. [c] Reaction carried out in a 2-oz. screw-cap bottle in an atmosphere of nitrogen which was rotated in a water-bath at 50° for twenty-four hours. [d] A crystal of *p*-*t*-butylcatechol was used as an inhibitor in the reaction. [e] A few crystals of trinitrobenzene were used as an inhibitor in the reaction. [f] Ten ml. of benzene used as solvent. [g] Reaction carried out in boiling benzene. [h] In this instance a certain amount of rubber-like material was formed, but this substance was soluble in ether and thus was easily removed from the aqueous solution of the dipotassium salt. Va was obtained from the first crop of crystals after two recrystallizations. VIa was obtained from the filtrate of Va after three recrystallizations. [i] The first crop of crystalline product was recrystallized twice more to give Vb. The filtrate from Vb on concentration gave a solid which after two recrystallizations gave VIb. [j] The first crop after a single recrystallization gave Vc; the filtrate from the first crop on concentration gave a second crop which after two additional recrystallizations gave VIc.

The formation of adducts with phenylmaleic anhydride offers a useful synthetic method for the preparation of compounds which would be difficult using other techniques. A further investigation of the reaction of this dienophile with vinylnaphthalenes is presently in progress.

## Experimental[6]

**Anthracene Adduct (9,10-Dihydroanthracene-9,10-endo-α,β-phenyl-α,β-succinic Anhydride).**—A solution of 2.0 g. (0.0115 mole) of phenylmaleic anhydride and 4.09 g. (0.0230 mole) of anthracene in 35.0 ml. of toluene was heated under reflux for one week. After distillation of the solvent under diminished pressure, an orange-colored solid remained. This residue was treated with 8 ml. of 45% aqueous potassium hydroxide and 100 ml. of water and then warmed. Most of the residue dissolved. On the addition of 75 ml. of toluene to the warm mixture two clear layers were obtained and separated. The aqueous layer containing the dipotassium salt of the adduct was washed with 100 ml. of toluene and 100 ml. of ether. The combined aqueous layers were added with vigorous stirring to 20 ml. of concd. hydrochloric acid. The colorless solid which formed was collected on a filter, dried in air and recrystallized from toluene–petroleum ether (high boiling) to give 2.76 g. of colorless prisms (68.3%), m. p. 166–168°. From the organic layers, 2.26 g. of anthracene was recovered. The yield based upon the quantity of anthracene consumed was 76%.

*Anal.* Calcd. for $C_{24}H_{16}O_3$: C, 81.80; H, 4.57. Found: C, 82.07; H, 4.73.

The experimental data for the formation of adducts with the six dienes used are summarized in Table I. The number of moles of diene and phenylmaleic anhydride and the procedure used in these cases was similar to that given for the reaction with anthracene, except that only ether was used to wash the aqueous solutions of the dipotassium salts of the adducts. All adducts crystallize as colorless prisms which melt with gas evolution. Crystallization was usually effected from ethyl acetate–petroleum ether (high boiling), sometimes from 95% ethanol or acetone–petroleum ether (high boiling).

The dimethyl esters of the diacid adducts were prepared by treating the free acids with an ethereal solution of diazomethane for ninety seconds and then destroying the excess diazomethane with a few drops of glacial acetic acid. After washing the ether solutions of the esters with 5% aqueous sodium bicarbonate, the ether was evaporated and the residues crystallized from methanol–water. All the esters, those otherwise noted in the table, crystallize as colorless prisms.

**Proof of Structure of the Isoprene Adducts.**—To a solution of 1.92 g. of Va in 50 ml. of water containing 0.8 g. of sodium hydroxide was added 3.0 g. of calcium oxide. This mixture was boiled for five minutes, evaporated to dryness on a steam-bath and finally dried in an oven at 110°. A mixture of this calcium salt with 6.5 g. of calcium oxide was placed in a hard glass test-tube 36 cm. long and 30 mm. in diameter in which there was a knife-edge indentation 10 cm. from the closed end. After mounting the test-tube in horizontal position, the closed end of the tube was heated with a free flame until no further condensation of a yellow-colored liquid in the open end of the tube was observed. This distillate was collected and distilled at atmospheric pressure to give 0.59 g. of a yellow oil, b. p. 265–275°.

This oil was added to a solution of 5 g. of potassium permanganate in 80 ml. of water following which 2.0 ml. of 10% aqueous sodium hydroxide was introduced. After heating the mixture under reflux with rapid mechanical stirring for twelve hours, 0.5 g. of potassium permanganate was added. At the end of eighteen hours, the solution was decolorized by the addition of 1.0 ml. of ethanol. The manganese dioxide was collected on a filter and washed well with hot water. The colorless alkaline filtrate was extracted twice with 25-ml. portions of ether, heated to boiling, treated with Norite and filtered. On acidification of the hot colorless filtrate with concd. hydrochloric acid, a white flocculent precipitate formed. After cooling the mixture, the solid material was collected on a filter, dried in air and recrystallized from ethanol–water to give 35 mg. of colorless clusters of needles; m. p. 223–225°. A mixed melting point determination with an authentic sample of *p*-phenylbenzoic acid (m. p. 223–225°) showed no depression. However, when a mixed melting point determination was carried out with an authentic sample of *m*-phenylbenzoic acid (m. p. 166–168°), the m. p. was 148–150°.

Using a similar procedure 280 mg. of VIa was degraded to a product which after recrystallization from ethanol–water gave 10 mg. of light-yellow-colored leaflets, m. p. 165–167°. When mixed with an authentic sample of *m*-phenylbenzoic acid there was no depression in melting point. However, when mixed with a sample of *p*-phenylbenzoic acid the melting point was 150–152°.

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(6) All melting points are uncorrected.

(7) Marvel and Williams, THIS JOURNAL, **70**, 3842 (1948).

**Proof of Structure of the 2-Ethyl-1,3-butadiene Adducts.**—The adduct Vb (1.35 g.) was degraded using the structure proof procedure described in detail for the isoprene adducts to give 30 mg. of *p*-phenylbenzoic acid (colorless needles), m. p. 223–225°. This product showed no melting point depression when mixed with an authentic sample of *p*-phenylbenzoic acid (m. p. 223–225°). However, when the product was mixed with an authentic sample of *m*-phenylbenzoic acid (m. p. 165–167°), the m. p. was 150–152°.

Six hundred milligrams of VIb was degraded in the same manner to give 15 mg. of *m*-phenylbenzoic acid (colorless plates), m. p. 164–165°. When this product was mixed with an authentic sample of *m*-phenylbenzoic acid, the m. p. of the mixture was 164–165°.

**Conversion of Va to an Anhydride.**—One gram of Va was heated in a test-tube by means of a Wood's metal bath at 200–210° for ten minutes. On melting, bubbles were observed but no carbon dioxide was evolved. The oil that formed resisted all attempts at crystallization. It was insoluble in 5% aqueous sodium bicarbonate but did dissolve in 50 ml. of 5% sodium hydroxide. When this alkaline solution was added to 10 ml. of concd. hydrochloric acid a colorless solid separated from solution. On recrystallization of this material from ethyl acetate–petroleum ether (high boiling) the colorless prisms obtained (m. p. 172–174°) gave no melting point depression when mixed with Va.

A similar oil was obtained when 1.0 g. of Va was heated under reflux with 10 ml. of acetic anhydride for five hours. This oil was reconverted to Va in the manner described above.

## Summary

1. Phenylmaleic anhydride has been shown to form Diels–Alder type adducts with anthracene, 1,3-butadiene, 2,3-dimethyl-1,3-butadiene, cyclopentadiene, isoprene, 2-ethyl-1,3-butadiene and 2-isopropyl-1,3-butadiene.

2. It has been established that the two adducts formed by each diene, isoprene and 2-ethyl-1,3-butadiene, are structural rather than stereoisomers.

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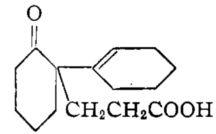
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF TEMPLE UNIVERSITY]

# Aminoalkyl Esters of 2-(β-Carboxyethyl)-2-($\Delta^1$-cyclohexenyl)-cyclohexanone[1]

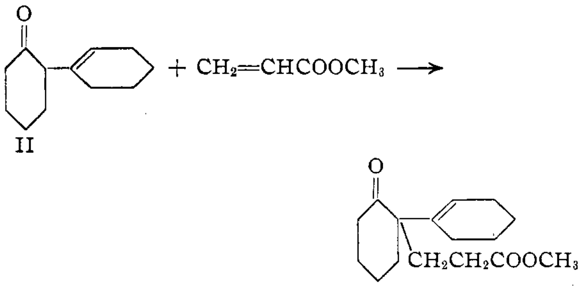
BY H. J. SCHNEIDER, T. W. RIENER AND H. A. BRUSON[2]

A large number of alkylaminoalkyl esters of aryl- and aralkylacetic and propionic acids, which have some analgesic or antispasmodic activity, are recorded in the literature. The preparation[3] of 2-(β-carboxyethyl)-2-($\Delta^1$-cyclohexenyl)-cyclohexanone (I) suggested the synthesis of alkylaminoalkyl esters of this acid for pharmacological evaluation.



I

These esters were obtained by transesterification of 2-(β-carbomethoxyethyl)-2-($\Delta^1$-cyclohexenyl)-cyclohexanone (III), which, in turn, was prepared by carbomethoxyethylation of 2-($\Delta^1$-cyclohexenyl)-cyclohexanone (II) with methyl acrylate. This condensation proceeded readily in the presence of a strong base; methanolic potassium hydroxide and Triton B were employed with some measure of success. However, the most satisfactory catalyst was found to be benzyltrimethylammonium methoxide. This compound was prepared according to the method of Meisenheimer[4] by the metathesis of benzyltrimethylammonium chloride and sodium methoxide in methanol.



II

III

The methyl ester, a colorless, high-boiling liquid, was hydrolyzed to the known acid (I). Small quantities of higher-boiling products were formed during the preparation of the methyl ester.

Transesterification of the methyl ester was carried out with β-dimethylaminoethanol, β-diethylaminoethanol and β-morpholinoethanol. Sodium and magnesium methoxides were suitable as catalysts for this reaction. The esters were obtained as high-boiling, viscous, light yellow liquids.

Benzyltrimethylammonium methoxide also catalyzed the condensation of (II) and methyl methacrylate to form 2-(β-carbomethoxypropyl)-2-($\Delta^1$-cyclohexenyl)-cyclohexanone.

**Pharmacological Activity.**—The alkylaminoalkyl esters of (I) were tested as analgesics. In general, they showed an intraperitoneal toxicity in mice at 400–600 mg./kg. The morpholinoethyl ester gave a 20–26% increase of pain threshold in dogs at doses of 75 mg./kg. The dimethyl- and diethylaminoethyl esters were completely inactive at this dose level.

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[1] Taken from a thesis submitted in June 1948, by H. J. Schneider to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree of Master of Arts.

[2] Address: Industrial Rayon Corp., Cleveland, Ohio.

[3] Bruson and Riener, THIS JOURNAL, **70**, 214 (1948).

[4] Meisenheimer, *Ann.*, **397**, 295 (1913).