of an NH or OH bond, excluding the possibility of an allylic addition such as that found with azodicarboxylate esters.[11] A weak band was found at 6.10 μ, indicating the presence of an isolated double bond, while the typical —N=O band had disappeared.

Experimental

Reagents.—Nitrosobenzene,[12] m.p. 68°, *p*-bromonitrosobenzene,[13] m.p. 94°, and *p*-nitroso-N,N-dimethylaniline,[14] m.p. 85°, were prepared by known procedures. Anthracene, 2,3-dimethyl-1,3-butadiene, and 1,3-cyclooctadiene were obtained from Columbia Organic Chemicals.

Kinetic Measurements.—The change of concentrations of the nitroso compounds were followed in the visible region (720–730 mμ) with a Beckman DB. Spectrograde dichloromethane was employed as the solvent. Solvent, dienes, and products did not absorb in the visible region. Solutions of the nitroso compounds were found to follow the Lambert-Beer law when the concentrations were between 0.025 and 0.002 mole/l.

In a typical run to obtain Guggenheim plots, the following concentrations were employed: diene, 2.5000 moles/l., and nitroso compound, 0.050 mole/l. Several Guggenheim plots were obtained for the reaction between nitrosobenzene and 2,3-dimethyl-1,3-butadiene at 2° and 25°, and for *p*-bromonitrosobenzene and the same diene at 2° (see Fig. 1).

p-Bromonitrosobenzene was treated with the same diene at 18°, 25°, and 30°, employing the following approximate concentrations: nitroso compound, 0.025 mole/l., and 2,3-dimethylbutadiene, 0.100 mole/l. A graph of time *vs.* log $b/a\ (a - x/b - x)$ yielded a straight line from which k was calculated.

Anthracene.—0.53 g. (3 mmoles) was treated with nitrosobenzene, 0.53 g. (5 mmoles) in chloroform, 75 ml., at room temperature. The optical density of the solution at 730 mμ remained unchanged after several hours standing, indicating that nitrosobenzene had not reacted. The solution was then refluxed under nitrogen for 2 hr. The optical density at 730 mμ was again unchanged.

Nitrosobenzene.—5.5 g. (51 mmoles) was mixed with 1,3-cyclooctadiene, 7.8 g. (72 mmoles) in ether, 50 ml. The optical density at 730 mμ was slightly reduced after 1 week of standing at 5°. After about 25 days of standing at 5°, the solution was concentrated to approximately 5 ml. by evaporation under reduced pressure. Ethyl alcohol, 5 ml., was added, and crystals precipitated after standing for 2 hr. at 5°. The yield of the isolated crude product was 0.5 g. (4.53%, based on nitrosobenzene), m.p. 80–83°. The crude product was purified by washing with ethanol, yielding 30 mg. of a white solid, m.p. 83.5–84.5°.

Anal.[15] Calcd. for $C_{14}H_{17}NO$: C, 77.73; H, 8.28; N, 6.48. Found: C, 77.78; H, 8.13; N, 6.40.

Infrared bands (determined in a potassium bromide pellet): 3.4 (m), 3.45 (s), 3.52 (s), 6.1 (w), 6.3 (s), 6.74 (s), 6.95 (s), 8.1 (s), 8.52 (s), 9.75 (s), 9.9 (m), 11.26 (m), 12.7 (s), 12.96 (m), 13.3 (s), 13.6 (m), and 14.48 (s) μ.

Acknowledgment.—Financial support of the Petroleum Research Fund enabled us to carry on this investigation.

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[11] B. T. Gillis and P. E. Beck, *J. Org. Chem.*, **27**, 1947 (1962); B. Franzus and J. H. Surridge, *ibid.*, **27**, 1951 (1962).

[12] "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 668.

[13] E. Bamberger, *Ber.*, **28**, 1222 (1895).

[14] A. I. Vogel, "Practical Organic Chemistry," Longmans Green and Co., New York, N. Y., 1957, p. 573.

[15] Microanalysis by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Free Radical Addition of Cyclic Ethers to Maleic Anhydride

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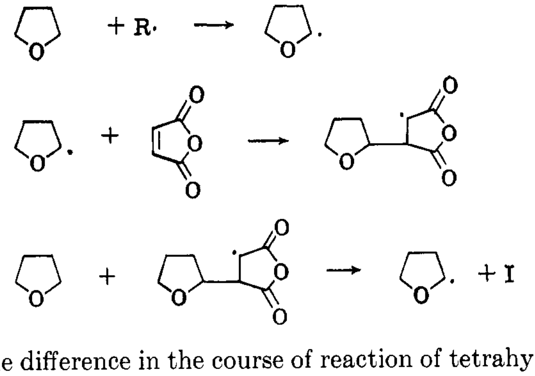
It has been found that free radicals initiate a reaction between tetrahydrofuran and maleic anhydride to form (tetrahydro-2-furyl)succinic anhydride in 70% yield. An analogous reaction using tetrahydro-2-methylfuran formed (tetrahydro-2-methyl-2-furyl)succinic anhydride in 70% yield. This reaction appears to be specific with respect to five-membered cyclic ethers since efforts to utilize other ethers either failed to yield a 1:1 adduct with maleic anhydride or gave only low conversions.

The free radical-promoted reactions of olefins with acetals and ortho esters have been studied extensively[2]; however, little is known relative to the behavior of simple ethers in this type of reaction. The formation of (α-alkoxybenzyl)succinic anhydrides by the addition of benzyl alkyl ethers to maleic anhydride in the presence of free radical initiators has been described.[3] More recently, the peroxide-induced reaction of various cyclic ethers with 1-octene was reported.[4] Ketonic products were obtained, and a chain mechanism involving α-hydrogen abstraction followed by decyclization of the ether was postulated.

The latter study prompts us to report the results of a similar investigation involving free radical-initiated reactions between cyclic ethers and maleic anhydride. Our results differ significantly from those reported by Wallace and Gritter[4] in that addition without ring opening has been observed as the major course of reaction. The reaction of tetrahydrofuran with maleic anhydride in the presence of free radical initiators was found to give a 70% yield of (tetrahydro-2-furyl)-succinic anhydride (I). The reaction probably proceeds by the following chain process.



The difference in the course of reaction of tetrahydrofuran with maleic anhydride and with 1-octene may arise from the double bond of maleic anhydride being more reactive than that of 1-octene. With the more reactive olefin, capture of the furyl radical might occur

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[1] Maumee Chemical Co., Toledo, Ohio.

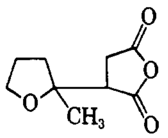
[2] For references see C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p. 287.

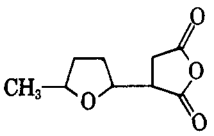
[3] T. Patrick, Jr., U. S. Patent 2,841,592 (1958).

[4] T. J. Wallace and R. J. Gritter, *J. Org. Chem.*, **27**, 3067 (1962).

before rearrangement. Some support of such a hypothesis may be found in the effect of temperature upon the reactions. Whereas a 41% yield of 4-dodecanone was obtained from the reaction of tetrahydrofuran with 1-octene at 150° by Wallace and Gritter,[4] with these same reactants at 70° we found only a trace of carbonyl-containing product and recovered the bulk of the starting materials unreacted. Comparable experiments with tetrahydrofuran and maleic anhydride gave 54–60% yields of I at 70° and 42% yield at 150°. The failure to find the product of the ring fission reaction (butyrylsuccinic anhydride) in the products from the maleic anhydride–tetrahydrofuran reactions was not considered surprising. Such a compound would be the anhydride of a β-keto acid and as such might be unstable. It would be expected that rearrangement of the furyl radical would proceed more rapidly at elevated temperatures, and the decrease in yield of I in going from 70 to 150° may arise from the production of increased amounts of butyrylsuccinic anhydride, which condensed to produce the large amount of residue.[5]

The reaction of maleic anhydride with tetrahydro-2-methylfuran gave a 70% yield of adduct under conditions which resulted in a 60% yield of I in the case of tetrahydrofuran. Nuclear magnetic resonance spectra indicate that the product is a mixture of diastereomers of II rather than III.


II


III

An azobisisobutyronitrile-catalyzed reaction between maleic anhydride and tetrahydrothiophene gave a 31% conversion to a 1:1 adduct. Benzoyl peroxide was ineffective as an initiator for this reaction.

Although it is reported that tetrahydropyran adds about as readily as tetrahydrofuran to 1-octene,[4] we have found the reactions of tetrahydropyran and of 1,4-dioxane with maleic anhydride to lead only to nondistillable products. It thus appears that the five-membered ring cyclic ethers can differ appreciably from the corresponding six-membered ring compounds in free-radical reactions.

Attempts were made to effect reactions of tetrahydrofuran with chloromaleic anhydride, citraconic anhydride, dimethyl acetylenedicarboxylate, and diethyl maleate. Only in the case of diethyl maleate was more than a trace (27%) of 1:1 adduct obtained.

Experimental

Reaction of Maleic Anhydride with Tetrahydrofuran.—A 216-g. quantity of purified tetrahydrofuran[6] was heated to reflux under a nitrogen atmosphere, and a solution of 3.7 g. (0.015 mole) of benzoyl peroxide and 49.0 g. (0.5 mole) of maleic anhydride in 144 g. (2.0 moles) of tetrahydrofuran was added with stirring over an 8-hr. period. The temperature of the refluxing mixture rose from 65 to 68° during the addition. Excess tetrahydrofuran was then removed from the product by distillation at reduced pressure (25 mm.). After a 3.7 g. crude benzoic acid fraction distilled, there was obtained 59.2 g. (70%) of I, b.p. 129–142° (0.5–2 mm.), and a 19.5-g. residue. The distillation was stopped when the pot temperature reached 220° since some decomposition was occurring as evidenced by the appearance of color in the distillate and a rise in the pressure. The product was redistilled to obtain colorless distillate, b.p. 105–110° (0.1 mm.), n^{25}D 1.4792.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92; neut. equiv., 85.1. Found: C, 56.84; H, 5.86; neut. equiv., 85.5.

The absence of aldehyde or ketone in the distillate was indicated by a negative result obtained with 2,4-dinitrophenylhydrazine test reagent.[7]

Experiments in which all of the reactants were present at the start of the reaction (10:1 ether–anhydride ratio) produced I in about 60% yield. The yield was further decreased to about 50% in going from a 10:1 to a 5:1 ratio of reactants. The decrease in the yield of I occurred largely with the production of larger quantities of nondistillable residue; essentially complete consumption of the maleic anhydride occurred.

In another experiment, a solution of tetrahydrofuran (5.0 moles) and maleic anhydride (0.5 mole) was heated at reflux in a Pyrex flask and illuminated by a sunlamp (General Electric, CG 401-E6) for 6 hr. There was obtained 52 g. (61%) of I and 28.6 g. of residue. A similar experiment using azobisisobutyronitrile (0.82 g., 0.005 mole) in place of light gave 54% of I.

The reaction was also carried out using *t*-butyl peroxide (3 mole % based on maleic anhydride) on twice the scale of the previous experiments. All the reactants were mixed before charging to a stainless steel autoclave and heating at 150–155° for 5 hr. There was obtained 71.1 g. (42%) of I and 76.3 g. of residue. The infrared spectrum and the refractive index of the product were identical with those of compound I obtained from reactions at lower temperatures and other initiators.

Preparation of the Dibutyl Ester of I.—This ester was prepared in order that the presence of the band of the tetrahydrofuran ring system (9.3 μ)[8] in the infrared spectrum might be observed without interference from the band of the cyclic anhydride system.

A solution of 43.0 g. (0.25 mole) of I, 200 ml. of *n*-butyl alcohol and 1.0 g. (0.006 mole) of *p*-toluenesulfonic acid was refluxed for 5 hr. while 2.7 ml. of water separated in a Dean–Stark trap. After removing the catalyst by washing with 5% sodium bicarbonate solution, the product was distilled under vacuum to yield 69.4 g. (93%) of the dibutyl ester, b.p. 149–153° (1 mm.), n^{25}D 1.4515. The infrared spectrum showed the anticipated band at 9.4 μ.

Anal. Calcd. for $C_{16}H_{28}O_5$: C, 64.06; H, 9.4; sapon. equiv., 150. Found: C, 63.92; H, 9.35; sapon. equiv., 151.

Reaction of Maleic Anhydride with Tetrahydro-2-methylfuran.—A solution of 49 g. (0.5 mole) of maleic anhydride, 1.21 g. (0.005 mole) of benzoyl peroxide and 430 g. (5.0 moles) of purified[6] tetrahydro-2-methylfuran was refluxed (75–80°) under a nitrogen atmosphere for 5 hr. Distillation yielded 65.3 g. (70%) of II, b.p. 121–152° (1 mm.), and 22.6 g. of residue. Redistillation through a 2 × 24-cm. column packed with glass helices gave a heart cut, b.p. 150–151° (6 mm.), n^{25}D 1.4752.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.67; H, 6.57; neut. equiv., 92.1. Found: C, 58.76; H, 6.69; neut. equiv., 92.3.

The n.m.r. spectrum of the product was compared with that of tetrahydro-2-methylfuran.[9] The spectrum of the product was in accord with structure II. The methyl proton line was observed to be split into a doublet (1.2-c.p.s. separation) probably because of the presence of two diastereomers. If the product had structure III, a much wider splitting, caused by spin coupling with the adjacent proton, would be expected. Such a splitting of the

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(5) The data presented fit also the alternate mechanism suggested in the work of Wallace and Gritter.[4] In the present case, the decreased yield of (tetrahydro-2-furyl)succinic anhydride at 150° could be due to an increased rate of removal of this product, and butyrylsuccinic anhydride is not, therefore, necessarily involved.

(6) The ether was purified by distillation from sodium benzophenone ketyl. M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 25.

(7) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 97.

(8) G. M. Barrow and S. Searles, *J. Am. Chem. Soc.*, **75**, 1175 (1953).

(9) The n.m.r. spectra were observed with a Varian Associates Model 4302 DP 60 high resolution spectrometer, field strength, 60 Mc. at 14 kilogauss. The spectra afford the first direct evidence that the initial site of hydrogen abstraction in free radical-catalyzed reactions of tetrahydrofurans with maleic anhydride is at position 2 of the tetrahydrofuran ring. If the initial free-radical attack were at any other position, the methyl would show spin–spin splitting as noted in the spectrum of tetrahydro-2-methylfuran.

methyl proton line (6 c.p.s.) was observed in the spectrum of tetrahydro-2-methylfuran.

The absence of aldehyde or ketone in the product was indicated by a negative test obtained with 2,4-dinitrophenylhydrazine test reagent.[7]

Reaction of Maleic Anhydride with Tetrahydrothiophene.—A solution of 5.0 g. (0.003 mole) of azobisisobutyronitrile, 24.5 g. (0.25 mole) of maleic anhydride and 220 g. (2.5 moles) of tetrahydrothiophene[10] was heated at 70–73° for 5 hr. under a nitrogen atmosphere. Distillation yielded 211 g. (96%) of tetrahydrothiophene, 10 g. (41%) of maleic anhydride, 14.2 g. (31%) of 1:1 adduct, b.p. 132–168° (1 mm.), and 7.2 g. of residue.

Anal. Calcd. for $C_8H_{10}O_3S$: S, 17.2; neut. equiv., 93.1. Found: S, 16.9; neut. equiv., 94.4.

A similar experiment using benzoyl peroxide in place of azobisisobutyronitrile yielded only recovered starting materials upon distillation.

Reaction of Maleic Anhydride with Tetrahydropyran.—A solution of 49 g. (0.5 mole) of maleic anhydride and 1.21 g. (0.005 mole) of benzoyl peroxide in 430 g. (5.0 moles) of purified[5] tetrahydropyran was heated at 69–71° for 6 hr. under a nitrogen atmosphere. Distillation of the product yielded 409 g. (95%) of tetrahydropyran, 19 g. (40%) of maleic anhydride, and 51.6 g. of residue. The residue solidified to an orange glass upon cooling.

A similar reaction was carried out in which no peroxide was used, but the reaction mixture was irradiated with a General Electric sunlamp while maintained at 85–90° for 6 hr. The product was identical with that of the previous experiment.

Reaction of Maleic Anhydride wth 1,4-Dioxane.—When a solution of 39.2 g. (0.4 mole) of maleic anhydride and 352 g. (4.0 moles) of purified[11] 1,4-dioxane was maintained at 96° and illuminated by a General Electric sunlamp for 8 hr., the product was found to consist of unreacted starting materials and 12.7 g. of residue. No trace of 1:1 adduct was detected.

Reaction of 1-Octene with Tetrahydrofuran.—A solution of 56.1 g. (0.5 mole) of 1-octene, 1.21 g. (0.005 mole) of benzoyl peroxide, and 360 g. (5.0 moles) of tetrahydrofuran was held at reflux (67–68°) for 8 hr. under a nitrogen atmosphere. After 3 hr. and after 5 hr., additional 1.21-g. portions of benzoyl peroxide were added. The product was distilled through a column packed with glass helices to yield 357 g. (99%) of tetrahydrofuran, 51.3 g. (91%) of 1-octene, and 8.6 g. of residue. A solid which separated from the residue was identified as benzoic acid by its infrared spectrum and its melting point. The residue gave a negative test with 2,4-dinitrophenylhydrazine reagent.[7] A trace of aldehyde or ketone was detected both by reagent and by infrared spectrum (5.8 μ) in a small intermediate fraction boiling between tetrahydrofuran and 1-octene.

A similar experiment employing 0.82 g. (0.005 mole) of azobisisobutyronitrile in place of benzoyl peroxide yielded a 1.2 g. fraction, b.p. 79–119° (4.5 mm.), n^{20}_{D} 1.4092, which showed a weak carbonyl band at 5.85 μ in its infrared spectrum. The bulk of the product was again unreacted starting materials.

Acknowledgment.—The authors wish to express their appreciation to Mr. W. E. Zitelli for assistance in the experimental work and to Mr. J. E. Graham for the determination and interpretation of infrared spectra. We are indebted to Dr. R. J. Kurland of Carnegie Institute of Technology for the n.m.r. spectra and their interpretation.

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(10) The tetrahydrothiophene was dried by distilling and discarding a small portion. It was then used without additional treatment.

(11) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 285.

Pyrimido[5,4-*e*]-*as*-triazines. II. The Preparation and Reactions of Some Heteroaromatic 5-Aminopyrimido[5,4-*e*]-*as*-triazines[1]

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Syntheses are described for the preparation of 5-amino-3-methyl- and 5-amino-3-ethylpyrimido[5,4-*e*]-*as*-triazine (VIIIa and VIIIb). These compounds are the first representatives of the pyrimido[5,4-*e*]-*as*-triazine ring system capable of resonance in both rings. Reaction of VIIIa and VIIIb with certain nucleophilic reagents under mild conditions produced other heteroaromatic pyrimido[5,4-*e*]-*as*-triazines.

In previous publications[3,4] from our laboratories we have reported the preparation of some dihydropyrimido[5,4-*e*)-*as*-triazines and the unsuccessful oxidization of 5-chloro-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (XII) to 5-chloropyrimido[5,4-*e*]-*as*-triazine (XIII).[4] Although a few other partially saturated pyrimido[5,4-*e*]-*as*-triazines have been reported,[5] a heteroaromatic representative of this ring system capable of resonance in both rings has yet to be described. This paper is concerned with the synthesis of some aromatic 5-amino- and 5-hydroxypyrimido-[5,4-*e*]-*as*-triazines and is part of our program directed toward the preparation of pteridine analogs having potential antifolic acid activity.

Treatment of ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)formimidate (IIa) with hydrazine in an attempt to prepare 5-amino-1,2-dihydropyrimido[5,4-*e*]-*as*-triazine (Va) failed to provide an identifiable product. In contrast, reaction of ethyl *N*-(4-amino-6-chloro-5-pyrimidinyl)acetimidate (IIb)[6] with a methanolic solution of hydrazine in phosphate buffer gave directly 5-amino-3-methylpyrimido[5,4-*e*]-*as*-triazine (VIIIa)[7–10] in 23% yield. Undoubtedly, in this conversion 5-amino-1,2-dihydro-3-methylpyrimido[5,4-*e*]-*as*-triazine (Vb) is an intermediate which undergoes

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(2) Affiliated with the Sloan-Kettering Institute.

(3) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **82**, 4592 (1960).

(4) C. Temple, Jr., R. L. McKee, and J. A. Montgomery, *J. Org. Chem.*, **28**, 923 (1963).

(5) (a) W. Pfleiderer and K. H. Schundehutte, *Ann.*, **615**, 42 (1958); (b) G. D. Daves, Jr., R. K. Robins, and C. C. Cheng, *J. Am. Chem. Soc.*, **84**, 1724 (1961); (c) E. C. Taylor, J. W. Barton, and W. W. Paudler, *J. Org. Chem.*, **26**, 4961 (1961).

(6) J. A. Montgomery and C. Temple, Jr., *ibid.*, **25**, 395 (1960).

(7) The tautomerization of this compound to a structure like VII should be considered possible in view of the results obtained from studies conducted with certain 4-aminopteridines.[8] For another viewpoint see ref. 9.

(8) E. C. Taylor and C. K. Cain, *J. Am. Chem. Soc.*, **71**, 2538 (1949).

(9) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952).

(10) Two nonequivalent Kekulé forms for the *as*-triazine ring of pyrimido-[5,4-*e*]-*as*-triazines are possible. The Kekulé form used in this paper is reported[11] to be the more stable for *as*-triazine itself, based on quantum-mechanical computations.

(11) A. Maccoll, *J. Chem. Soc.*, 670 (1946).