Anal. Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18; N, 8.02. Found: C, 68.72; H, 5.43; N, 7.92.

Reaction of terephthalamic acid with ethyl chloroformate and triethylamine. A solution of terephthalamic acid (1.4 g., 0.0085 mole) and triethylamine (1.72 g., 0.017 mole) in 20 ml. of dichloromethane was cooled to 0–5° and 1.9 g. (0.018 mole) of ethyl chloroformate was added. Stirring was continued for 3.5 hr. at room temperature after the addition. The mixture was filtered to remove triethylamine hydrochloride and the solvent was removed under reduced pressure. The residue was washed several times with ether. The ether-insoluble material (1.4 g.) melted at 140–155°. The ether-soluble material (0.2 g.) melted with decomposition at 90–95°. The infrared spectra and melting points of these products preclude the presence of more than a trace of ethyl *p*-cyanobenzoate which has a reported melting point of 50°.[25]

Mixed anhydride of benzoic and ethylcarbonic acids prepared in presence of ethanol. A stirred solution of 12.2 g. (0.1 mole) of benzoic acid, 4.6 g. (0.1 mole) of ethanol and 10.1 g. (0.1 mole) of triethylamine in 100 ml. of dichloromethane was stirred at 0° while ethyl chloroformate (10.8 g., 0.1 mole) was added dropwise over 30 min. The temperature was kept below 0° during the addition. After the addition the external cooling bath was removed and the reaction mixture was stirred for 3 hr. The mixture was filtered and the filtrate washed with water, 5% sodium carbonate solution, water and dried over magnesium sulfate. The drying agent was removed by filtration and the solvent removed under reduced pressure. The clear, colorless liquid which remained, n_D^{25} 1.4930, showed absorption in the carbonyl region of its infrared spectrum (liquid film) at 1775 cm.$^{-1}$ (s) and 1715 cm.$^{-1}$ (w). The spectrum was identical with that for the mixed anhydride of benzoic and ethyl carbonic acids (n_D^{25} 1.4941) obtained by the procedure described above[14] except that no ethanol was added and the reaction time was 1 hr. An attempt was made to distill the crude product in a semimicro distilling apparatus. A vacuum of 1 mm. was applied and the distillation pot heated slowly. Nothing distilled until the temperature of the pot reached 140°; then the pressure rose to 4 mm. and vigorous decomposition of the product began.

Dehydration of benzamide with ethyl chloroformate and triethylamine. A solution of 2.8 g. (0.023 mole) of benzamide in 25 ml. of acetone and 2.3 g. (0.023 mole) of triethylamine was cooled to 0–5°. Ethyl chloroformate (2.5 g., 0.023 mole) was added dropwise with stirring. After the addition, the cooling bath was removed and the reaction was stirred at room temperature for 3 hr. The reaction mixture was diluted with water and extracted three times with dichloromethane. The dichloromethane extracts were dried over magnesium sulfate and solvent was removed under vacuum. An infrared spectra of the solid residue (2.4 g.) indicated traces of benzonitrile. The residue was washed with ether which left a white solid (2.0 g.), m.p. 119–121.5°. Recrystallization from aqueous ethanol raised the melting point to 123–125°. A mixture melting point with the starting benzamide (m.p. 125–127.8°) was 124–127°.

Acknowledgment. We are indebted to Miss Olive M. Garty for the vapor phase chromatographic analyses and to Mr. William Birch and Mr. J. T. Commerford for technical assistance. We are especially indebted to Dr. J. M. Whelan, Jr. for many helpful discussions of this work.

BOUND BROOK, N. J.

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[25] K. H. Slotta and R. Kethur, *Ber.*, **71**, 335 (1938).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE UNION CARBIDE PLASTICS CO.]

The Synthesis of *N*-Substituted Isomaleimides

ROBERT J. COTTER, CAROL K. SAUERS, AND JOHN M. WHELAN

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N-Alkyl and *N*-aryl substituted isomaleimides and bisisomaleimides have been prepared by dehydration of the corresponding *N*-substituted maleamic acids with *N,N'*-dicyclohexylcarbodiimide, ethyl chloroformate-triethylamine, and trifluoroacetic anhydride–triethylamine. *N*-Substituted isomaleimides were isomerized to the symmetrical *N*-substituted maleimides in the presence of sodium acetate or triethylammonium acetate. An improvement in the synthesis of *N*-alkyl maleimides is also reported.

The synthesis of three isomaleimides has been previously recorded in the literature. Piutti[1] has claimed the preparation of *N*-(*p*-methoxyphenyl)isomaleimide (I, R = p-$CH_3OC_6H_5$—) and *N*-(*p*-ethoxyphenyl)isomaleimide (I, R = p-$C_2H_5OC_6H_5$—) by acetyl chloride dehydration of the corresponding maleamic acids (II). Roderick[2] has recently shown that the compounds obtained by Piutti do not possess the isomaleimide structure but instead are the α-chloro-*N*-(*p*-alkoxyphenyl)-succinimides. Tsou, Barrnett, and Seligman[3] have dehydrated *N*-(4-hydroxy-1-naphthyl)maleamic acid with trifluoroacetic anhydride and obtained *N*-(4-hydroxy-1-naphthyl)isomaleimide. This is the only substantiated example of an isomaleimide in the literature. Attempts[3] to prepare other isomaleimides using the trifluoroacetic anhydride reagent were unsuccessful. Mild dehydration of phthalanilic acid with acetyl chloride was shown to give the hydrochloride of *N*-phenylisophthalimide which on careful treatment with potassium hydroxide solution allowed the isolation of *N*-

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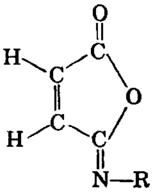
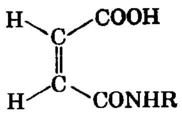
(1) (a) A. Piutti, *Atti. reale accad. Lincei, Classe sci. fis. mat. e nat.*, [5] **18**, II, 312 (1909); *Chem. Abstr.*, **4**, 2451 (1910); (b) A. Piutti and E. de'Conno, *Mem. reale accad. Lincei, Classe sci. fis. mat. e nat.*, [5] **8**, 793 (1911); (c) L. H. Flett and W. H. Gardner, "*Maleic Anhydride Derivatives*, John Wiley & Sons, Inc., New York, N. Y., 1952, p. 108.

(2) W. R. Roderick, *J. Am. Chem. Soc.*, **79**, 1710 (1957).

(3) K. C. Tsou, R. J. Barrnett, A. M. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955).

phenylisophthalimide.[4] Roderick[2] has shown that this method is inapplicable to the synthesis of *N*-substituted isomaleimides. Thus, no general method for the synthesis of *N*-substituted isomaleimides has been previously available. In contrast to the lack of syntheses for isomaleimides, maleimides (IV) have been prepared by a variety of methods,[5] and their possible utility has been extensively investigated.


I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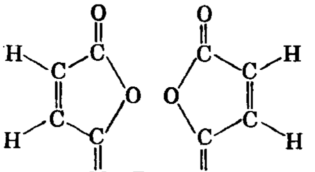
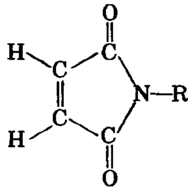

III


IV

We wish to describe two syntheses for *N*-substituted isomaleimides (I) and bisisomaleimides (III) which we believe to be general in scope. The starting materials are the corresponding maleamic acids. The first method employs *N*,*N'*-dicyclohexylcarbodiimide, a reagent which has found application in the synthesis of amides[6] from carboxylic acids and amines. With simple carboxylic acids, the carbodiimides either dehydrate the acids to the corresponding anhydrides or react to form acyl ureas.[7] However, when *N*-phenylmaleamic acid was treated with *N*,*N'*-dicyclohexylcarbodiimide in dichloromethane at 25°, neither of these products was isolated. Instead, a yellow, crystalline compound isomeric with *N*-phenylmaleimide (IV, R = C_6H_5—) was obtained in 93% yield. We have assigned the *N*-phenylisomaleimide structure (I, R = C_6H_5—) to this material. This compound absorbed strongly in its infrared spectrum at 1791 cm.$^{-1}$ because of the five-membered ring lactone and at 1680 cm.$^{-1}$ because of the carbon-nitrogen double bond. This type of absorption in the infrared is identical with that reported for *N*-(4-hydroxy-1-naphthyl)isomaleimide.[3] It also possessed an elemental analysis corresponding to a molecular formula of $C_{10}H_7O_2N$. The ultraviolet spectrum, measured in dichloromethane, showed absorption at 228 mμ (ϵ = 8600) and 345 mμ (ϵ = 4010). These data are all consistent with the isomaleimide structure. None of the symmetrical *N*-phenylmaleimide (IV, R = C_6H_5—) could be isolated from this reaction. *N*,*N'*-Dicyclohexylcarbodiimide was also used to prepare *N*-*n*-butylisomaleimide, *N*,*N'*-hexamethylenebisisomaleimide, bis(4-*N*-phenylisomaleimido)-methane, *N*-(*o*-chlorophenyl)isomaleimide, and *N*-(*o*-tolyl)isomaleimide. The spectral data and elemental analyses for all of these compounds are consistent with the *N*-substituted isomaleimide structure. The yields obtained by this synthesis for *N*-alkyl isomaleimides were about 50%, whereas the *N*-aryl isomaleimides were obtained in yields of 89–100%. As this synthesis has been successful for the preparation of *N*-alkyl and *N*-aryl isomaleimides and bis-isomaleimides, we believe the method to be a general one.

The second synthetic method for isomaleimides employed triethylamine and ethyl chloroformate. Treatment of a solution of *N*-phenylmaleamic acid and triethylamine in dichloromethane at 0–5° with ethyl chloroformate, gave a 46% yield of *N*-phenylisomaleimide. Similarly, *N*-*n*-butylisomaleimide was prepared in yields of 77–90% by this method. None of the isomeric *N*-*n*-butylmaleimide could be detected in the freshly prepared, purified product by vapor phase chromatographic analysis. The ethyl chloroformate–triethylamine reagent also dehydrated bis(4-*N*-phenylmaleamic acid)methane to the corresponding bisisomaleimide in 47% yield.

All of the *N*-substituted isomaleimides that have been prepared are crystalline solids except for *N*-*n*-butylisomaleimide. The aromatic compounds are yellow or yellow-orange in color. The solid isomaleimides are stable compounds and may be stored indefinitely in a dry atmosphere. In the presence of moisture they slowly hydrolyze to the expected maleamic acids. The only liquid isomaleimide that has been prepared, *N*-*n*-butylisomaleimide, slowly decomposed on standing at room temperature, but it could be stored under dry nitrogen at 0° with little decomposition.

Hydrolysis of these *N*-substituted isomaleimides is catalyzed by acids and may be autocatalytic. The failure of trifluoroacetic anhydride dehydration of *N*-substituted maleamic acids to yield *N*-substituted isomaleimides (except for the synthesis of *N*-(4-hydroxy-1-naphthyl)isomaleimide) may be due to the instability of isomaleimides in the presence of acids. We have found that adding

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(4) (a) P. H. van der Muelen, *Rec. trav. chim.*, **15,** 282 (1896). (b) S. Hoogewerff and W. A. van Dorp, *Rec. trav. chim.*, **21,** 339 (1902). (c) M. L. Sherrill, F. L. Schaeffer, and E. P. Shoyer, *J. Am. Chem. Soc.*, **50,** 474 (1928).

(5) (a) N. E. Searle, U. S. Patent **2,444,536** (1948); *Chem. Abstr.*, **42,** 7340 (1948). (b) H. W. Arnold and N. E. Searle, U. S. Patent **2,462,835** (1949). (c) L. E. Coleman, Jr., J. F. Bork, and H. Dunn, Jr., *J. Org. Chem.*, **24,** 135 (1959). (d) D. H. Marrian, *J. Chem. Soc.*, 1515 (1949). (e) P. Kovacic and R. W. Hein, *J. Am. Chem. Soc.*, **81,** 1187 (1959).

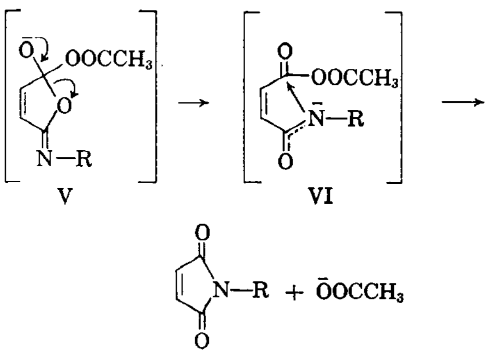
(6) (a) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77,** 1067 (1955); (b) J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc.*, **78,** 1367 (1956).

(7) (a) H. G. Khorana, *Chem. Revs.*, **53,** 145 (1953); (b) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80,** 6204 (1958).

enough triethylamine to neutralize completely the trifluoroacetic acid that was formed allowed the isolation of *N*-phenylisomaleimide in 50% yield from the reaction of *N*-phenylmaleamic acid with trifluoroacetic anhydride. These conditions may provide another general synthesis for isomaleimides. The fact that only *N*-(4-hydroxy-1-naphthyl)-isomaleimide could be prepared by dehydration with trifluoroacetic anhydride alone indicates that this isomaleimide and/or its protonated form possesses added stability which provides resistance to the hydrolysis reaction.[8,9] This stabilization would slow down the subsequent hydrolysis step, thus allowing isolation of the isomaleimide from the acid solution.

It was mentioned earlier that acetyl chloride has been employed for the dehydration of amic acids but that recent work indicated it possessed no utility for the preparation of isomaleimides from maleamic acids. We have found that acetyl chloride with added triethylamine to neutralize the acidic by-products dehydrated *N*-substitued maleamic acids to the symmetrical *N*-substituted maleimides. For example, *N*-*n*-butylmaleimide was obtained in 39% yield by dehydration of *N*-*n*-butylmaleamic acid with this reagent. Thus, acetyl chloride appears to give only the symmetrical product in the dehydration of maleamic acids[2] although the isoimides are obtained from phthalamic acids[4] with this reagent. In addition, dehydration of *N*-*n*-butylmaleamic acid with acetic anhydride–triethylamine either at 0–5° or in refluxing benzene (80°) gave *N*-*n*-butylmaleimide, although a small amount of the corresponding isomaleimide was formed in the reaction run at 0–5°. The symmetrical *N*-substituted maleimides are also formed in the acetic anhydride–sodium acetate dehydrations of *N*-substituted maleamic acids.[5] The use of triethylamine instead of sodium acetate with acetic anhydride for the synthesis of *N*-alkyl maleimides usually gave better yields.

N-Substituted isomaleimides are isomerized to the corresponding *N*-substituted maleimides in the presence of sodium acetate or triethylammonium acetate. Thus, *N*-phenylmaleimide was formed in 90% yield when *N*-phenylisomaleimide was heated at 90° with sodium acetate and acetic anhydride. Treatment of a 0.003*M* solution of *N*-*n*-butylisomaleimide in benzene at reflux with two equivalents each of triethylamine and acetic acid for ninety minutes gave a mixture containing approximately 40% of *N*-*n*-butyl-isomaleimide and 60% of *N*-*n*-butylmaleimide. The same reagents isomerized *N*,*N*′-hexamethylenebisisomaleimide to *N*,*N*′-hexamethylenebismaleimide in 34% yield. Heat alone did not cause these isomerizations, as *N*-phenylisomaleimide was unaffected by heating in acetic anhydride without added sodium acetate. In addition, *N*-*n*-butylisomaleimide could be prepared from *N*-*n*-butylmaleamic acid by dehydration with ethyl chloroformate and triethylamine in benzene at reflux. The isomerization of isomaleimides to maleimides which is catalyzed by acetate ion may proceed through nucleophilic attack of the acetate ion on the carbonyl carbon of the isomaleimide. Subsequent ring opening (V) to the mixed anhydride followed by displacement of the acetate ion by the nitrogen of the amide ion (VI) would yield the maleimide. A similar acetate ion attack at the carbonyl carbon atom has been postulated for the acetate ion catalysis of the hydrolysis of phenyl acetate.[10]



The ease of isomerization of *N*-substituted isomaleimides to *N*-substituted maleimides under the conditions described above suggests the possibility that isomaleimides may be the primary dehydration products of maleamic acids when acetyl chloride–triethylamine and acetic anhydride–triethylamine (or sodium acetate) are employed. Isomerization of the isomaleimides to maleimides under the conditions of synthesis could account for the isolation of maleimides. The detection of a small amount of *N*-*n*-butylisomaleimide in the product of the dehydration of *N*-*n*-butylmaleamic acid with acetic anhydride–triethylamine at low temperatures (0–5°) indicated that the symmetrical maleimides are not the exclusive primary products of these dehydrations. This possibility cannot be resolved without a detailed study of the kinetic of the isomerization and dehydration reactions.

The formation of *N*-substituted isomaleimides by dehydration of *N*-substituted maleamic acids with *N*,*N*′-dicyclohexylcarbodiimide, ethyl chloro-

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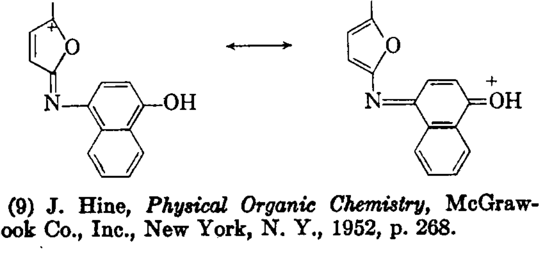
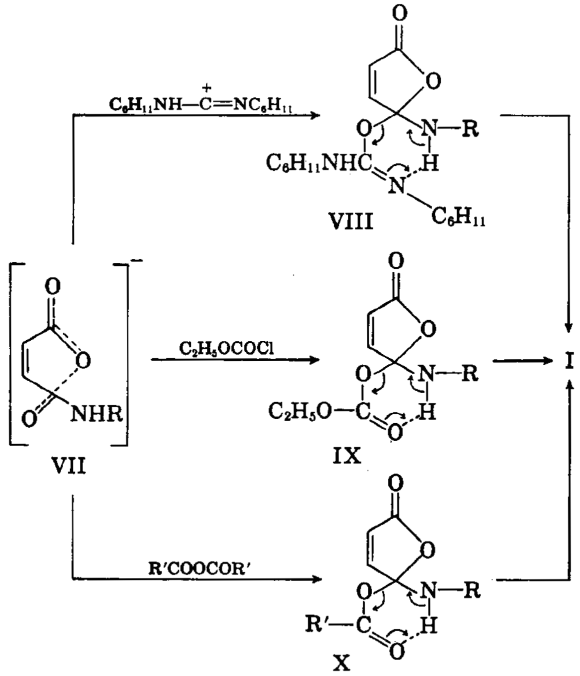
(8) Protonation of the carbonyl oxygen of *N*-(4-hydroxy-1-naphthyl)isomaleimide would give a species which would be stabilized by resonance, *viz.*:



(9) J. Hine, ***Physical Organic Chemistry***, McGraw-Hill Book Co., Inc., New York, N. Y., 1952, p. 268.

(10) M. L. Bender and M. C. Neveu, *J. Am. Chem. Soc.*, 80, 5388 (1959).

formate–triethylamine, trifluoroacetic anhydride–triethylamine, and acetic anhydride–triethylamine probably proceeds by similar mechanisms. Donation of a proton from the maleamic acid to the tertiary base or to *N,N'*-dicyclohexylcarbodiimide[11] could lead to a ring-closed structure like VII. Further reaction with the dehydrating agents might lead to species like VIII, IX, and X which could decompose *via* the indicated *quasi* six-membered ring transition states into the isomaleimides. Internal catalysis by carboxylate ion in hydrolysis of methyl hydrogen phthalate[12] and acyl salicylates[13] has been demonstrated. Interaction of the carboxylate anion of maleamic acids with the amide function to produce a species like VII is very probable. As the isomaleimide syntheses are carried out in nonaqueous media in the presence of acylating agents, hydrolysis of VII is avoided and dehydration takes place. The formation and decomposition of VIII, IX, and X through a cyclic transition state would explain the exclusive formation of the *N*-substituted isomaleimides in those reactions where no acetate ion is present to catalyze their isomerization to *N*-substituted maleimides.



EXPERIMENTAL[14]

N-n-Butylisomaleimide. Method A. Dehydration using ethyl chloroformate–triethylamine. Triethylamine (10.1 g., 0.1 mole) was added rapidly through a dropping funnel to a stirred slurry of *N-n*-butylmaleamic acid (17.2 g., 0.1 mole) in 100 ml. of anhydrous dichloromethane in a dry flask externally cooled by an ice salt bath. The resulting solution of triethylammonium *N-n*-butylmaleamate was cooled to 0–5° and ethyl chloroformate (11.9 g., 0.11 mole) was added dropwise at a rate slow enough to maintain the temperature below 5°. Carbon dioxide evolution and precipitation of triethylamine hydrochloride began almost immediately and continued throughout the addition. The reaction mixture was stirred for 1 hr. after the addition during which time it warmed to 20°. Triethylamine hydrochloride was removed by filtration and the filtrate was washed with water. After the organic layer was dried, the solvent was removed under reduced pressure and the residue distilled. The product, 12.1 g. (79%), b.p. 62–67° (1.0–1.2 mm.), n_D^{25} 1.4868–1.4870, was a clear, colorless liquid which developed a pale pink color on standing. The infrared spectrum of a liquid film possessed absorption at 1802 cm.$^{-1}$ (s) and 1698 cm.$^{-1}$ (s). When a 10% excess of triethylamine was used, the yield was raised to 90%. A sample purified by preparative vapor phase chromatography had n_D^{25} 1.4885. Its retention time on a silicone column at 190° and 25 p.s.i. was 5.0 min.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.98; H, 7.22; N, 9.25.

When the reaction was run on the same scale in 200 ml. of refluxing benzene for 1 hr., the yield was 65% of *N-n*-butylisomaleimide as determined by infrared and vapor phase chromatographic analyses. No *N-n*-butylmaleimide was detected in either the sample prepared at 0–5° or the sample prepared in refluxing benzene.

Ethyl N-n-butylmaleamate. It was necessary to use rigorously dried solvents for these dehydrations of *N-n*-butylmaleamic acid. When the solvents were not dry, ethyl *N-n*-butylmaleamate was formed at the expense of *N-n*-butylisomaleimide. However, this ester could also be prepared deliberately even with dry solvents by adding ethanol to the initial reaction mixture. The yields were in the 40–68% range, b.p. 125–128° (1.5 mm.), n_D^{25} 1.4761. Infrared absorption (liquid film) occurred at 3280 cm.$^{-1}$, 1732 cm.$^{-1}$ (s), 1640 cm.$^{-1}$, 1550 cm.$^{-1}$, and 675 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{17}O_3N$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.94; H, 8.25; N, 7.10.

The dibromide of ethyl *N-n*-butylmaleamate was prepared by treating this ester with bromine in chloroform. It melted at 79–81° after recrystallization from ether.

Anal. Calcd. for $C_{10}H_{17}O_3NBr_2$: C, 33.45; H, 4.77; N, 3.89. Found: C, 33.34; H, 4.75; N, 3.46.

Method B. Dehydration using N,N'-dicyclohexylcarbodiimide. To a slurry of 8.6 g. (0.05 mole) of *N-n*-butylmaleamic acid in 50 ml. of dichloromethane, a solution of 10.3 g. (0.05 mole) of *N,N'*-dicyclohexylcarbodiimide in 50 ml. of dichloromethane was added dropwise over a 20-min. period. A white, crystalline precipitate began to form when about half of the carbodiimide had been added. The mixture was stirred at room temperature for 3 hr., followed by removal of the precipitate by filtration. The precipitate was shown to be dicyclohexylurea by a mixture melting point with an authentic sample. The filtrate was concentrated and the residue was distilled to yield *N-n*-butylisomaleimide, 4 g. (52%), b.p. 80–83° (3 mm.), n_D^{25} 1.4890. The infrared spectrum of this product was identical with that obtained by Method A above.

N-n-Butylmaleimide. Method A. Dehydration using acetic anhydride-triethylamine. A solution of 17.3 g. (0.1 mole) of

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[11] The first step in the reaction of carbodiimides with acids has been postulated to be donation of a proton to nitrogen. See reference 7a, p. 154.

[12] M. L. Bender, F. Chloupek, and M. C. Neveu, *J. Am. Chem. Soc.*, **80**, 5384 (1958).

[13] E. R. Garrett, *J. Am. Chem. Soc.*, 79, 3401 (1957); J. D. Chanley, E. M. Gindler, and H. Sobotka, *J. Am. Chem. Soc.*, **74**, 4347 (1952); D. Davidson and L. Auerbach, *J. Am. Chem. Soc.*, **75**, 5984 (1953).

[14] Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Infrared Spectrophotometer, model 137. Vapor phase chromatographic analyses were obtained on a Perkin-Elmer Vapor Fractometer, model 154-C. Microanalyses were performed by Drs. G. Weiler and F. Strauss, Oxford, England and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

N-*n*-butylmaleamic acid and 21 g. (0.21 mole) of triethylamine in 250 ml. of dichloromethane was cooled by an external ice salt bath. The mixture was stirred while 10.2 g. (0.1 mole) of acetic anhydride was added dropwise. After the addition, stirring was continued for 3 hr. followed by removal of the solvent under reduced pressure. The residue was dissolved in 1:1 ether-pentane and this solution was washed with water, dried and concentrated under reduced pressure. Distillation of the residue gave 8.5 g. (56%) b.p. 60–65° (1–2 mm.) of a clear liquid which showed absorption in its infrared spectrum at 1780 cm.$^{-1}$ (w) and 1698 cm.$^{-1}$ (s), indicating the maleimide structure. Vapor phase chromatographic analysis showed that this product contained 92.5% of *N*-*n*-butylmaleimide, 5.9% of *N*-*n*-butylisomaleimide, and 1.6% of a low boiling unknown component. The retention time on a silicone column at 190° and 25 p.s.i. (helium) for *N*-*n*-butylmaleimide was 4.4 min.

Method B. Dehydration using acetyl chloride-triethylamine. A mixture of *N*-*n*-butylmaleamic acid (17.3 g., 0.1 mole) and triethylamine (21 g., 0.21 mole) in 200 ml. of dry ether was stirred at room temperature while acetyl chloride (7.8 g., 0.1 mole) was added dropwise with stirring. A thick precipitate of triethylamine hydrochloride began to form almost immediately. The mixture was stirred for 16 hr., filtered, and the filtrate was concentrated. The residue was dissolved in benzene, washed with dilute, aqueous sodium hydroxide, and water. The benzene was removed under reduced pressure and the residue distilled to yield 6 g. (39%) of a clear liquid, b.p. 50–55° (0.5 mm.). Vapor phase chromatographic analysis of this product showed it to be *N*-*n*-butylmaleimide uncontaminated with *N*-*n*-butylisomaleimide.

N,N'-Hexamethylenebisisomaleimide. A slurry of 62.8 g. (0.2 mole) of *N,N'*-hexamethylenebismaleamic acid in 1 l. of dichloromethane was stirred vigorously while 82.4 g. (0.4 mole) of *N,N'*-dicyclohexylcarbodiimide in dichloromethane was added dropwise over a 45-min. period. The mixture was stirred for 6 hr. and then allowed to remain unagitated for an additional 16 hr. The *N,N'*-dicyclohexylurea which precipitated was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was passed through a column of Florisil in benzene. Concentration of the benzene eluates yielded 29 g. (52%) of white crystals, m.p. 94–96°. The infrared spectrum of a Nujol mull of this product exhibited strong absorption at 1802 cm.$^{-1}$ and 1698 cm.$^{-1}$ A sample that was recrystallized to a constant-melting point from 1:1 benzene-ether melted at 95.5–97.5°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.58; H, 5.75; N, 10.20.

N-Phenylisomaleimide. Method A. Dehydration using ethylchloroformate-triethylamine. A slurry of 47 g. (0.25 mole) of *N*-phenylmaleamic acid in 300 ml. of dichloromethane was cooled with an ice salt bath while 25 g. (0.25 mole) of triethylamine was added dropwise with stirring. The solution was stirred and cooled to <5° followed by dropwise addition of 27.3 g. (0.25 mole) of ethyl chloroformate at a rate so as to maintain the temperature below 10°. Evolution of carbon dioxide began during the first few minutes of the addition and the solution became bright yellow. After the addition was completed, the reaction mixture was stirred an additional hour at 10° and then allowed to warm to room temperature. Triethylamine hydrochloride was removed by filtration and the filtrate was washed with water. The solvent was removed under reduced pressure and the residue was distilled to yield 27.5 g. (63%) of a pale, yellow liquid at 119–130° (1 mm.) which crystallized, m.p. 40–60°. Recrystallization from carbon tetrachloride gave 20 g. (46%) of product, m.p. 57–62°. A mixture melting point with *N*-phenylisomaleimide prepared by Method B was undepressed.

Method B. Dehydration using N,N'-dicyclohexylcarbodiimide. A slurry of 15.6 g. (0.082 mole) of *N*-phenylmaleamic acid in 150 ml. of dichloromethane was treated with 16.7 g. (0.081 mole) of *N,N'*-dicyclohexylcarbodiimide in 30 ml. of dichloromethane by a dropwise addition over a 20-min. period. The mixture was stirred for 2 hr. at room temperature followed by filtration to remove the *N,N'*-dicyclohexylurea (17.9 g., 98%) that had precipitated. The solvent was removed under reduced pressure and the residue, 13.2 g. (93%) crystallized in yellow prisms, m.p. 60–62°. A sample was further purified by solution in benzene and chromatography on a Florisil column prepared with pentane. The product that was obtained was recrystallized three times from 1:1 ether–petroleum ether (b.p. 39–54°) and dried *in vacuo*, m.p. 61.5–62.5°.

Anal. Calcd. for $C_{10}H_7O_2N$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.61; H, 4.17; N, 8.27.

The infrared spectrum of a melted film possessed absorption at 1791 cm.$^{-1}$ (s) and 1680 cm.$^{-1}$

Method C. Dehydration using trifluoroacetic anhydride-triethylamine. A mixture of 10 g. (0.052 mole) of *N*-phenylmaleamic acid and 10 g. (0.1 mole) of triethylamine in 50 ml. of dichloromethane was cooled with an ice bath. Trifluoroacetic anhydride (11 g., 0.052 mole) was added dropwise with stirring over a 10-min. period. The mixture was allowed to remain at room temperature for 16 hr., washed with water, dried, and concentrated under reduced pressure. The residue was dissolved in benzene and passed through a column of Florisil. The yellow eluate was concentrated to yield 4.5 g. (50%) of yellow crystals, m.p. 58–60°. A mixture melting point with *N*-phenylisomaleimide prepared by Method B was undepressed.

Bis(4-N-phenylisomaleimido)methane. Method A. Dehydration using ethylchloroformate-triethylamine. To a slurry of 19.7 g. (0.05 mole) of bis(4-*N*-phenylmaleamic acid)methane[15] in 125 ml. of dichloromethane at 0–5°, 10.1 g. (0.1 mole) of triethylamine was added with stirring. The mixture was stirred and cooled to −5° and 11.9 g. (0.11 mole) of ethyl chloroformate was added dropwise over a 20-min. period. The temperature of the reaction mixture was maintained below 7° during the addition and for an additional 30 min. after it was completed. The reaction mixture was then stirred without external cooling for 35 min. The amine hydrochloride was removed by filtration and the filtrate was washed with water and 10% sodium bicarbonate solution. The organic solution was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crystalline residue, 8.5 g. (47%) melted at 145–150°. A mixture melting point with bis(4-*N*-phenylisomaleimido)methane prepared by Method B was undepressed.

Method B. Dehydration using N,N'-dicyclohexylcarbodiimide. To a slurry of 19.7 g. (0.05 mole) of bis(4-*N*-phenylmaleamic acid)methane in 50 ml. of dichloromethane and 20 ml. of ether, a solution of 20.6 g. (0.1 mole) of *N,N'*-dicyclohexylcarbodiimide in dichloromethane was added dropwise over a 40-min. period with stirring. Stirring was continued for 3 hr. after the addition was completed, the *N,N*-dicyclohexylurea that had precipitated was removed by filtration, and the product was recovered from the filtrate by removal of the solvent under reduced pressure. The yield was 16 g. (89%) of yellow crystals, m.p. 150–151°. A mixture melting point with bis(4-*N*-phenylmaleimido)methane was depressed, m.p. 120–145°. The infrared spectrum of a Nujol mull possessed strong absorption at 1795 cm.$^{-1}$ and 1680 cm.$^{-1}$ An analytical sample prepared by passage through a column of Florisil in benzene and subsequent recrystallization from 1:1 benzene-ether melted at 155–156°.

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.81; H, 4.31; N, 7.66.

N-(o-Tolyl)isomaleimide. To a slurry of 43 g. (0.21 mole) of *N*-(*o*-tolyl)maleamic acid in 300 ml. of dichloromethane, a solution of 41.2 g. (0.2 mole) of *N,N'*-dicyclohexylcarbo-

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[15] I. A. Murphy, Ph.D. thesis, Indiana University, p. 37, September 1957.

diimide in 40 ml. of dichloromethane was added dropwise over a 30-min. period. The reaction mixture was stirred at room temperature for 24 hr., followed by removal of the precipitated *N,N'*-dicyclohexylurea by filtration. The filtrate was concentrated by distillation and the residue was dissolved in benzene, and passed through a column (1" × 10") of Florisil in benzene. The product, yellow-orange crystals, m.p. 37–40°, weighed 39 g. (100%) and exhibited a carbonyl absorption at 1790 cm.$^{-1}$ in the infrared spectrum of a melted film.

Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.85; H, 5.02; N, 7.54.

N-(o-Chlorophenyl)isomaleimide. To a slurry of 45 g. (0.2 mole) of *N*-(*o*-chlorophenyl)maleamic acid in 1 l. of dichloromethane, a solution of 41.2 g. (0.2 mole) of *N,N'*-dicyclohexylcarbodiimide in 40 ml. of dichloromethane was added dropwise over a 30-min. period. The mixture was stirred at room temperature for 24 hr., followed by filtration of the *N,N'*-dicyclohexylurea and distillation of the solvent under reduced pressure. The residue in benzene was passed through a column of Florisil and the eluates were concentrated to yield 40 g. (97%) of yellow crystals, m.p. 60–66°. Recrystallization of a sample from 1:1 benzene–petroleum ether (b.p. 39–54°) gave an analytical sample, m.p. 65–67°.

Anal. Calcd. for $C_{10}H_6O_2NCl$: C, 57.85; H, 2.91; N, 6.75. Found: C, 58.35; H, 2.73; N, 6.58.

The infrared spectrum of a liquid film showed strong carbonyl absorption at 1800 cm.$^{-1}$

Isomerization of N-n-butylisomaleimide to N-n-butylmaleimide. A solution of 5.0 g. (0.033 mole) of *N*-*n*-butylisomaleimide, 6.06 g. (0.06 mole) of triethylamine, and 3.6 g. (0.06 mole) of acetic acid in 100 ml. of benzene was heated at reflux for 90 min. The solution was cooled, washed with water, dilute sodium hydroxide solution, and again with water. The benzene was removed under reduced pressure and the residue was distilled to yield a clear liquid, b.p. 50–55° (0.5 mm.). Vapor phase chromatographic analysis of this material showed it to be a mixture containing 40% *N*-*n*-butylisomaleimide, 59.4% *N*-*n*-butylmaleimide and 0.6% of an unknown impurity. The recovery was 3.5 g. (70%).

Isomerization of N-phenylisomaleimide to N-phenylmaleimide. A mixture of 5.0 g. (0.029 mole) of *N*-phenylisomaleimide, 1.0 g. (0.012 mole) of anhydrous sodium acetate and 15 ml. of acetic anhydride was heated on the steam bath for 1 hr. After the mixture had cooled to 25°, it was poured into 100 ml. of water causing long, yellow needles to separate. These were collected and dried, 4.5 g. (90%) m.p. 90–91°. A mixture melting point with an authentic sample of *N*-phenylmaleimide was undepressed. When sodium acetate was absent in this reaction, the starting material was recovered.

Isomerization of N,N'-hexamethylenebisisomaleimide to N,N'-hexamethylenebismaleimide. A solution of 4 g. (0.014 mole) of *N,N'*-hexamethylenebisisomaleimide, 1.8 g. (0.03 mole) of acetic acid, and 2.6 g. (0.026 mole) of triethylamine in 200 ml. of dry benzene was heated under reflux for 16 hr., cooled, and washed with water. The benzene was removed under reduced pressure and the residue, 1.4 g. (35%) was recrystallized from isopropyl alcohol, m.p. 136–141°. A mixture melting point with authentic *N,N'*-hexamethylenebismaleimide was undepressed.

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The Chemistry of Maleimide and Its Derivatives.
II. Maleimide and *N*-Methylolmaleimide

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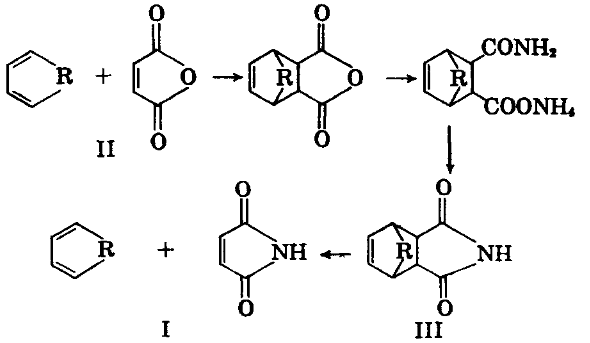
Maleimide was conveniently synthesized by preparation and pyrolitic decomposition of 3,6-*endo*-methylene-Δ^4-tetrahydrophthalimide. A variety of new *N*-substituted derivatives of maleimide were prepared. The olefinic bonds of maleimide and the derivatives were reactive in vinyl type polymerization under conditions of free radical or anionic initiation.

In an earlier paper,[1] a practical preparation of maleimide (I) by way of *N*-carbamylmaleimide was reported. In this paper, an alternate route for preparation for I and certain aspects of the chemistry of I are presented.

Preparation of I. The sequence of reactions shown in Chart A provides I in yields varying with the substituent R of the diene, II. Selection of cyclopentadiene (II, R = —CH₂—) was dictated by such factors as economy, convenience and ease of hydrolysis of the imide, III.

Chemistry of I. There are two reactive sites on the maleimide ring—the carboximide function and the double bond. Each exerts an influence upon

CHART A



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[1] P. O. Tawney, R. H. Snyder, C. E. Bryan, R. P. Conger, F. S. Dovell, R. J. Kelly, and C. H. Stiteler, *J. Org. Chem.*, 25, 56 (1960).