

N,N'-Biisomaleimide and Its Cyclic Isomers

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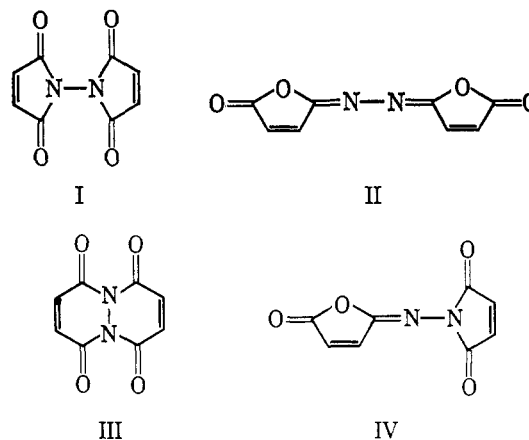
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The compound reported to be N,N'-bimaleimide is instead an isomer, N,N'-biisomaleimide. Authentic N,N'-bimaleimide was synthesized and its structure was unequivocally proved. Proof of structure for another isomer, 1,4,6,9-tetraketopyridazo[1,2-a]pyridazine, was also obtained. Criteria for assigning structure in this series are discussed. Using these, we have shown that the compound reported to be N-acetylaminomaleimide is also an isoimide. The reaction of N,N'-biisomaleimide with amines, hydrazines, and alcohols, where ring-opened products containing a dimaleylhydrazide unit are obtained, are described.

Very early in our work on N,N'-bisuccinimide¹ and its six-membered ring isomer we discovered that the compound reported² to be N,N'-bimaleimide (I) is in fact N,N'-biisomaleimide (II). This class of compound, of which N,N'-biisomaleimide is the first example, has not been discussed or investigated previously even though there has been some recent interest in the chemistry of N-alkyl- and N-arylisomimides derived from maleamic acids and phthalamic acids. For example, Cotter and co-workers³ have prepared N-butylisomaleimide along with some N-arylisomaleimides and a biisomaleimide where the isomaleimide rings are separated by a hexamethylene group by dehydration of the corresponding maleamic acids. Similarly, Kretov,⁴ Roderick,⁵ and co-workers have each prepared a series of N-arylisomaleimides. The latter also prepared a similar series of N-arylisophthalimides from phthalamic acids. Important references to older work are summarized in the above publications.

An important problem in the chemistry of isoimides has been establishing criteria for distinguishing between isomeric isoimide and imide structures. The problem is amplified in the case of N,N'-biisomaleimide and its analogs, since one must distinguish among four isomers, I-IV. In our first paper we shall describe the synthesis and related proof of structure for the isomers I-III, with particular emphasis on establishing criteria for structural assignments. An application of these criteria to the proof of structure of the related N-acetylaminomaleimide will be given. Also, some reactions of II with nucleophiles which demonstrate in part the



synthetic usefulness of this type of compound will be described.

Results

Synthesis and Proof of Structure for N,N'-Biisomaleimide.—In our initial search for simple routes to N,N'-bisuccinimide¹ we attempted to reduce catalytically N,N'-bimaleimide, which was reported by Feuer and Rubinstein² as the product from the dehydration of 1,2-bis(3-carboxyacrylyl)hydrazine (V) by thionyl chloride. We obtained a yellow compound from this reaction having the correct composition and the same melting point and infrared bands at 5.6 and 6.1 μ as described by Feuer. The compound also had a single intense absorption in the ultraviolet, $\lambda_{\max}^{\text{CH}_3\text{CN}}$ 292 $m\mu$ (ϵ 1.8×10^4). From these properties, it immediately became apparent that the original structural assignment was incorrect. In particular, Table I shows that maleimides generally have intense absorption near 220 $m\mu$ and relatively weak absorption at around 300 $m\mu$ in the ultraviolet. Furthermore, maleimides have characteristically broad carbonyl bands in the infrared with maxima near 5.8 μ .

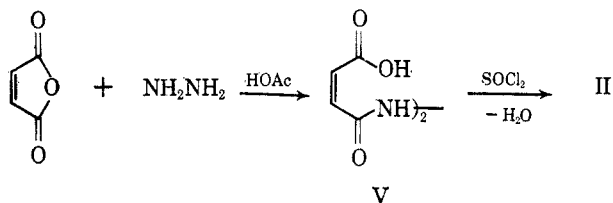
(1) E. Hedaya, R. L. Hinman, and S. Theodoropoulos, *J. Am. Chem. Soc.*, **85**, 3052 (1963).
 (2) H. C. Feuer and H. Rubinstein, *ibid.*, **80**, 5873 (1958).
 (3) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).
 (4) A. E. Kretov, N. E. Kyl'chitskaya, and A. F. Mal'nev, *Zh. Obshch. Khim.*, **31**, 2415 (1961).
 (5) (a) W. R. Roderick and P. L. Bhatia, *J. Org. Chem.*, **28**, 2018 (1963);
 (b) W. R. Roderick, *ibid.*, **29**, 745 (1964).

In contrast, the spectral properties of the yellow compound can be convincingly accounted for by the isoimide structure II. From Table I it is clear that isoimides may have intense absorption in the ultraviolet around 300 m μ . Much more complete and convincing is the collection of infrared data in Table I which shows that isoimides generally have two sharp bands in the infrared at 5.6 and ca. 5.9 μ . Furthermore, a survey of some 20 isoimides reported in the literature indicates that there is no exception to this generalization. These absorptions can be associated with the anhydride-like carbonyl and the imine bonds present in the isoimide ring.³⁻⁵ The lack of any feature suggestive of an imide chromophore in both the ultraviolet and infrared spectra of the yellow compound rules out the isoimide-imide structure IV.

We were unable to obtain an acceptable nmr spectrum for N,N'-biisomaleimide because of its insolubility and instability at elevated temperatures in solvents such as dimethyl sulfoxide. It is clear that II could be distinguished from I, III, and IV by nmr spectroscopy.

Further compelling evidence for the N,N'-biisomaleimide assignment was obtained by the synthesis and unequivocal proof of structure of N,N'-bimaleimide and the pyridazinedione III (see below).

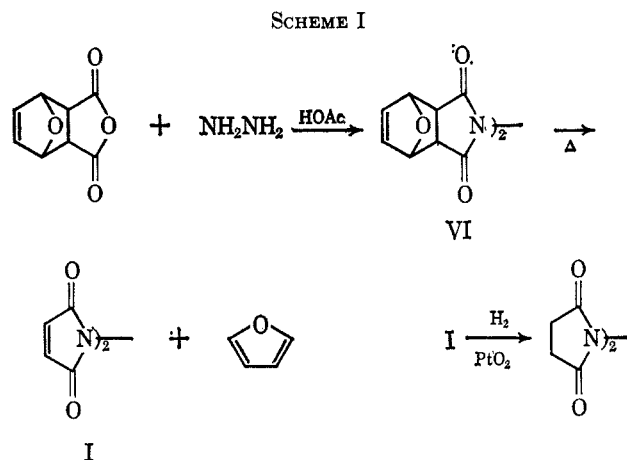
A survey of dehydrating agents showed that N,N'-biisomaleimide also can be obtained from trifluoroacetic anhydride, acetic anhydride, and acetyl chloride, with the first or last being the most dependable. Previous workers have shown that both trifluoroacetic anhydride⁵ and dicyclohexylcarbodiimide³ can be used to generate isoimides from maleamic acids, while the use of acetyl chloride or acetic anhydride without added base has not been reported. We have made no serious attempt to optimize yields.



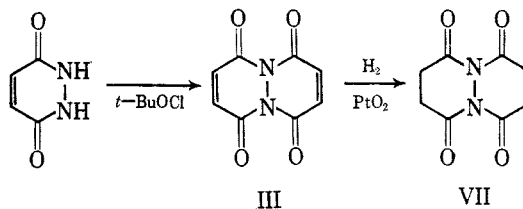
Synthesis and Proof of Structure for N,N'-Bimaleimide (I).—N,N'-Bimaleimide was prepared in a straightforward manner by cracking the biimide VI, which is obtained directly from the reaction of the furan adduct of maleic anhydride and hydrazine. (Scheme I). Unequivocal chemical proof of structure was obtained by reduction of N,N'-bimaleimide to N,N'-bisuccinimide, whose structure had been previously proved.¹

Spectral evidence, involving nmr, infrared, and ultraviolet data, offers further support for the structural assignment. First, the nmr spectrum in deuteriochloroform consists of only one line at 6.0 ppm. The ultraviolet and infrared (carbonyl) data for I are summarized in Table I along with some representative imides, and it can be seen that N,N'-bimaleimide has both broad carbonyl absorption and ultraviolet spectrum more characteristic of imides than of isoimides.⁶

(6) N,N'-Bimaleimide, like a number of other N,N'-biimides, is a thermally stable compound which can be easily sublimed and melts reversibly. Consequently, we feel that the maleimidyl radical cannot have any special



Synthesis and Proof of Structure for 1,4,6,9-Tetraketopyridazo[1,2-a]pyridazine (III).—Kealy⁷ reported that III could be obtained by treating maleic hydrazide with *t*-butyl hypochlorite in acetone at low temperatures. We have repeated his reaction under slightly modified conditions and have isolated the same material. Unequivocal proof of structure was obtained by catalytic reduction to perhydro-1,4,6,9-tetraketopyridazo[1,2-a]pyridazine (VII), whose structure had been proved previously.¹ The spectral properties of III are consistent with the assigned structure as the data in Table I shows.



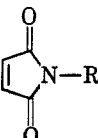
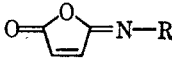
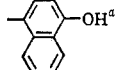
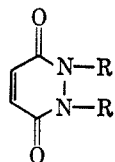

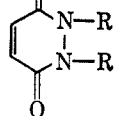
The Reaction of Aniline with N,N'-Biisomaleimide and Its Isomers.—By analogy to the facile reactions of maleic anhydride, N,N'-biisomaleimide would be expected to undergo ring-opening reactions at the carbonyl groups with nucleophiles. In fact, when N,N'-biisomaleimide (II) was combined with at least 2 equiv of aniline in acetic acid at room temperature, a fast reaction occurred as indicated by the rate of solution (15 min). The product obtained in essentially quantitative yield is the diamide VIIIa on the basis of elemental analysis and infrared and nmr spectra. The latter in particular shows only vinyl protons and aromatic protons in the correct ratio, while the infrared spectrum has characteristic NH and amide absorption. The same product was obtained from dimethyl sulfoxide solvent, but at a slower conversion rate.

In contrast, when N,N'-bimaleimide (I) was similarly combined with aniline in acetic acid, an adduct was obtained in approximately 60% yield after 3 hr at room temperature which appears to incorporate one molecule of I and two of aniline. Various structures (but not VIIIa) are compatible with the infrared and nmr data. However, from the nmr data it is clear that addition to the carbon-carbon double bond of N,N'-bimale-

stability just as no special stability can be assigned to the succinimidyl radical: E. Hedaya, L. M. Kibler, R. L. Hinman, and S. Theodoropoulos, *J. Am. Chem. Soc.*, **86**, 2727 (1964).

(7) T. J. Kealy, *ibid.*, **84**, 966 (1962).

TABLE I. SPECTRAL PROPERTIES OF SOME MALEIMIDES, ISOMALEIMIDES, AND PYRIDAZINEDIONES

R	λ_{co} , μ	Medium	λ_{max} , $m\mu$	$10^{-4}\epsilon$	Solvent
					
H	5.88 (br)	KBr	216 223 (sh)	1.52 1.30	95% EtOH
C ₂ H ₅ ^a	5.85 (br)	...	217 224 310	1.27 1.07 0.05	95% EtOH
C ₄ H ₉ ^b	5.90 (br)	Neat
C ₆ H ₅	5.85 (br)	KBr	220 320	1.81 0.05	95% EtOH
C ₆ H ₄ OCH ₃ - <i>p</i> ^c	5.80 (br)	Nujol
C ₆ H ₄ CH ₃ - <i>p</i> ^c	5.79 (br)	Nujol
C ₆ H ₄ N(CH ₃) ₂ - <i>p</i> ^c	5.82 (br)	Nujol
I	5.75 (br)	KBr	215 253	1.92 1.65	95% EtOH
					
C ₆ H ₅	5.60, 6.00	KBr	231 342	1.16 1.11	Dioxane
C ₄ H ₉ ^b	5.55, 5.90	Neat	243
	5.56, 5.98
C ₆ H ₄ OCH ₃ - <i>p</i> ^c	5.56, 5.95	Dioxane
C ₆ H ₄ CH ₃ - <i>p</i> ^c	5.55, 5.93	Dioxane
II	5.6, 6.1	KBr	292	1.80	CH ₃ CN
					
H, H	6.04 (br)	KBr	209 225 (sh) 315	1.34	95% EtOH
CH ₃ , CH ₃ ^d	6.15	Nujol	210 340	1.6 0.26	...
SO ₂ C ₆ H ₅ , H ^d	5.80	Nujol	208 260 267 274	1.52 0.24 0.26 0.11	...
					
CH ₃ C, H ^d	5.80, 6.00	KBr	216 285	1.44 0.41	...
III	5.79, 5.92	Nujol	228 340	1.10 0.20	Dioxane

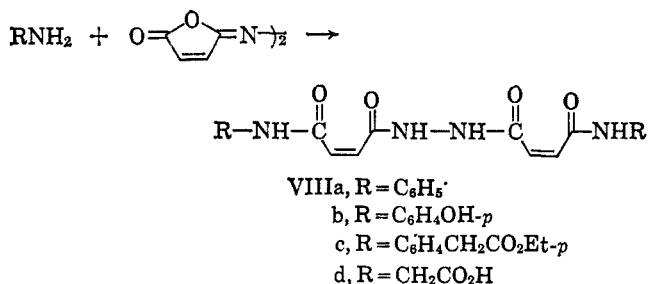
^a K. Tsou, P. J. Baronett, and A. M. Seligman, *J. Am. Chem. Soc.*, **77**, 4613 (1955). ^b R. J. Cotter, C. K. Sauer, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961). ^c W. R. Roderick, *ibid.*, **28**, 2018 (1963). ^d H. Rubinstein, Ph.D. Dissertation, Purdue University, 1958.

imide must occur in contrast to the isomeric isoimide (see Experimental Section).

The pyridazinedione III reacts with aniline in acetic acid, giving maleic hydrazide and what appears to be a mixture of the dianilide of maleic and/or fumaric acid and possibly an intermediate reaction product. It is again clear that this isomer reacts differently than the biisoimide. In both this reaction and the preceding reaction of N,N'-bimaleimide we were primarily concerned with ascertaining whether they would give the same product (VIIIa) isolated in the reaction with N,N'-biisomaleimide. As soon as we were satisfied that

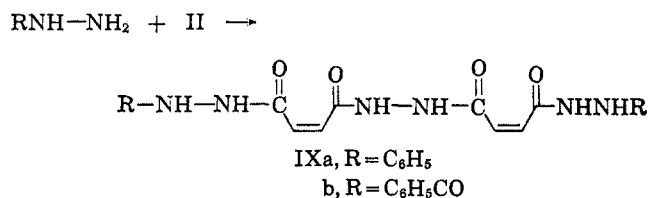
the products were different on the basis of the preliminary results no further work was carried out.

Reaction of N,N'-Biisomaleimide (II) with Other Amines and Hydrazines.—The reaction of N,N'-biisomaleimide occurs with a wide variety of amines other than aniline, including amino acids such as glycine or *p*-aminophenylacetic acid, giving the expected ring-opened products (VIII). The reactions are carried out in either acetic acid or dimethyl sulfoxide solvents at room temperature as above. In all cases, spectral properties are consistent with the assigned structure.

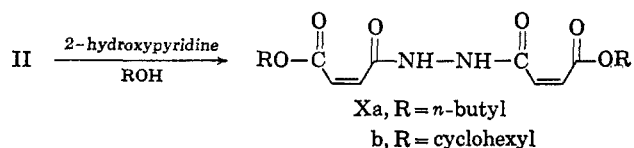


The reaction of *p*-hydroxyaniline with II is interesting because the product is the amide rather than the possible ester (the product is soluble in 10% sodium hydroxide and insoluble in water). This demonstrates that the amino group is more reactive than the hydroxy function, as one would expect from the relative basicity of anilines and phenols.

The reaction of bisomaleimide (II) with hydrazine or hydrazides also proceeds straightforwardly in acetic acid to give IX. Structure proof is again based on the infrared and nmr spectra of the products, with the most characteristic feature of the former being broad NH absorption near 3.0 μ and intense, broad absorption at 6.0–6.5 μ.



Catalyzed Reaction of N,N'-Bisomaleimide (II) with Alcohols.—When N,N'-bisomaleimide (II) was refluxed in alcohols (*e.g.*, methanol) no reaction occurred. However, when an alkoxide base was added, reaction occurred, but the products were high-melting, unrecrystallizable materials which had ill-defined infrared and nmr spectra. When pyridine was used as a catalyst, rapid reaction again occurred, and the highly colored products were similarly intractable. It was ultimately found that when 2-hydroxypyridine was used as a catalyst in alcohol solvents a clean reaction occurred to give crystalline products which could be purified and identified as the expected ring-opened esters. The yields of products having characteristic infrared and nmr spectra were about 60%. The principal features of the infrared spectra are the NH absorption and broad carbonyl absorption between 5.7 and 6.2 μ, while the nmr spectrum displays the anticipated ratio of vinyl hydrogens along with signals owing to alkyl or phenyl groups. An interesting vinyl pattern consisting of two superimposed AB patterns is observed for Xa (R = *n*-butyl), suggesting the presence of *cis-trans* isomers.



Discussion

Criteria for Distinguishing Biisoimides and Their Isomers.—The spectral and chemical criteria, which can be derived from our discussion above, for distin-

guishing among isomeric bisomaleimides, maleimides, or pyridazinediones and which will be used and amplified in later discussions can be summarized as follows.

(a) N,N'-Biisomaleimides have two sharp absorptions in the infrared occurring at 5.6 and 5.9–6.0 μ, while isomeric maleimides and pyridazinediones have broad absorption with a maximum at 5.7–6.0 μ. (b) N,N'-Biisomaleimides have a single intense maximum at around 300 mμ (in the absence of other chromophores), while isomeric imides or pyridazinediones have their most intense absorption at around 220 mμ. (c) N,N'-Biisomaleimides react rapidly with amines and alcohols (the latter catalyzed by 2-hydroxypyridine) with the position of attack being the anhydride-like carbonyl groups, rather than the double bond, giving ring-opened derivatives incorporating the bimaleyl-hydrazine unit. The isomeric structures I and III react differently, apparently giving a succinimide derivative in the former and maleic hydrazide in the latter.

Criterion a is the most general and has been used in the literature on isoimides practically exclusively. Roderick^{5a} has pointed out that for a number of N-arylisoimides there is no difficulty in seeing the characteristic twin carbonyl absorptions, but he has reported one example of an isophthalimide and another saturated isoimide (N-methyl-α-camphorisoimide) where the carbonyl absorption appears close to that anticipated for the imide.

Criterion b we feel will be of general usefulness for N,N'-biisoimides, particularly where the isoimide ring is unsaturated. In these cases the isomeric imides or pyridazines are cross-conjugated and consequently large differences may be expected, with the isoimide having more intense absorption at longer wavelengths. Since N,N'-bisomaleimide (II) incorporates an azine system, it is of interest to compare the spectrum of II with various azines. The azine derived from crotonaldehyde absorbs⁸ at 277 mμ (ε 3.60 × 10⁴), while that from 2,4-hexadienal absorbs at 338 mμ (ε 7.30 × 10⁴), thus bracketing the absorption for N,N'-bisomaleimide. Braude⁹ has pointed out that the extension of conjugation in α,β-unsaturated ketones by a terminal carbonyl group leads to a smaller bathochromic shift compared to similar extension of conjugation by a carbon-carbon double bond. Consequently, on this basis, one would predict that N,N'-bisomaleimide would have absorption at longer wavelength than crotonaldehyde azine but at lower wavelengths than 2,4-hexadienal azine. However, it must be emphasized that these are at best only very qualitative comparisons because of the obvious differences in structure between the biisoimide and azines.

It is unfortunate that more ultraviolet data on N-alkyl- and N-arylisoimides have not been reported since it is probable that it would provide one with another criterion for structural assignments in this series.

Criterion c is perhaps the most important for chemical purposes. The difference in reactivity between N-arylisoimaleimides and N-arylmaleimides previously has been noted by Roderick,^{5a} who showed that the former reacts with piperidine in benzene solvent at the carbonyl but the latter reacts with the olefinic

(8) E. R. Blout and M. Fields, *J. Am. Chem. Soc.*, **70**, 189 (1948).

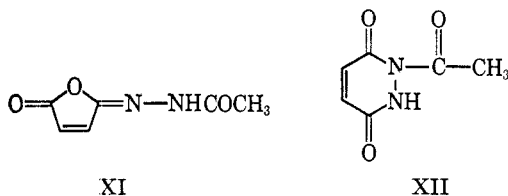
(9) E. A. Braude, "Determination of Organic Structures by Physical Methods," Academic Press Inc., New York, N. Y., 1955, p 131.

double bond, giving succinimides. This was used as a criterion for structural assignment. Our results show that the ring-opening reaction of isoimides with amines may be quite general since our example involves widely differing structural types and reaction conditions (bi-isoimide compared to isoimide, aniline instead of piperidine as the nucleophile, acetic acid solvent instead of benzene).

We cannot definitely conclude on the basis of our preliminary results that N,N'-bimaleimide (I) reacts at the olefinic double bond under our reaction conditions even though spectral evidence for a succinimide ring was obtained. It is clear though that the reaction course is different from that of isoimide isomer.

The reaction of the pyridazinedione isomer most likely involves initial production of a ring-opened N-acyl-substituted maleic hydrazide which subsequently reacts with another molecule of aniline, giving maleic hydrazide. Evidence for the existence of stable enolic forms of N-substituted maleic hydrazides has been recently obtained¹⁰ and special stability has been associated with this ring system.

A good example of the application of these criteria is the proof of structure for N-acetylisoimaleimide (XI). In a recent note, Feuer and Asunkus¹¹ described a series of N-substituted aminomaleimides along with their rearrangement to pyridazinediones. We have repeated the preparation of the N-acetyl derivative and find that it is instead N-acetylaminoisomaleimide. The infrared spectrum in the carbonyl region consists of four major bands at 5.62, 5.85, 5.95, and 6.10 μ , while the ultraviolet spectrum has one maximum at λ_{\max} 304 m μ (ϵ 1.82 \times 10⁴). These data are completely consistent with the isomaleimide isomer but not with the imide isomer (Table I). Conclusive evidence was obtained from the nmr spectrum which shows only an AB pattern of four lines in the vinyl region in the correct area ratio with the line owing to the methyl protons. The rearrangement of the isoimide AB pattern to another AB pattern, presumably owing to the pyridazinedione (XII) described by Feuer and Asunkus, was also observed in the nmr in trifluoroacetic anhydride solvent. It is very probable that the other rearrangements observed by the above workers¹¹ were isoimide-pyridazinedione transformations rather than the imide-pyridazinedione type reported.



Isomerism in the Isoimide Series and in Their Reaction Products with Nucleophiles.—One previously un-discussed interesting feature inherent in the cyclic isoimide structure is the possibility of geometrical isomerism about the C=N bond. Two isomers can be written for isoimides similar to those found in oxime derivatives, while three isomers are possible for N,N'-biisomaleimides. No good criteria for distinguishing

isomers nor chemical evidence for such isomerism has been obtained as yet. Again, nmr would be an obvious tool for detecting such isomerism.

The possibility of also obtaining *cis-trans* isomers in the products from the reaction of N,N'-biisomaleimide with amines or alcohols clearly exist. No attempt has been made to separate and distinguish isomers, even though evidence for such isomerism was found in the reaction products from *n*-butyl alcohol by nmr. It is probable that when the reaction with nucleophiles occurs under mild conditions and low temperatures the *cis,cis* configuration of the carbon-carbon double bonds in the biisoimide is retained in the product.

Experimental Section

All infrared spectra were obtained on a Beckman IR-5A instrument in potassium bromide pellets or Nujol mulls. Ultraviolet spectra were recorded on a Beckman DK-2 spectrophotometer. Solvents were Spectrograde acetonitrile, dioxane, or 95% ethanol. Nmr spectra were obtained on a Varian A-60 instrument and data are expressed in parts per million relative to tetramethylsilane. All melting points are uncorrected.

Preparation of 1,2-Bis(3-carboxyacrylyl)hydrazine.—A cold solution of hydrazine hydrate in acetic acid was prepared by slowly adding 5.00 g (0.1 mole) of 99–100% hydrazine hydrate to 25 ml of cold glacial acetic acid. This was added to a solution of 19.6 g (0.2 mole) of maleic anhydride in 100 ml of glacial acetic acid. The temperature was maintained below 25° throughout the addition and then the reaction mixture was let stand at 25° for 3 hr. The crude hydrazide was filtered off and washed thoroughly with ethanol. After this was dried *in vacuo* for 3 hr, 19.9 g (85%) of product was obtained, mp 183–184° (lit.² mp 183–184°).

Preparation of N,N'-Biisomaleimide.—1,2-Bis(3-carboxyacrylyl)hydrazine (2.0 g, 0.008 mole) was refluxed for 5 hr in trifluoroacetic anhydride. After cooling, 1.5 g of crude product was filtered off. Recrystallization from dimethylformamide gave 1.0 g (60%) of yellow crystals of N,N'-biisomaleimide, mp 260°. The same material could be obtained from refluxing thionyl chloride after 7 hr in approximately the same yield as described by Feuer.² A 50% yield of the biisoimide was obtained in refluxing acetyl chloride after 48 hr. Low yields were obtained in pure acetic anhydride at 95° after 5 hr. From a refluxing mixture of 3 g of diacid, 25 ml of benzene, and 10 ml of acetic anhydride a 36% yield of product was obtained after recrystallization.

Anal. Calcd for C₄H₂NO₂: C, 50.00; H, 2.04; N, 14.58. Found: C, 50.14; H, 2.32; N, 14.39.

Preparation of N,N'-Bi(7-oxabicyclo-2,2,1-5-heptenedicarboximide) (VI).—3,6-Endoxo-1,2,3,6-tetrahydrophthalic anhydride (16.6 g, 0.1 mole) was dissolved in 100 ml of glacial acetic acid. Hydrazine hydrate (99%, 2.5 g, 0.05 mole) was added over a period of 15 min with stirring. The mixture was kept at room temperature for 1 hr and at 50–60° for 1 hr more, and then let stand overnight. The white precipitate (7.6 g) was filtered off and washed thoroughly with methanol. After concentration of the mother liquor, an additional 1.1 g of product was obtained to give a total yield of 56%; mp 171–173°.

Anal. Calcd for C₈H₆NO₃: C, 58.53; H, 3.68; N, 8.53. Found: C, 58.35; H, 3.48; N, 8.51.

Preparation of N,N'-Bimaleimide (I).—The bimide VI (4.0 g) was heated over a sand bath at 180–200°. The solid slowly melted with vigorous furan evolution. After 3–5 min the yellowish liquid was cooled. Recrystallization of the residue from methanol gave 2.0 g (87% yield) of crude product, mp 165°. A second recrystallization from benzene gave white crystals, mp 176–178°.

Anal. Calcd for C₄H₂NO₂: C, 50.00; H, 2.04; N, 14.58. Found: C, 50.28; H, 2.24; N, 14.77.

Reduction of N,N'-Bimaleimide (I).—A mixture of 0.4 g (2 mmoles) of N,N'-bimaleimide, 50 ml of acetone, and 0.2 g of platinum oxide catalyst was kept under 50 psi of hydrogen pressure with shaking at room temperature for 24 hr. The mixture was heated to reflux temperature and filtered. After concentration, 380 mg (76%) of N,N'-bisuccinimide was obtained which

(10) (a) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1523 (1964); (b) O. Ohashi, M. Mashima, and M. Kubo, *Can. J. Chem.*, **42**, 970 (1964); (c) D. M. Miller, *ibid.*, **33**, 1806 (1955).

(11) H. C. Feuer and J. P. Asunkus, *J. Org. Chem.*, **27**, 4684 (1962).

was identical on the basis of infrared and mixture melting point with authentic material.¹

Preparation of 1,4,6,9-Tetraketopyridazo[1,2-*a*]pyridazine (III).—*t*-Butyl hypochlorite (11.0 g) in 250 ml of acetone was cooled to -77° . To this solution 15.0 g of the potassium salt of maleic hydrazide was added with stirring. The green solution was stirred at -77° for 4 hr and then slowly allowed to warm to room temperature and let stand overnight. The inorganic precipitate was filtered, and the filtrate was concentrated to one-fifth of the initial volume. After this was cooled on Dry Ice, a yellow solid was filtered off: yield 3.25 g (30%), mp 245° (lit.⁷ mp 247°).

Reduction of 1,4,6,9-Tetraketopyridazo[1,2-*a*]pyridazine (III).—A mixture of III (1.0 g) and 0.5 g of platinum oxide in 25 ml of acetone was kept under 50 psi of hydrogen pressure for 24 hr at room temperature with shaking. The catalyst was filtered off, the filtrate was concentrated to 20 ml, and a white crystalline precipitate was obtained. This was washed with acetone to give 200 mg of material (20% yield), mp 250° , which was identical on the basis of infrared and melting point with authentic perhydro-1,4,6,9-tetraketopyridazo[1,2-*a*]pyridazine.¹ About 400 mg of unreduced starting material was recovered from the filtrate.

Reaction of *N,N'*-Biisomaleimide with Aniline.—*N,N'*-Biisomaleimide (1.0 g, 0.005 mole) was combined with 1.0 g of aniline (0.011 mole) in 30 ml of acetic acid and stirred overnight at room temperature. The insoluble isomide went into solution after 15 min. Ether (50 ml) was added and the filtered precipitate was washed with additional ether, to give 1.93 g of product, mp 205° (yield $\sim 100\%$). The same reaction occurs in dimethyl sulfoxide solvent.

The product has characteristic broad bands in the infrared at ca. 3.0 (NH) and 6.0 μ (CO) and absorption in the nmr spectrum at 6.5 ppm (vinyl) and between 7.0 and 8.0 ppm (aromatic) in an approximate area ratio 2:5 (deuteriodimethyl sulfoxide).

Anal. Calcd for $C_{14}H_{11}N_2O_2$: C, 63.48; H, 4.97; N, 14.80. Found: C, 63.32; H, 5.18; N, 14.58.

Reaction of *N,N'*-Bimaleimide (I) with Aniline.—*N,N'*-Bimaleimide (0.5 g, 2.5 mmoles) and aniline (0.7 g, 7.5 mmoles) was stirred at room temperature in 20 ml of glacial acetic acid. After 4 hr, excess ether was added and the mixture was filtered to give 0.48 g of a white compound, mp 193° . This was recrystallized from dioxane to give material with the same melting point. The product is insoluble in 10% hydrochloric acid. No further discrete products were obtained from the mother liquor.

The product has infrared bands at 3.0, 5.8, and 6.0 μ characteristic of NH, imide carbonyl, and amide carbonyl, respectively. The nmr spectrum in trifluoroacetic acid solvent consists of four broad bands at 3.2–3.7, 5.5, 6.6, and 7.2–7.7 ppm (area ratio 3:2:2:10, respectively).

Reaction of 1,4,6,9-Tetraketopyridazo[1,2-*a*]pyridazine (III) with Aniline.—The tetraketopyridazopyridazine II (0.5 g, 2.5 mmoles) was combined with excess aniline (0.7 g, 7.5 mmoles) in 20 ml of glacial acetic acid and stirred for 4 hr at room temperature. The mixture was filtered and the precipitate was washed thoroughly with ether to give 150 mg of material (30%), identical on the basis of infrared and melting point with maleic hydrazide. The filtrate was concentrated and 420 mg of a solid mixture was obtained. The nmr and infrared spectra of this mixture suggest the presence of maleic acid dianilide (and possibly its geometrical isomer), more maleic hydrazide, and possibly an intermediate reaction product. There is little indication of unreacted starting material.

Reaction of *N,N'*-Biisomaleimide with *p*-Aminophenol.—The reaction was carried out as in the aniline reaction. The precipitated solid was filtered off and washed with ethanol and then ether to give the product in essentially quantitative yield, mp 200° . This was recrystallized from dimethylformamide–water to give material with mp 204° . The product dissolves in 10% sodium hydroxide but is insoluble in 10% hydrochloric acid. The infrared spectrum has characteristic broad absorptions at 2.8–3.2 and 6.0–6.3 μ .

Anal. Calcd for $C_{15}H_{11}N_2O_3$: C, 58.53; H, 4.42; N, 13.65. Found: C, 58.30; H, 4.58; N, 13.41.

Reaction of *N,N'*-Biisomaleimide with Glycine.—Glycine (0.8 g, 0.011 mole) was refluxed in 50 ml of glacial acetic acid until solution occurred. *N,N'*-Biisomaleimide (1.0 g, 0.005 mole) was added and immediately went into solution before precipitation of a yellowish solid occurred. The reaction mixture was stirred overnight and filtered. The precipitate was washed

with ether and recrystallized from water to give 1.5 g of product, mp 171 – 173° , in 88% yield. The product has very broad characteristic infrared bands at 3.0–4.8 and ca. 6.3 μ .

Anal. Calcd for $C_6H_7N_2O_4$: C, 42.10; H, 4.11; N, 16.36. Found: C, 42.06; H, 4.17; N, 16.03.

Reaction of *N,N'*-Biisomaleimide with Ethyl *p*-Aminophenylacetate.—The reaction was carried out as in the case of aniline to give the product in close to quantitative yield. Recrystallization from 1-propanol gave material with mp 192 – 194° (collapses, resolidifies, and melts at 278 – 280°). The infrared spectrum has characteristic broad bands at 3.0–3.3, 5.8, and 6.0–6.3 μ .

Anal. Calcd for $C_{14}H_{15}N_2O_4$: C, 61.08; H, 5.49; N, 10.17. Found: C, 60.76; H, 5.42; N, 10.13.

Reaction of *N,N'*-Biisomaleimide with Phenylhydrazine.—The reaction was carried out as in the case of aniline to give a nearly quantitative yield of product, which was recrystallized from dimethylformamide–water. The material appears to collapse at 218° and melts at 248 – 250° . There are characteristic broad bands in the infrared spectrum at 3.1, 6.0, and 6.2 μ .

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 58.81; H, 4.93; N, 20.57. Found: C, 58.75; H, 5.20; N, 20.70.

Reaction of *N,N'*-Biisomaleimide with Benzoyl Hydrazine.—The reaction was carried out as in the case of aniline to give the product in 70% yield. The product was washed thoroughly with hot methanol to give material with mp 190° . Characteristic broad bands are observed in the infrared spectrum at 3.2, 6.0, and 6.3 μ .

Anal. Calcd for $C_{11}H_{10}N_2O_3$: C, 56.89; H, 4.34; N, 18.09. Found: C, 56.27; H, 4.41; N, 17.73.

Reaction of *N,N'*-Biisomaleimide with 1-Butanol.—*N,N'*-Biisomaleimide (1.0 g, 0.005 mole) and 0.2 g of 2-hydroxypyridine were refluxed with stirring for 30 min in excess 1-butanol. The homogeneous reaction mixture was concentrated under vacuum, leaving a liquid residue. This was dissolved in methylene chloride and extracted with 0.1 *N* hydrochloric acid. The methylene chloride layer gave an oily residue which crystallized on standing. Recrystallization from ether gave the product in essentially quantitative yield: mp 100 – 101° .

The product has an infrared spectrum with characteristic NH absorption at around 6.3 μ . The nmr spectrum shows vinyl absorption consisting of two superimposed AB patterns at around 6.5 ppm, OCH₂ absorption at 4.5 ppm, and broad alkyl absorption between 1 and 2 ppm, all in the predicted area ratio (trifluoroacetic acid solvent).

Anal. Calcd for $C_8H_{12}NO_3$: C, 56.45; H, 7.10; N, 8.22. Found: C, 56.35; H, 6.85; N, 8.50.

Reaction of *N,N'*-Biisomaleimide with Cyclohexanol.—*N,N'*-Biisomaleimide (1.0 g, 0.005 mole) and 0.2 g of 2-hydroxypyridine were heated with stirring at 100 – 110° in 50% excess cyclohexanol until the mixture became homogeneous. The reaction mixture was cooled and the excess cyclohexanol was washed out with hexane. Recrystallization of the residue from acetone gave the product in 70% yield: mp 185° .

The infrared has characteristic NH, ester carbonyl, and double bond absorptions as in the 1-butanol product and the nmr spectrum is consistent with the assigned structure.

Anal. Calcd for $C_{10}H_{14}NO_3$: C, 61.20; H, 7.19; N, 7.13. Found: 60.97; H, 7.11; N, 7.56.

Preparation of *N*-Acetylaminoisomaleimide (X).—1-Acetyl-2-(3-carboxyacrylyl)hydrazine was cyclized in acetic anhydride as described by Feuer and Asunkus.¹¹ *N*-Acetylaminoisomaleimide was obtained in ca. 30% yield as a white solid, mp 164 – 165° , having infrared bands at 5.62, 5.85, 5.95, and 6.10 μ . Feuer and Asunkus gave mp 164 – 165° and infrared bands at 5.62, 5.87, and 5.95 μ for their material, described as *N*-acetylaminoisomaleimide.

N-Acetylaminoisomaleimide has an nmr spectrum in deuteriochloroform (containing a little acetic acid to increase solubility) consisting of an AB pattern in the vinyl region with $J_{AB} = 6.0$ cps, $\delta_A = 7.26$ ppm, and $\delta_B = 6.89$ ppm, and methyl group resonance at 2.38 ppm. In pure deuteriochloroform essentially the same spectrum is observed but less intensely because of increased dilution. In trifluoroacetic anhydride the decay of an initial AB pattern with $J_{AB} = 6$ cps and the growth of another with $J_{AB} = 13$ cps was observed.

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