The fractions collected at 20-mm. pressure were the following: (1) 118–120°, 7.1 g., $n^{22}\text{D}$ 1.6266; (2) 120–135°, 1.2 g., $n^{22}\text{D}$ 1.6325; (3) 136–148°, 0.6 g., $n^{22}\text{D}$ 1.6572; (4) 149–152°, 3.4 g., $n^{22}\text{D}$ 1.6612; (5) 153–157°, 3.5 g., $n^{22}\text{D}$ 1.6620; (6) 157–158°, 1.5 g., $n^{22}\text{D}$ 1.6625. The residue (12.4 g.) was extracted with three portions of hot petroleum ether (b.p. 30–60°) to yield upon evaporation of the solvent semisolid crops (fractions 7, 8, and 9). Fractions 1 and 2 were shown to be mainly quinoline (38%) by infrared spectral comparison with an authentic sample and by the preparation of a picrate, m.p. 202–204°. Admixture with authentic quinoline picrate (m.p. 202–204°) gave no depression in melting point. By comparison with the authentic infrared spectra of all of the known bromoquinolines[1] fractions 3 and 4 were shown to contain 3-bromoquinoline and a new substance, contaminated with small amounts of quinoline. In a similar fashion, fractions 5 and 6 were shown to contain 3-bromoquinoline and the same unknown component in approximately equal amounts. By careful study of the infrared spectra of these fractions and by reference to the spectra of the known bromoquinolines[1] all the new infrared bands, not ascribable to the presence of 3-bromoquinoline, occurred only in the spectrum of authentic 4-bromoquinoline: 650, 758, 805, 834, 868, 962, 1050, 1280, 1370, and 1550 cm.$^{-1}$. Characteristic, intense infrared bands of the 2-, 5-, 6-, 7-, and 8-bromoquinolines were completely absent in the infrared spectra of fractions 1–6; this rules out their occurrence in these pyrolysis products in other than minute quantities (*cf. infra*). Fraction 7 possessed an infrared spectrum resembling a mixture of 3- and 4-bromoquinolines, together with new bands at 660, 810, 910, 960 (broadening), 1100, 1165, 1345, and 1490 cm.$^{-1}$. Again, all these new bands were found in the infrared spectrum of authentic 3,4-dibromoquinoline. Fractions 8 and 9 displayed infrared spectra identical with that of fraction 7, except that weak, unassigned bands occurred at 702, 830, and 1670 cm.$^{-1}$. The residue from the petroleum ether extractions consisted of an intractable mixture of polybromoquinolines melting over the range 75–200°, whose infrared spectrum had no definite OH, NH or C=O absorptions but pronounced, broad absorptions in the 950–975-cm.$^{-1}$ region (vicinal trisubstituted benzenoid or pyridinoid system).

(b) In similar runs of 0.20-mole size, where the heating period was extended over 2–3 hr., the isolated bromoquinoline was largely 4-bromoquinoline, contaminated with small amounts of 3- and 5-bromoquinolines. Thus upon distillation of the crude product, after a forerun of quinoline, the main fraction was collected at 140–145° (7 mm.), $n^{22}\text{D}$ 1.6620. The infrared spectrum was superposable with that of 4-bromoquinoline, except for weak bands indicative of small amounts of recovered 3-bromoquinoline and weak bands at 950, 1035, and 1215 cm.$^{-1}$, characteristic of 5-bromoquinoline. This fraction was heated at reflux with 12 *N* sulfuric acid for 12 hr. The solution was made basic with sodium hydroxide solution and extracted with ether to remove the unchanged bromoquinolines. The aqueous layer was brought to neutrality with sulfuric acid and then evaporated to dryness. Extraction of the solid residue with dry acetone and evaporation of the acetone extract left a solid residue. This solid was shown to be 4-hydroxyquinoline by the comparison of its infrared spectrum with that of an authentic sample.

(c) The presence of free bromine in the pyrolysis was verified by conducting the reaction in the presence of phenol. Over a 30-min. period an intimately mixed paste of 27.5 g. (0.095 mole) of 3-bromoquinoline hydrobromide and 9.4 g. (0.10 mole) of pure phenol was heated up to 300° under a nitrogen atmosphere. The temperature was maintained at 300 ± 5° for 1 hr. under reflux of the phenol. Thereafter the excess phenol was distilled at atmospheric pressure. Treatment of the cooled residue with sodium hydroxide solution and extraction with ether yielded an aqueous layer of sodium phenoxides. The latter solution was treated with chloroacetic acid according to published directions[7] to yield 0.10 g. of the crude phenoxyacetic acid, melting over the range 140–150°. Recrystallized thrice from hot water, the product formed colorless, flat needles, m.p. 157–159°. Mixture melting point and infrared spectral comparison with an authentic sample (m.p. 158–159°) showed the product to be *p*-bromophenoxyacetic acid.

The ether layer from the pyrolysis work-up was evaporated and the residual oil was extracted with hot, dilute tartaric acid solution. Treatment of the tartaric acid extracts with ammonium hydroxide and isolation by ether extraction provided 4.0 g. (32%) of quinoline, $n^{22}\text{D}$ 1.6300; picrate, m.p. 201–203°.

Pyrolysis of 6-Bromoquinoline Hydrobromide.—In an analogous fashion 15.7 g. (0.054 mole) of 6-bromoquinoline hydrobromide was heated at 300 ± 2° for 90 min. under a nitrogen atmosphere. The initially cream-colored solid gradually became a dark melt as hydrogen bromide gas was evolved. Usual work-up and distillation gave 10.0 g. (89% recovery) of pale yellow oil, b.p.$_{21}$ 167–168°, $n^{25}\text{D}$ 1.6599, with no forerun. By examination of its infrared spectrum the distillate was shown to be pure 6-bromoquinoline; no bands characteristic of quinoline or any other bromoquinoline were present.

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(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, N. Y., 1960, p. 264.

The Chemistry of Cyclic Hydrazides.[1] VIII. The Preparation of Substituted N-Aminomaleimides and Their Conversion to N-Substituted Maleic Hydrazides[2]

HENRY FEUER AND JOHN P. ASUNSKIS

Department of Chemistry, Purdue University, Lafayette, Indiana

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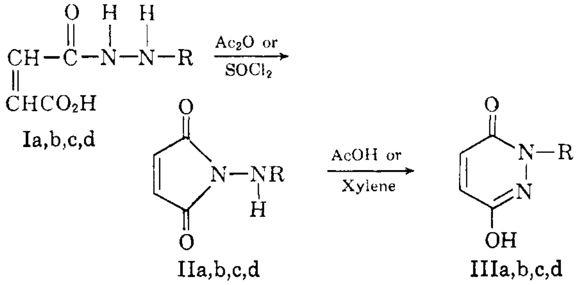
In 1958, we reported a novel preparation of substituted N-aminomaleimides and their subsequent rearrangement to N-substituted maleic hydrazides. This work deals with the preparation of new aryl and alkyl derivatives of N-aminomaleimides and the study of the electrical effect of substituents, situated on the amino nitrogen, on



a. R = —$COCH_3$; b. R = —$SO_2C_6H_5$; c. R = —$C_6H_3(NO_2)_2$-*m*; d. R = —C_6H_5.

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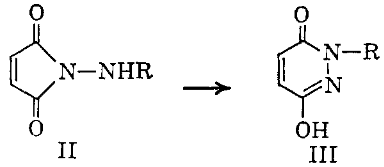
[1] Previous pertinent paper in this series, H. Feuer and H. Rubintein, *J. Am. Chem. Soc.*, **80**, 5873 (1958).

[2] From the M.S. thesis of John P. Asunskis, Purdue University, August, 1961.

TABLE I

REARRANGEMENT OF N-AMINOMALEIMIDES TO MALEIC HYDRAZIDES



II

III

N-Aminomaleimide			Method[a]		Maleic hydrazide		
	R	M.p. (dec.)	(a) Yield %	(b) Yield %		R	M.p. (dec.)
IIa	$COCH_3$	164–165	56	59	IIIa[1]	$COCH_3$	160–162
IIb[1]	$SO_2C_6H_5$	157–159	50	55	IIIb[1]	$SO_2C_6H_5$	212
IIc	$C_6H_3(NO_2)_2$-*m*	182–183	68	65	IIIa	$C_6H_3(NO_2)_2$-*m*	230–232
IId	C_6H_5	143–144	94	90	IIId	C_6H_5	255–256

[a] See Experimental.

the transformation of the five-membered maleimide to the six-membered maleic hydrazide.

Compounds Ia, Ib, Ic, and Id were prepared from maleic anhydride and the appropriate substituted hydrazine.[1] In the subsequent conversion of the acid hydrazides to the maleimides, it was established that acetic anhydride could be employed in place of thionyl chloride as the cyclizing agent. Previously,[1] the reaction of 1-acetyl-2-(3-carboxyacryloyl)hydrazine (Ia) with thionyl chloride was found to yield only gummy materials which could not be purified. However, we now report that N-acetylaminomaleimide (IIa) has been obtained in high yield when Ia was treated with acetic anhydride at room temperature. In contrast, the cyclization of 1-phenyl-2-(3-carboxyacryloyl)hydrazine (Id) to N-phenylaminomaleimide (IId) proceeded only in thionyl chloride. When acetic anhydride was employed, the six-membered maleic hydrazide, 2-phenyl-6-hydroxy-3(2H)-pyridazinone[3] (IIId) was obtained directly. It is believed that the acetic acid produced as a byproduct in the reaction catalyzed this transformation. It is not known whether IId is an intermediate in this transformation but it was established subsequently that IId was readily converted to IIId in the presence of acetic acid.

The conversion of compounds IIa, IIb, IIc and IId to the maleic hydrazides IIIa, IIIb, IIIc, and IIId was readily accomplished with refluxing anhydrous acetic acid or in anhydrous xylene at 120°. The yields of these conversions are enumerated in Table I. The data in Table I indicate that the rearrangement of II to III occurs more readily with maleimides in which the amino nitrogen is more basic. The dependence of this transformation on the high electron density on the amino nitrogen is further substantiated by the fact that in the preparation of 1-butyl-2-(3-carboxyacryloyl)-hydrazine from butylhydrazine oxalate and maleic anhydride, the six-membered 2-butyl-6-hydroxy-3-(2H)-pyridazinone[4] was obtained directly. Neither the free acid nor the maleimide could be isolated.

The rearrangements of IId to IIId were carried out with crude IId, the elemental analysis of which indicated that it contained four molecules of water. Attempts at purification in solvents such as acetone or ethanol caused the transformation to IIId on warming.

Experimental

Reagents.—Thionyl chloride (Matheson, Coleman and Bell), b.p. 77–78° was redistilled and used immediately. Acetic anhydride was redistilled and the fraction, b.p. 138–139°, was used. Acetic acid was purified by freezing and distilling the frozen solution *in vacuo* at room temperature.

1-(2,4-Dinitrophenyl)-2-(3-carboxyacryloyl)hydrazine (Ic).—Twenty grams of 2,4-dinitrophenylhydrazine was added at room temperature to 9.8 g. of maleic anhydride dissolved in 200 ml. of acetic acid. Stirring the solution for 6 hr. and then filtering gave 28.5 g. of Ic, m.p. 190–192° dec. which was purified by dissolution in benzene and reprecipitating with petroleum ether (b.p. 30–60°).

Anal. Calcd. for $C_{10}H_8O_7N_4$: C, 40.55; H, 2.72; N, 18.92. Found: C, 40.42; H, 3.00; N, 19.12.

N-Acetylaminomaleimide (IIa).—Acetic anhydride (100 ml.) and 4.0 g. of 1-acetyl-2-(3-carboxyacryloyl)hydrazine were stirred at room temperature for 24 hr. Removal of the solvent *in vacuo* at room temperature afforded 3.45 g. (96% yield) of IIa. Recrystallizing from hot ethanol or dissolving IIa in benzene and reprecipitating with petroleum ether (b.p. 30–60°) gave m.p. 164–165° dec.; $\gamma_{\max}^{\text{Nujol}}$ 5.62, 5.87, and 5.95 μ (carbonyl).

Anal. Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92; N, 18.18. Found: C, 47.01; H, 4.01; N, 18.30.

N-(2,4-Dinitrophenyl)aminomaleimide (IIc).—The procedure employed was similar to that used for preparing IIa, except that 50 ml. of thionyl chloride and 4 g. of compound Ic were refluxed for 3 hr. Dissolving the reaction product in benzene and reprecipitating with petroleum ether (b.p. 30–60°) gave 3.50 g. (93% yield) of IIc, m.p. 182–183° dec.; $\gamma_{\max}^{\text{Nujol}}$ 5.60 μ (ring carbonyl).

Anal. Calcd. for $C_{10}H_6O_6N_4$: C, 43.17; H, 2.17; N, 20.14. Found: C, 43.44; H, 2.41; N, 20.25.

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(3) J. Druey, *et al.*, *Helv. Chim. Acta*, **37**, 510 (1954).

(4) H. Feuer and R. Harmetz, *J. Am. Chem. Soc.*, **80**, 5877 (1958).

N-Phenylaminomaleimide (IId).—The procedure was similar to that of compound IIc except that 4 g. of Id[3] was employed. There was obtained 2.55 g. (94%) of IId. Dissolution in benzene at room temperature and reprecipitation with petroleum ether (b.p. 30–60°) gave m.p. 143–144° dec. The compound was very hygroscopic; on standing, the melting point decreased to 101–102° dec. Attempts to recrystallize IId from hot solvents resulted in its conversion to 2-phenyl-6-hydroxy-3(2H)-pyridazinone (IIId).

Anal. Calcd. for $C_{10}H_8O_2N_2 \cdot 4H_2O$: C, 46.15; H, 6.15; N, 10.76. Found: C, 46.42; H, 4.38; N, 10.59.

Rearrangement of N-aminomaleimides to N-substituted Maleic Hydrazides.—Typical procedures are described for the preparation of 2-(2,4-dinitrophenyl)-6-hydroxy-3(2H)-pyridazinone (IIIc) from IIc.

Method (a).—Four grams of IIc was refluxed for 24 hr. in 50 ml. of anhydrous acetic acid. Several successive freezings of the solution gave 2.12 g. of product and evaporation of the combined mother liquors left an oil which on treatment with ether gave an additional 0.62 g. (total yield, 68%) of material. Dissolution in benzene followed by reprecipitation with petroleum ether (b.p. 30–60°) gave IIIc, m.p. 230–232° dec.; $\gamma_{\max}^{\text{Nujol}}$ 5.79 μ (ring carbonyl).

Anal. Calcd. for $C_{10}H_6O_6N_4$: C, 43.17; H, 2.17; N, 20.14. Found: C, 43.25; H, 2.30; N, 20.44.

Method (b).—Four grams of IIc was heated for 24 hr. at 120° in anhydrous xylene. Work-up of the reaction mixture as described in method (a) gave a 60% yield of IIIc. A mixture melting point determination with an authentic sample of IIIc which was obtained by method (a) gave no depression and the infrared spectra were superimposable.

IIIc also was prepared in 91% yield by refluxing 1-(2,4-dinitrophenyl)-2-(3-carboxyacryloyl)hydrazine (Ic) for 5 hr. in glacial acetic acid.

2-Butyl-6-hydroxy-3(2H)-pyridazinone.—To 4.9 g. of maleic anhydride in 150 ml. of chloroform was added 8.0 g. of butylhydrazine oxalate at room temperature. The mixture was stirred for 5 hr. and then filtered to give 11.4 g. (88% yield) of 2-butyl-6-hydroxy-3(2H)-pyridazinone, m.p. 125–127° after recrystallization with ethanol. A mixture melting point determination with an authentic sample[4] was undepressed and the infrared spectra were superimposable.

Some Observations on the Synthesis of Phthaloylamino Acids

ELIAHU HOFFMANN AND HANNA SCHIFF-SHENHAV

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

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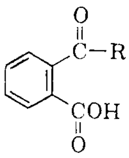
The synthesis of phthaloylamino acids by fusion of phthalic anhydride with an amino acid may lead to appreciable racemization.[1] Optically active phthaloyl-L-threonine and phthaloyl-O-acetyl-L-serine have been prepared in suspension of hot dioxane.[2] Other investigations have been carried out in order to establish optimal reaction conditions,[3] but the reported procedures do not seem to be satisfactory.[4] In order to obtain high yields without racemization it seems necessary to effect the synthesis of the phthaloylamino acids and their intermediate N-substituted phthalamic acids in solution and at moderate temperatures. The intermediate N-substituted phthalamic acids can be prepared in good yields at room temperature by stirring a solution of phthalic anhydride in an organic–water miscible solvent to which an equimolar aqueous solution of an amino acid and triethylamine has been added. During the course of the reaction one more equivalent of triethylamine is added to keep the solution at neutral pH. Under these conditions and with the quantities used (0.01–0.025 mole) the reaction is practically complete after forty-five minutes. Table I gives the phthalamic acids prepared and their yields and purities in terms of molecular weight calculated and determined by titration. Purification by recrystallization proved difficult because in boiling water hydrolysis is appreciable and in organic solvents of moderate boiling point (80–100°) partial cyclization to phthaloylamino acids seems to take place.

TABLE I

SYNTHESIS OF N-SUBSTITUTED PHTHALAMIC ACIDS



(Reaction solvent: tetrahydrofuran)

R	M.p., °C.	Mol. wt. Calcd.	Mol. wt. Found	Yield,[a] %
Glycine	100–102 (lit. 105–106)[b]	223	220	81
DL-Alanine	95–97	237	238	76
DL-Valine	170–171 dec.	265	270	74
DL-Phenylalanine	162–164 dec.	313	310	80

[a] These compounds are somewhat soluble in aqueous acidic solution and do not precipitate easily. Actual yields might therefore be higher since the phthaloylamino acids prepared from these solutions (Table II) give higher yields.

[b] *Cf.* ref. 7.

Phthalamic acid itself is known to undergo hydrolysis in water at acidic pH and the reaction kinetics have been investigated.[5] It has also been reported that some phthalamic acids can be dehydrated to phthalimide derivatives in dilute aqueous solution under certain conditions.[6] It is therefore interesting to note that phthalamic acid itself as well as phthalanilic acid and the *N*-substituted phthalamic acids in Table I do undergo

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[1] J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley & Sons, Inc., New York, N. Y., 1961, p. 902.

[2] J. C. Sheehan, M. Goodman, and G. P. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).

[3] A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

[4] F. Weygand and J. Kaelicke, *Ber.*, **95**, 1031 (1962).

[5] M. L. Bender, Y. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

[6] G. Drefahl and F. Fischer, *Ann.*, **610**, 166 (1957); F. Fischer, G. Preisser, and D. Strauss, *Ann.*, **643**, 110 (1961).