(0.4 mole) of ethyl chloroacetate was added all at once, and the resulting mixture was refluxed for five hours. The mixture was cooled, the *p*H adjusted to *ca.* 3 with a few drops of concentrated hydrochloric acid, distributed between water and ether, and the layers separated. The ether layer was washed twice with 10% sodium carbonate solution, and the alkali wash was added to the aqueous layer. The ether layer was dried over anhydrous sodium sulfate, and then the ether was evaporated. The residue (22.5 g.) was the diester III, m. p. 64–68°. Crystallization from dilute ethanol gave 21.4 g. (38%) of white needles, m. p. 70–71° (reported[2] m. p. 72°). The aqueous layer was acidified and filtered. The slightly tan solid obtained after drying melted at 240–245°. After two recrystallizations from dilute ethanol (Norite), the acid I (16.2 g., 36%) was obtained in the form of short white needles, m. p. 248–249° (reported[2] m. p. 251°). The ethyl ester of this acid could be prepared in the usual manner with boron fluoride-etherate as catalyst. After crystallization from dilute ethanol the ester melted at 70–71°, and there was no depression on admixture of the ester described above. The aqueous filtrate remaining after removing the acid was exhaustively extracted with ether. The ether extract was washed with saturated salt solution and dried over anhydrous sodium sulfate. The residue remaining after evaporation of the ether consisted of about 2 g. of a dark, viscous oil, which could not be induced to crystallize and was not further investigated. When the reaction was carried out with the use of one mole of ethyl chloroacetate and two moles of base, diester III (13%) and diacid I (18%) were isolated as described above. From the aqueous filtrate there was obtained by ether extraction 23% of the acid II, which was obtained as faintly yellow prisms, m. p. 149–150.5° (reported[2] m. p. 152°), after crystallization from a mixture of ethyl acetate and chloroform. When one mole of ethyl chloroacetate and one mole of base were used, 7% of the acid II and 23% of the ester IV were isolated. The ester crystallized from very dilute ethanol as white needles, m. p. 125–126°.

Anal.[7] Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.25; H, 6.23.

Reaction of 2,5-Dihydroxyacetophenone with Morpholine and Sulfur.—The following experiment is typical of many carried out. A mixture of 5 g. of 2,5-dihydroxyacetophenone, 7.8 g. of morpholine and 1.0 g. of sulfur was refluxed for two hours. At the end of that time the reaction mixture was nearly black. On cooling, the product of the reaction was found to be a dark, tough resin that was insoluble in all boiling organic solvents except acetone, and the resin was only slightly soluble in that reagent. If the reaction was carried out under conditions that carefully excluded air, the dark reaction mixture on cooling deposited a dark tarry product that was soluble in boiling alcohol, insoluble in boiling chloroform, but no crystalline product could be isolated. If the reaction was carried out under nitrogen for only fifteen minutes, about 20% of the starting ketone could be recovered in rather an impure state. Attempts to hydrolyze the tarry product with 10% sodium hydroxide were fruitless.

2,5-Dihydroxyacetophenone.—To a suspension of 44 g. of hydroquinone in 36 g. of glacial acetic acid well cooled in an ice–salt-bath, boron fluoride gas was bubbled in until 25 g. had been absorbed. The mixture was gently heated on the steam-bath for an hour, at which time all the hydroquinone had dissolved and the solution was colored a deep cherry red. After standing for twelve hours at room temperature, the mixture was decomposed by pouring it into a solution of 25 g. of sodium acetate dissolved in 150 cc. of water. The solid that separated was collected and the filtrate was extracted two times with 200-cc. portions of ether. The ether was evaporated and the residue added to the precipitate previously collected. The combined solid material was refluxed for fifteen minutes with a solution of 20 g. of sodium hydroxide dissolved in 200 cc. of water. The mixture was cooled, acidified; the precipitate was collected, washed. After crystallization from a mixture of ethanol and water, 16 g. (67% based on unrecovered hydroquinone) of yellow-green needles were obtained, m. p. 203–204° (reported[8] 202–203°). From the filtrate 26 g. of hydroquinone of good quality, m. p. 171–172°, could be isolated.

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[7] Analysis performed by William R. Ruby of these Laboratories.

[8] Amin and Shah, "Organic Syntheses," **28**, 42 (1948). A bibliography of the various methods used in the preparation of the ketone is given here.

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The Reaction of Itaconic Acid with Primary Amines

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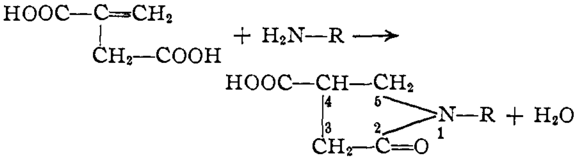
The condensation of primary amines with methylenesuccinic acid (itaconic acid) to give carboxypyrrolidones has apparently been studied in the case of only four amines, aniline, *p*-toluidine, phenylhydrazine and α-naphthylamine.[1] The probable mechanism of type reaction of pyrrolidonation is[2]



In the present report, forty-five amines have been investigated in the hope of establishing the limits of this type of reaction. Four of these amines condensed with itaconic acid in the presence of water, the medium used by the earlier investigators. A modification of the original method, fusion of the reactants, was required to bring about reaction in thirty-two cases. The results are summarized in Table I.

The nine amines which failed to react by either method were 2,4,6-trichloroaniline, 2,4,6-tribromoaniline, 2-nitroaniline, 2,4-dinitroaniline, 2,5-dimethoxyaniline, 2,5-diethoxyaniline, 2-carboxyaniline, sulfathiazole and sulfanilic acid. The reaction therefore appears to be limited both by the nature and the position of the substituents in the amine.

Experimental[3]

A mixture of itaconic acid, the amine and water (in the ratio of one acid molecule to each amino group) was refluxed for forty-five to sixty minutes

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[1] Gottlieb, *Ann.*, **77**, 284 (1851); Michael and Palmer, *Am. Chem. J.*, **9**, 199 (1887); Scharfenberg, *Ann.*, **254**, 149 (1889); Anschütz and Reuter, *ibid.*, **254**, 129 (1889).

[2] The numbering of the ring positions is that used in *Chemical Abstracts* 1-R-4-carboxy-2-pyrrolidones, rather than that appearing in Beilstein and the earlier papers, 1-R-3-carboxy-5-pyrrolidones.

[3] Technical grade itaconic acid, generously supplied by the Pfizer Co. and melting at 165–171°, was used throughout since carefully purified acid, melting at 167.5–168.5°, gave the same results. All of the amines were purified. All melting points are uncorrected; melting points below 300° were determined with a Fisher–Johns heating block, those above 300° with a Thiele tube by the capillary method.

TABLE I

Amine	R group of pyrrolidone	Yield, %	M. p., °C.	N, %[a] Calcd.	N, %[a] Found	Neut. equiv. Found	Mol. wt.[b] Calcd.	Mol. wt.[b] Found
Aniline[d]	Phenyl	89	189–190[c]	6.84	6.63	205	205	205
o-Toluidine	2-Tolyl	62	152–153	6.40	6.30	220	219	219
m-Toluidine	3-Tolyl	85	129–130	6.40	6.26	219	219	212
p-Toluidine	4-Tolyl	88	187–188[c]	6.40	6.32	219	219	219
Benzylamine[d]	Benzyl	75	143–144	6.40	6.39	219	219	213
Cyclohexylamine	Cyclohexyl	81	185–186	6.63	6.54	211	211	214
3,5,5-Trimethylhexylamine	3,5,5-Trimethylhexyl	82	93– 94	5.48	5.34	255	255	250
Phenylhydrazine[d]	Anilino	76	196–197[c]	12.72	11.22	220	220	221
o-Aminodiphenyl	2-Diphenyl	79	166–167	4.98	4.76	282	281	283
p-Aminodiphenyl	4-Diphenyl[g]	91	249–250 d.	4.98	4.87	282	281	285
α-Naphthylamine	α-Naphthyl	81	211[c]	5.49	5.24	256	255	253
β-Naphthylamine	β-Naphthyl	98	213	5.49	5.36	255	255	251
p-Aminoazobenzene	Azobenzene[f,g]	68	242–244 d.	13.60	11.75	309	309	315
o-Chloroaniline	2-Chlorophenyl	52	144–145	5.86	5.74	239	240	250
m-Chloroaniline	3-Chlorophenyl	84	135–136	5.86	5.79	240	240	236
p-Chloroaniline	4-Chlorophenyl[h]	87	150–151	5.86	5.68	240	240	239
p-Bromoaniline	4-Bromophenyl[i]	71	172–173	4.94	4.91	284	284	289
Chloroanisidine	2-Methoxy-5-chlorophenyl	83	197–198	5.22	5.18	272	270	284
2,4-Dichloroaniline	2,4-Dichlorophenyl[j]	43	75– 76[p]	5.12	5.16	274	274	277
2,5-Dichloroaniline	2,5-Dichlorophenyl	42	194	5.12	5.07	274	274	270
m-Nitroaniline	3-Nitrophenyl[e]	61	186–187	11.11	10.47	251	250	255
p-Nitroaniline	4-Nitrophenyl[k,e]	31	175–176	11.11	10.52	251	250	253
o-Aminophenol	2-Hydroxyphenyl	79	182	6.34	6.23	219	221	225
m-Aminophenol	3-Hydroxyphenyl	79	216–217	6.34	6.29	218	221	222
p-Aminophenol	4-Hydroxyphenyl	77	201–202	6.34	6.23	219	221	224
o-Anisidine	2-Methoxyphenyl	60	165	5.96	5.75	235	235	233
p-Anisidine	4-Methoxyphenyl	86	172–173	5.96	5.64	235	235	237
β-(3,4-Dimethoxyphenyl)-ethylamine	β-(3,4-Dimethoxyphenyl)-ethyl	77	129	4.78	4.75	291	293	277
m-Aminobenzoic acid	3-Carboxyphenyl	68	261	5.63	5.48	125	249	...
p-Aminobenzoic acid	4-Carboxyphenyl	67	287–288 d.	5.63	5.53	125	249	...
p-Phenylenediamine[d]	4-Aminophenyl[l]	72	209–210 d.	12.71	12.51	209	220	...
p-Phenylenediamine[d]	4-Aminophenyl-HCl[e]	..	242–245 d.	10.85	10.24	128	257	...
p-Phenylenediamine	*p*-Pyrrolidonylphenyl[m]	78	296–297 d.	8.44	8.36	166	332	...
Benzidine	*p*-Pyrrolidonyldiphenyl[n,g]	77	319–322 d.	6.87	6.76	...	...	...
Sulfanilamide	4-Sulfoamidophenyl[o]	74	212–214	9.86	9.58	272	284	286
Sulfaguanidine	Sulfaguanido	61	240–243 d.	17.15	17.10	300	326	...

[a] Gunning, Arnold and Dyer modified Kjeldahl method; nitro and azo compounds were first reduced with salicylic acid and zinc dust. [b] Rast camphor method. [c] Melting point consistent with that in Beilstein, Vol. XXII, 285–286. [d] Reaction in water; fusion in all other cases. [e] Yellow. [f] Orange. [g] Slightly soluble in bases. [h] Also prepared by the action of sulfuryl chloride on the phenyl compound (R = phenyl). [i] Also prepared by bromination, in acetic acid, of the phenyl compound. [j] Also prepared by the action of sulfuryl chloride on the phenyl compound. [k] Also prepared by the nitration of the phenyl compound. [l] Also prepared by the reduction of the 4-nitrophenyl compound by tin and hydrochloric acid. [m] Also prepared by the reaction of the 4-aminophenyl compound with itaconic acid (91%); prepared, too, from *p*-phenylenediamine in 12% yield in water. [n] Also prepared from 1-(*p*-aminodiphenyl)-4-carboxy-2-pyrrolidone and itaconic acid, by fusion, in 83% yield. [o] Also prepared from the *p*-sulfonyl chloride of the phenyl compound by reaction with ammonia; the sulfonyl chloride, m. p. 273–275° dec., 165–167° rapid heating, was prepared by the action of chlorosulfonic acid on the phenyl compound; hydrolysis of the sulfonyl chloride gave the sulfonic acid, m. p. 335–337° d. [p] Melting point questionable.

or until the odor of the amine was faint, after which the mixture was chilled in an ice-bath. The product was filtered, washed with cold water and then dissolved in aqueous sodium hydroxide, treated with charcoal, filtered and acidified with dilute hydrochloric acid. The precipitated pyrrolidone was recrystallized from water, dilute alcohol, alcohol, dilute acetic acid or dilute hydrochloric acid. Most of the products were colorless; exceptions are noted in the table.

When the above method gave no evidence of reaction, the dry reactants were maintained at the fusion point for ten to twenty minutes in a flask attached to a reflux condenser. After the molten mass had cooled, water was added and the product isolated as indicated above.

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