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[Contribution from the Wellcome Research Laboratories]

Maleamic and Citraconamic Acids, Methyl Esters, and Imides

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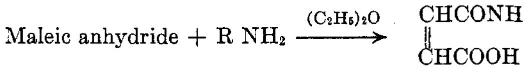
A series of maleamic and citraconamic acids has been made by the reaction of primary and secondary aliphatic and heterocyclic amines with maleic and citraconic anhydrides. Methyl esters have been prepared from several of these acids. It has been found possible to prepare *N*-alkylmaleimides and citraconimides by cyclization of the *N*-alkylmaleamic and citraconamic acids under much milder reaction conditions than had formerly been used.

The preparation of numerous maleamic and citraconamic acids, their methyl esters, and their imides was undertaken because these substances were needed as intermediates for various other projects. Except for a few primary amines[1–4] the reaction of aliphatic amines with maleic anhydride had not been investigated. A few maleamic acids have been mentioned but not well characterized in recent patents.[5,6] The reaction of amines with citraconic anhydride has not been reported. Although considerable work has been described both in the literature and in patents on *N*-arylmaleamic acids and imides,[7] little investigation has been devoted to the synthesis of *N*-alkylmaleimides and citraconimides. Only the *N*-methyl- and *N*-ethylmaleimides[2,8,9] have been reported in the early literature. One or two other *N*-alkylmaleimides have been referred to in some recent patents, but no descriptions of the method of preparation or characterization of the products was given. *N*-Phenylcitraconimide has been reported by Reissert.[10]

The presentation of the material of the current work has been subdivided, for convenience, according to the types of compounds involved.

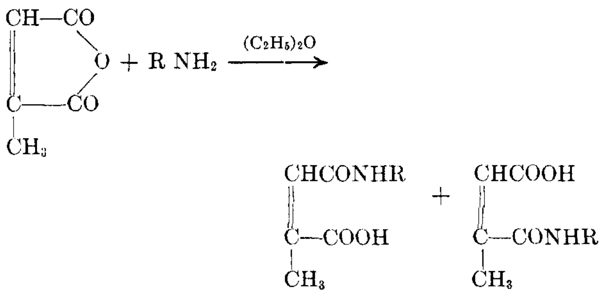
I. *Maleamic and citraconamic acids.* A. *Maleamic acids* (Table I A). Maleic anhydride reacted with a variety of primary and secondary aliphatic and heterocyclic amines, equimolar amounts of the reactants being used in cold dilute ether solution.



$$\text{Maleic anhydride} + \text{R NH}_2 \xrightarrow{(C_2H_5)_2O} \begin{array}{l}\text{CHCONHR}\\ \|\\ \text{CHCOOH}\end{array}$$

Excellent yields of the crystalline maleamic acids resulted in most cases. In a few instances, as with some of the heterocyclic amines, the yields of the maleamic acids were poorer. The amine salt of the maleamic acid was obtained as a side product in some of these runs. A few of these have been isolated and characterized (see Experimental section).

B. *Citraconamic acids* (Table I B). Several representative amines reacted with citraconic anhydride under conditions similar to those described above. In these reactions primary amines invariably gave a mixture of two *isomeric* amide acids in excellent yields. These mixtures of isomers could usually be separated by their differential solubilities in suitable solvents. When secondary amines were used in this reaction only a single product was isolated. The latter result is consistent



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(1) R. Anschütz, *Ber.*, **20**, 3214 (1887).

(2) A. Piutti and E. Giustiniani, *Gazz. chim. ital.*, **26 I** 431 (1896).

(3) Y. Liwschitz, Y. Edlitz-Pfeffermann, and Y. Lapidoth, *J. Am. Chem. Soc.*, **78**, 307 (1956).

(4) L. E. Coleman, Jr., J. F. Bork, and H. Dunn, Jr., *J. Org. Chem.*, **24**, 135 (1959).

(5) J. M. Weiss and R. P. Weiss, U. S. Patent **2,306,918**, Dec. 29, 1942.

(6) J. J. Giammaria, U. S. Patent **2,727,862**, Dec. 20, 1955.

(7) N. E. Searle, U. S. Patent **2,444,536**, July 6, 1948. This single patent is cited, since it is directly related to the current work.

(8) E. Giustiniani, *Gazz. chim. ital.*, **22 I**, 169 (1892).

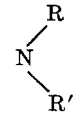
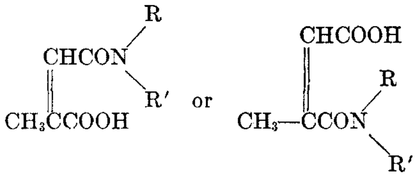
(9) A. Piutti, *Gazz. chim. ital.*, **18**, 483 (1888).

(10) A. Reissert and F. Tiemann, *Ber.*, **19**, 623 (1886).

TABLE I

A. *N*-Substituted Maleamic Acids

HOOCCH=CHCONRR′

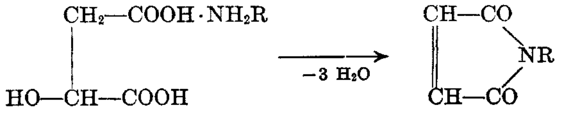
No.		M.P.°	Yield, %	Crystn. solvent[a]	Formula	Analyses Carbon, % Calcd.	 Found	 Hydrogen, % Calcd.	 Found
1	CH_3NH[j]	167–168	75	Ac	$C_5H_7NO_3$	46.5	46.5	5.4	5.2
2	C_2H_5NH	123	90	M	$C_6H_9NO_3$	50.4	50.5	6.3	6.4
3	*n*-C_3H_7NH	98–99	95	M	$C_7H_{11}NO_3$	53.5	53.7	7.0	7.1
4	*n*-C_4H_9NH	85	90	M	$C_8H_{13}NO_3$	56.2	56.3	7.6	7.5
5	*n*-$C_6H_{13}NH$	78	95	Ac·E	$C_{10}H_{17}NO_3$	60.3	60.6	8.6	8.5
6	*n*-$C_8H_{17}NH$	84–85	90	M	$C_{12}H_{21}NO_3$	63.5	63.3	9.3	9.1
7	$C_6H_{11}NH$[b]	150	80	Ch·E	$C_{10}H_{15}NO_3$	60.9	61.0	7.6	7.5
8	$C_6H_5CH_2NH$[c,j]	142	95	M	$C_{11}H_{11}NO_3$	64.4	64.2	5.4	5.7
9	$C_6H_5CH_2CH_2NH$[j]	136–137	90	Ac	$C_{12}H_{13}NO_3$	65.8	65.9	6.0	5.9
10	$(C_2H_5)_2N$[d]	41	80	Ac·E	$C_8H_{13}NO_3$	56.2	56.0	7.6	7.2
11	(*n*-$C_6H_{13})_2N$	130	60	B·E	$C_{16}H_{29}NO_3 \cdot H_2O$	63.7	63.4	10.2	9.7
12	$(CH_2)_4N$[e]	95	80	M·E	$C_8H_{11}NO_3$	56.8	56.1	6.5	6.2
13	$(CH_2)_5N$[f]	80–81	60	Ac·E	$C_9H_{13}NO_3$	59.0	59.1	7.1	7.0
14	$O(C_2H_4)_2N$[g]	120–121	95	Ac·E	$C_8H_{11}NO_4$	51.9	52.1	6.0	6.0
15	$CH_3N(C_2H_4)_2N$[h]	196	95	M	$C_9H_{14}NO_3 \cdot H_2O$	50.4	50.6	7.4	7.5
				B. *N*-Substituted Citraconamic Acids					
									
16	*n*-C_3H_7NH	α[i]140	60	A	$C_8H_{13}NO_3$	56.1	55.8	7.6	7.0
		β 122	35	Æ			56.7		7.4
17	$C_6H_5CH_2NH$	α 132	60	A	$C_{12}H_{13}NO_3$	65.7	65.8	5.9	5.4
		β 142	35	Æ			65.7		5.7
18	C_6H_5NH	α 172	65	A	$C_{11}H_{11}NO_3$	64.4	64.9	5.4	5.4
		β 184	30	Æ			64.3		5.2
19	$(CH_2)_4N$[e]	α 110	95	A	$C_9H_{13}NO_3$	59.1	59.0	7.1	7.4

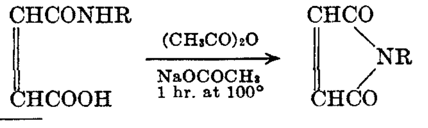
[a] A = ethanol; Ac = acetone; Æ = ethylacetate; B = benzene; Ch = chloroform; E = ether; M = methanol. [b] C_6H_{11} = cyclohexyl. [c] Reported by M. Frankel *et al. J. Am. Chem. Soc.*, **75**, 330 (1953). [d] Reported by M. L. Stein *et al. Ricerca Sci.*, **22**, 1007 (1952); *Chem. Abstr.*, **47**, 6872 (1953). [e] Pyrrolidino. [f] Piperidino. [g] Morpholino. [h] *N*′-Methylpiperazino. [i] The α and β designations have been used arbitrarily to specify the different isomers. The α symbol was used for the isomer which was less soluble in alcohol and which was obtained in larger amount. No assignment of specific structures of the two isomers has been attempted so far. [j] Kjeldahl nitrogen analyses were obtained for the following compounds: No. 1: Calcd.: 10.7% N; Found: 10.5. No. 8: Calcd.: 6.8% N; Found: 6.6. No. 9: Calcd.: 6.6% N; Found: 6.3.

with the findings of other investigators[11] who showed that the reaction of secondary amines with camphoric anhydride gave only one product.

II. *Methyl esters of the acids* (Table II). Methyl esters of several of the maleamic and citraconamic acids were prepared by refluxing an acetone suspension of the dry potassium salt of the acids with excess methyl iodide for a period of six to twelve hours.

III. *Maleimides and citraconimides* (Table III). Only the *N*-methyl- and N-ethylmaleimides[2,8,9] were reported in the older literature and these were made by a rather drastic pyrolytic decomposition of the alkylammonium salts of malic acid or of the *N*-alkylmaleamic acids. These procedures entailed elevated reaction temperatures and yields were not high. Even the more recent procedure reported by Coleman and co-workers[4] used high temperatures and called for heating maleamic acids for two or more hours at 180°. Yields were poor and accompanied by considerable polymer formation. Repetition of Coleman's[4] method in these laboratories led to similar findings. It has now been found that the milder reaction conditions used by Searle[7] for the preparation of *N*-aryl maleimides worked very well for the cyclization of *N*-alkylmaleamic acids to *N*-alkylmaleimides also, and yields of 50–70% were readily obtained.





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(11) K. Auwers and H. Schnell, *Ber.*, **26**, 1524 (1893).

TABLE II

METHYL ESTERS OF MALEAMIC ACIDS

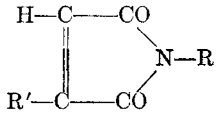
$CH_3OOCCH{=}CHCONRR'$

No.	NRR_1	M.P.-B.P.°	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
20	*n*-Propylamino[a]	122/1 μ	60	$C_9H_{15}NO_3$	58.4	58.7	8.1	7.6
21	*n*-Butylamino	85/1 μ	75	$C_9H_{15}NO_3$	58.4	58.1	8.1	7.7
22	*n*-Amylamino	110/10 μ	60	$C_{10}H_{17}NO_3$	60.3	60.4	8.5	8.5
23	*n*-Hexylamino	53	60	$C_{11}H_{19}NO_3$	61.9	62.2	8.9	8.8
24	*n*-Octylamino	64	90	$C_{13}H_{23}NO_3$	64.7	64.7	9.6	9.4
25	Benzylamino	132/4 μ	70	$C_{12}H_{13}NO_2$	65.7	65.7	6.0	6.3
26	Dimethylamino	60/2 μ	70	$C_7H_{11}NO_3$	53.4	53.5	7.0	6.5
27	Diethylamino[b]	124/2 μ	60	$C_8H_{13}NO_3$	56.2	56.1	7.6	7.5
28	Piperidino[c]	56	85	$C_{10}H_{15}NO_3$	60.9	61.0	7.6	8.0

[a] Citraconic methyl ester obtained from the *alpha* isomer, m.p. 140°. [b] See Ref. (d) Table I (A). [c] Crystallized from ether/pentane.

TABLE III

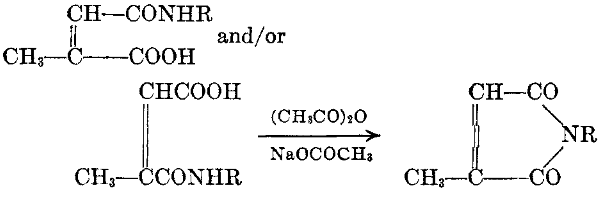
N-SUBSTITUTED MALEIMIDES AND CITRACONIMIDES



No.	R	R′	M.P.-B.P.°	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
29	Methyl[a,b]	H	96	60	$C_5H_5NO_2$	54.1	54.3	4.5	4.7
30	*n*-Propyl[a]	H	80	60	$C_7H_9NO_2$	60.4	60.1	6.4	5.9
31	*n*-Butyl	H	97/8 mm.	60	$C_8H_{11}NO_2$	62.7	62.4	7.2	7.2
32	*n*-Hexyl	H	115/5 mm.	50	$C_{10}H_{15}NO_2$	66.3	65.7	8.3	8.5
33	*n*-Octyl	H	142/5 mm.	60	$C_{12}H_{19}NO_2$	68.9	68.9	9.1	9.2
34	Benzyl[a]	H	93	70	$C_{11}H_9NO_2$	70.6	70.6	4.8	4.9
35	Phenyl[a,c]	CH_3	98	60	$C_{11}H_9NO_2$	70.6	70.8	4.8	4.9
36	Benzyl[a]	CH_3	29	60	$C_{12}H_{11}NO_2$	71.5	71.3	5.5	5.6

[a] Crystallized from ether. [b] Reported in references 2 and 8. It was prepared there by a different procedure. [c] Ref. 10.

The method of Searle[7] worked equally well for the conversion of *N*-alkylcitraconamic acids to *N*-alkylcitraconimides. The same *N*-alkylcitraconimide was obtained by the cyclization of either of the two isomeric *N*-alkylcitraconamic acids or of a crude mixture of the two.



EXPERIMENTAL[12]

Only a few typical procedures are described here in detail. The chemical and physical properties and analyses of the products are collected in Tables I–III.

N-n-Propylmaleamic acid. A solution of 6 g. (0.1 mole) of freshly distilled *n*-propylamine in 100 cc. of anhydrous ether was added dropwise over 0.5 hr. to a well stirred solution of 10 g. (0.1 mole) of maleic anhydride in 300 cc. of anhydrous ether at 0°. A white precipitate of *N-n*-propylmaleamic acid was formed immediately upon addition of the amine. The reaction mixture was stirred for 1 hr. longer. The precipitate was collected, washed with ether, and recrystallized from a methanol-ether mixture. The purified sample melted at 99° and was obtained in 95% yield.

N-n-Propylcitraconamic acids (α and β isomers). When 0.1 mole quantities of *n*-propylamine and freshly distilled citraconic anhydride were combined according to the method described above, a 95% yield of a crude mixture of amide–acid isomers was obtained. A solution of 16.5 g. of the crude mixture in 150 cc. of boiling absolute ethanol gave, on cooling, 8 g. of thick needle crystals melting at 140° (*alpha* isomer). Concentration of the filtrates gave 2.5 g. of a mixture of the isomeric acids. The mother liquors were evaporated to dryness and the residue upon recrystallization from ethyl acetate gave 5.5 g. of prisms melting at 122° (*beta* isomer).

Mono(N′-methylpiperazinoamide) of maleic acid. By the procedure described above 0.1 mole amounts of maleic anhydride and *N*-methylpiperazine gave 19.5 g. (98–100%) of the corresponding amide acid. This product was recrystallized from methanol-ether mixtures and the monohydrate melted at 196°.

Monopiperidinoamide of maleic acid. In a similar reaction maleic anhydride and piperidine reacted to give the corresponding amide acid. This was isolated and purified by recrystallization from mixtures of acetone, ether, and hexane. The purified sample melted at 80–81° and was obtained in 50–60% yield.

In this case and a few others, unusual difficulty was encountered in obtaining a pure product in high yield. In several of these cases formation of the amine salt of the amide acid appeared to be a complicating factor. It is not understood why this should have been true in only a very few of all

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(12) All melting and boiling points are uncorrected.

the compounds made of this type. Several examples of the amine salts of the amide acids, which were obtained in a relatively pure state, are given below.

N-Ethylmaleamic acid ethylammonium salt. This byproduct was obtained in 15% yield from the mother liquors of *N*-ethylmaleamic acid and was recrystallized from a methanol/ether mixture; m.p. 235°. It was soluble in water and decolorized permanganate readily.

Anal. Calcd. for $C_8H_{16}N_2O_3$: C, 51.4; H, 8.03. Found: C, 51.3; H, 8.14.

N-Cyclohexylmaleamic acid cyclohexylammonium salt. The mother liquor from the crystallization of the *N*-cyclohexylmaleamic acid from methanol yielded the byproduct on addition of anhydrous ether. Recrystallized from methanol/ether; m.p. 181°.

Anal. Calcd. for $C_{16}H_{27}N_2O_3$: C, 65.3; H, 8.83. Found: C, 65.4; H, 8.73.

N-n-Octylmaleamic acid methyl ester. A solution of 12 g. (0.05 mole) of *N-n*-octylmaleamic acid and 2.8 g. (0.05 mole) of potassium hydroxide in 100 cc. of absolute alcohol was evaporated to dryness *in vacuo.* A suspension of the dry potassium salt in 150 cc. of dry acetone containing 20 cc. of methyl iodide was refluxed for 6 hr. The precipitated potassium iodide was removed and the filtrate evaporated. The ester was taken up in ether, washed with 5% sodium bicarbonate solution, and dried over anhydrous potassium carbonate. On evaporation to a small volume and cooling, the ester separated as a waxy solid melting at 64°. The yield was 90%.

N-n-Butylmaleimide. A mixture of 34 g. (0.2 mole) of *N-n*-butylmaleamic acid, 100 cc. of acetic anhydride, and 10 g. of sodium acetate was heated on a steam bath (at 100°) for 1 hr. This reaction mixture was poured into 300 cc. of ice water and stirred for 2 hr. The aqueous mixture was extracted with ether and the ether layer was dried over anhydrous sodium sulfate. The ether was evaporated and the residue was distilled *in vacuo.* The product, *N-n*-butylmaleimide, boiled at 97–99°, at 8 mm. and a yield of 17 g. (55–60%) was obtained.

The distillation residue from this preparation gave 3 g. of a solid. After recrystallization from ethanol 1–2 g. of crystals was obtained which melted at 270–272°. This substance was insoluble in water or dilute sodium bicarbonate solution, and decolorized dilute potassium permanganate solution instantly. On the basis of these results and the analytical data given below this compound seemed to be *N,N'*-di-*n*-butylfumaramide. The *trans* configuration about the double bond was confirmed by an infrared peak at 10.2 mμ.[13]

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.8; H, 9.7. Found: C, 64.0; H, 9.6.

The alcohol filtrates from the above diamide upon concentration gave 1 g. of another solid. This was recrystallized from mixtures of alcohol, ether, and hexane and melted at 198–199°. It was insoluble in water, but soluble in dilute sodium bicarbonate and in alcohol, and it decolorized dilute potassium permanganate solution instantly. Infrared spectra showed this, too, has a *trans* (10.2 mμ peak)[13] configuration about the double bond. This would be then the *trans* isomer of the starting (*cis*) maleamic acid.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.2; H, 7.6. Found: C, 56.1; H, 7.5.

Similarly the distillation residues from the work up of the cyclization of several other maleamic acids gave products analogous to those obtained with the *N-n*-butyl compound.

N,N'-di-n-Hexylfumaramide. This product melted at 241–242° after recrystallizations from ethanol. It decolorized dilute potassium permanganate solution rapidly and had the characteristic *trans* infrared peak at 10.3 mμ.[13]

Anal: Calcd. for $C_{16}H_{30}N_2O_2$: C, 68.2; H, 10.9. Found: C, 67.8; H, 11.1.

Small amounts of the *trans* amide acid seemed to be present in this run, too, but were not obtained in analytically pure form.

N,N'-di-n-Octylfumaramide. This product crystallized from ethanol, melted at 230–231°, and had the *trans* infrared peak at 10.2 mμ.

Anal. Calcd. for $C_{20}H_{38}N_2O_2$: C, 71.0; H, 11.3. Found: C, 71.0; H, 11.5.

N-Benzylcitraconimide. A mixture of 22 g. (0.1 mole) of the mixture of isomeric *N*-benzylcitraconamic acids, 6 g. of anhydrous sodium acetate, and 100 cc. of acetic anhydride was heated with stirring until the internal temperature reached 60–70°. Heating and stirring were maintained for 1 hr. This reaction was mildly exothermal. After cooling, the reaction mixture was poured into ice water and stirred for 4 hr. Free acid was neutralized with sodium carbonate and the product was extracted with ether. After washing with sodium bicarbonate and drying over potassium carbonate, evaporation of the ether layer gave the *N*-benzylcitraconimide. The dark product was recrystallized from methanol, after treating with Darco, and gave colorless crystals melting at 29° and boiling at 189–190° at 26 mm.

Acknowledgment. We wish to thank Mr. Charles K. Marr for the microanalyses reported in this work.

TUCKAHOE, N. Y.

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(13) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., (1954) p. 8.