[Contribution from the Rollin H. Stevens Memorial Laboratory of the Detroit Institute of Cancer Research]

The Synthesis of 1-Substituted 5(4H)Tetrazolinones[1a,b]

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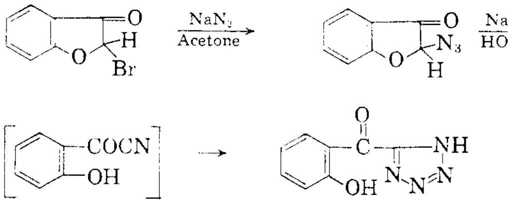
Benzoyl cyanide (I), on treatment with sodium azide in glacial acetic acid, is converted to phenyl isocyanate (IIa). These same reactants in *n*-butyl alcohol give *n*-butyl benzoate as the major product. On the other hand, the interaction of benzoyl cyanide and aluminum azide in anhydrous tetrahydrofuran affords 1-phenyl-5(4H)tetrazolinone (IIIa) (1-phenyl-5-hydroxytetrazole) in 30% yield. The transitory formation of IIa is postulated to explain the latter observation. In accord with this assumption it was found that IIa under the same conditions gave IIIa in 75% yield. In addition, a group of six 1-*p*-substituted phenyl-5(4H)tetrazolinones (III) have been prepared from the corresponding aryl isocyanate in yields ranging from 58–76%. An acyl halide may be employed instead of an isocyanate as demonstrated by the conversion of acetyl and benzoyl chloride to 1-methyl-5(4H)tetrazolinone and IIIa, respectively. Infrared measurements (Nujol) indicate a strong absorption in the carbonyl region (5.83–5.86 μ) of the spectra for each of these tetrazoles. The apparent dissociation constants of III have been measured and compared with values reported for the corresponding 5-arylaminotetrazoles. Ultraviolet absorption studies show characteristic maxima for III in the region of 240–310 mμ.

The decomposition of 2-azido-3(2H)benzofuranones in glacial acetic acid containing sodium azide (hydrazoic acid) leads to the formation of 5-*o*-hydroxybenzoyltetrazoles.[2] It was suggested that the reaction (eq. 1) involves the formation of *o*-hydroxybenzoyl cyanides as direct precursors of the ketones.



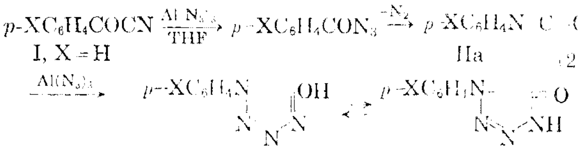
(1)

The present study was prompted by the possibility that α-ketonitriles might afford a more direct and general synthesis of 5-acyltetrazoles. However, it was observed that the interaction of benzoyl cyanide (I) and sodium azide in glacial acetic acid produced a vigorous exothermic reaction, accompanied by the evolution of gas and the formation of phenyl isocyanate (IIa). The latter was detected by quenching the reaction mixture with water which converted IIa to *sym*-diphenylurea. On the other hand, I, sodium azide, acetic acid in about 3:4:4 molar ratio in *n*-butyl alcohol[3] gave *n*-butyl benzoate (56% yield) as the major product.[4]

Dornow and Lüpfert have recently demonstrated that the reactions of α-ketonitriles are in many cases analogous to those of acyl halides.[5] The present observations are in accord with this analogy. Moreover, the ease of replacement of the cyanide residue in I by azide ion would seem to preclude *o*-hydroxybenzoyl cyanides as plausible intermediates in the formation of aryl 5-tetrazolyl ketones.

Recently, an elegant procedure was described for the conversion of nitriles to 5-substituted tetrazoles through the use of aluminum azide, generated *in situ*, in anhydrous tetrahydrofuran.[6,7] Application of this method to I gave a white acidic solid, m.p. 189–190° dec., which exhibited strong absorption in the carbonyl region (5.83 μ, Nujol) of the infrared. However, the composition, $C_7H_6N_4O$, of the product together with its neutral equivalent, 162, eliminated 5-benzoyltetrazole ($C_8H_6N_4O$, mol. wt. 174) from further consideration. On the other hand, the data proved to be consistent with the properties ascribed to 1-phenyl-5(4H)tetrazolinone[8] (IIIa) (1-phenyl-5-hydroxytetrazole), m.p. 187°, which was first obtained from the fusion of potassium tetrazole-5-sulfonate with potassium hydroxide.[9,10]

On the basis of the observations recorded above, it was tentatively assumed that phenyl isocyanate (IIa), generated according to the sequence outlined in equation 2, was the direct precursor of IIIa. In accord with this assumption, it was found that the interaction of IIa and aluminum azide in anhydrous tetrahydrofuran afforded IIIa in 75% yield. Moreover, this transformation was successfully extended to the preparation of a group of six 1-*p*-substituted phenyl-5(4H)tetrazolinones



(2)

IIIa, X = H
b, X = CH_3
c, X = CH_3O
d, X = Cl
e, X = Br
f, X = NO_2

(III) from the corresponding aryl isocyanate in yields ranging from 58 to 76% (*cf.* Table I). Following the completion of this phase of the study it was found that benzoyl chloride, on treatment with excess aluminum azide in tetrahydrofuran, gave IIIa in 43% yield. Similarly acetyl chloride

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[1] (a) This work was supported in part from institutional grants to the Detroit Institute of Cancer Research from the American Cancer Society, Inc., and the American Cancer Society, Southeastern Michigan Division, and in part by grant no. CY-2903 from the National Cancer Institute, National Institutes of Health, Public Health Service. (b) Presented before the Division of Organic Chemistry of the American Chemical Society, Chicago, Ill., September 8, 1958.

[2] K. Fries and K. Saftien, *Ber.*, **59**, 1246 (1926).

[3] R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

[4] It is presumed that tetrazole is also formed in this reaction. However, no attempt was made to isolate it.

[5] A. Dornow and S. Lüpfert, *Chem. Ber.*, **90**, 1780 (1957), and preceding papers.

[6] E. Wiberg and H. Michaud, *Z. Naturforsch.*, **9b**, 496 (1954).

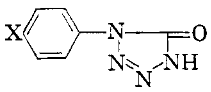
[7] H. Behringer and K. Kohl, *Chem. Ber.*, **89**, 2648 (1956).

[8] The lactam structure and the corresponding nomenclature is employed throughout on the basis of infrared measurements (*vide infra*).

[9] M. Freund and H. Hempel, *Ber.*, **28**, 78 (1895).

[10] R. Stollé and Fr. Henke-Starke, *J. prakt. Chem.*, **124**, 283 (1930), showed that the same product is obtained from treatment of tetrazole-5-sulfonic acid with 2 *N* potassium hydroxide.

TABLE I



1-ARYL-5(4H)TETRAZOLINONES (III)

X	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found
H	75	189–190 d.[a]	$C_7H_6N_4O$	51.85	51.95	3.73	3.80	34.55	34.85	162	162
CH_3	65	183.5–184.5	$C_8H_8N_4O$	54.54	54.77	4.58	4.67	31.81	32.21	176	177
CH_3O	76	181.5–182.5	$C_8H_8N_4O_2$	50.00	49.71	4.19	4.00	29.16	29.01	192	193
Cl	72	206–207 d.	$C_7H_5N_4OCl$	42.76	42.85	2.56	2.98	28.50	28.36	196	197
Br	64	218.5–219.5 d.[b]	$C_7H_5N_4OBr$	34.88	35.16	2.09	2.12	23.24	23.68	241	240
NO_2	58	217–218 d.	$C_7H_5N_5O_3$	40.58	40.83	2.43	2.70	33.81	34.22	207	207
NH_2	80[c]	173–174	$C_7H_7N_5O$	47.45	47.92	3.98	4.11	39.53	39.94	177	178

[a] Lit. (see ref. 9 and 10) 187°, 188°. [b] Lit. (see ref. 10) 216°. [c] Obtained by the catalytic reduction of the corresponding nitro compound IIIf (see Experimental section).

gave 1-methyl-5(4H)tetrazolinone in 30% yield. These observations, thus, lend evidence to the reaction path depicted by equation 2 and, in addition, provide an extension of the analogy between α-ketonitriles and acyl halides.

Prior to the present study examples of 1-substituted 5(4H)tetrazolinones were limited to the 1-methyl-,[10,11] 1-phenyl- and 1-*p*-bromophenyl[12] derivatives which were obtained by indirect and tedious methods. The present procedure employing an isocyanate provides a convenient route to this class of compounds. On the other hand, the use of acyl halides would appear to be of potentially wider application since it offers the advantage of smoothly accomplishing a multi-step process in a single operation.

It has long been known that monosubstituted carbamyl azides[13] can be obtained from isocyanates and hydrazoic acid.[14–16] However, this group of azides has proved resistant to both the Curtius rearrangement[17] and base-induced cyclization to tetrazole derivatives.[18] Instead, the azide moiety is replaced by any one of several nucleophiles, through a carbonyl addition-elimination reaction, with the formation of the corresponding carbamic acid derivative.[18]

On the basis of these considerations, it seems unlikely, then, that the cyclization of the conjugate base of an arylcarbamyl azide, derived, perhaps, from the addition of azide ion to an isocyanate, represents a plausible path for the formation of III. Rather, it is suggested that the coördination of aluminum azide with the aryl isocyanate, which presents four possibilities (Fig. 1), represents the initial step in the reaction scheme.

The formation of an aluminum salt of III from the first two requires a separation of azide ion from the complex, recombination at the electrophilic carbon atom followed by cyclization. The second pair (3 and 4), on the other hand, should afford the salt by direct cyclization.

The relative merit of these paths may be assessed on the basis of precedent from other reactions together with the evidence derived from the present study. In regard to the first two possibilities, coördination at the nitrogen atom of the isocyanate (2) should be preferred since nitrogen is more nucleophilic and more basic than oxygen. However, an equilibrium between 1 and 2 must also be considered.

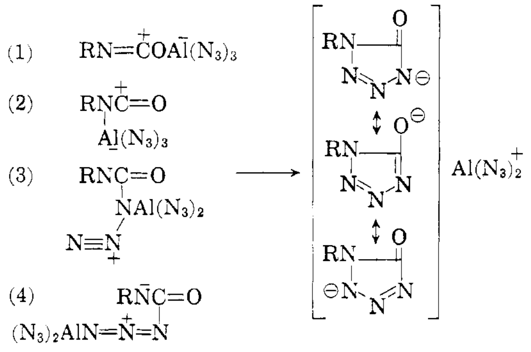


Fig. 1.

In general, aluminum compounds coördinate readily, although when polarizable anions are attached, such as alkoxide, the coördination is not as strong. The possibility of coördination by the azide moiety, as in 3 and 4, is suggested by evidence that the alkylated or arylated nitrogen atom of an azide can be protonated to some extent.[19] On the other hand, Staudinger's study of the interaction of phosphines and azides supports the susceptibility of the terminal nitrogen atom of the azide chain to attack.[20] However, the interpretation is not unequivocal and it is not clear whether the phosphorus atom in R_3P and $(RO)_3P$ should be considered nucleophilic, electrophilic or both.

The evidence available at this time does not warrant a firm conclusion in regard to the reaction path. However, any one of the schemes (1,2,3 and 4) can explain the difference between sodium azide and aluminum azide since the azide groups

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(11) K. Hattori, E. Lieber and J. P. Horwitz, THIS JOURNAL, **78**, 411 (1956).

(12) Obtained from the bromination of IIIa (see ref. 10).

(13) *Chemical Abstracts* prefers "carbamoyl azide."

(14) A. Hantzsch and A. Vagt, *Ann.*, **314**, 339 (1901).

(15) E. Oliveri-Mandala and F. Noto, *Gazz. chim. ital.*, **43**, I, 514 (1913).

(16) E. Oliveri-Mandala and E. Calderaro, *ibid.*, **43**, I, 538 (1913).

(17) F. L. Scott, *Chemistry & Industry*, 959 (1954).

(18) F. L. Scott, A. Koczarski and J. Reilly, *Nature*, **170**, 922 (1952).

(19) J. H. Boyer and F. C. Carter, *Chem. Revs.*, **54**, 1 (1954).

(20) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).

in $Al(N_3)_3$ are undoubtedly strongly polarized by Al^{+3}, far more than they would be by Na^+.

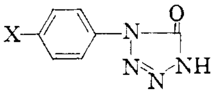
An analysis by Lieber and co-workers of the infrared absorption spectra of thirteen 5-substituted tetrazoles in Nujol showed that only 5-amino- and 5-hydrazinotetrazole gave bands in the double bond (6.0 μ) region.[21] This absorption has, therefore, been attributed to the potentially tautomeric amino and hydrazino groups rather than the $>C=N-$ linkage in the ring.[22]

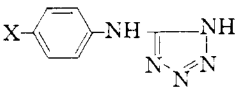
Each of the 1-aryl-5(4H)tetrazolinones exhibited a relatively strong absorption in Nujol between 5.83 and 5.87 μ. Furthermore, IIIa dispersed in KBr revealed an unmistakable peak at 3.15 μ.[23] These observations indicate that lactam structures (III) with association due to hydrogen bonding best describe the solid state of this potentially tautomeric system.

The 1-aryl-5(4H)tetrazolinones are colorless acidic solids which are soluble in aqueous alkali, alkali carbonates and bicarbonates. Typical weak acid titration curves were obtained in the potentiometric determination of apparent acid dissociation constants in 50% ethanol. The influence of the ring substituent on the acidity of the 1-aryl-5-(4H)tetrazolinones is small relative to the effects observed in the corresponding 5-arylaminotetrazoles (*cf.* Table II).[24] In the latter case the displacement of the constants is explained on the basis of the assumption that an *o*- or *p*-substituent is placed in conjugation with the tetrazole ring by resonance through the amino group. However, such resonance interaction in the case of III would not bring the nitrogen atom bearing the proton into conjugation, as shown in Fig. 2. This consideration together with the small displacement of the acid dissociation constants indicates that the main effects are probably of an inductive nature.

TABLE II

APPARENT ACIDIC DISSOCIATION CONSTANTS OF 1-ARYL-5(4H)TETRAZOLINONES AND THE CORRESPONDING 5-ARYLAMINOTETRAZOLES



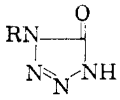


X	$p'K_a$[a]	$p'K_a$[b]
NH_2	5.75	6.53
CH_3O	5.63	6.00
CH_3	5.61	5.95
H	5.53	5.81
Cl	5.31	. .
Br	5.26	. .
NO_2	4.81	4.87

[a] All values determined in 50% ethanol by volume at 27°.
[b] These values were obtained in 50% ethanol at 27° and are assumed by the present authors to be apparent dissociation constants (see ref. 24).

The ultraviolet absorption spectra of the 1-aryl-5(4H)tetrazolinones were examined in both acidic and basic media in the region of 210–320 mμ (*cf.* Table III). Each structure exhibited a prominent maxima between 244 and 320 mμ in the presence of acid. In an alkaline medium these maxima are shifted slightly to longer wave lengths, but the general shape of the curve remains the same. In addition an absorption band of weaker intensity was detected in several cases in the region of 229–235 mμ. That the latter absorption band is due to the tetrazole nucleus is suggested by the observations: The parent structure and its 1-methyl derivative are essentially transparent between 240 and 320 mμ. However, each compound exhibits a single maximum of between 225 and 230 mμ in an alkaline medium. The principal maxima noted in Table III must therefore arise from the resonance interaction of the substituted benzene nucleus (Fig. 2) producing a displacement of the primary band of benzene (203 mμ).[25]

TABLE III



ULTRAVIOLET ABSORPTION MAXIMA OF SOME 1-SUBSTITUTED 5(4H)TETRAZOLINONES

R	λ_{max}, mμ 0.01 *N* HCl 95% CH_3OH	ε	λ_{max}, mμ 0.01 *N* NaOH 95% CH_3OH	ε
H	213	3216	226	3302
	. . .	. . .	. . .	. . .
CH_3	218.5	3190	228	3750
	. . .	. . .	. . .	. . .
C_6H_5	. . .	. . .	229	6367
	244.5	9639	253	9315
p-$NH_2C_6H_4$	. . .	. . .	. . .	. . .
	247	11859	260	13983
p-$CH_3C_6H_4$	. . .	. . .	. . .	. . .
	247.5	10278	254	10507
p-$CH_3OC_6H_4$	. . .	. . .	. . .	. . .
	251	10521	254.5	11866
p-ClC_6H_4	. . .	. . .	234	8788
	250	14030	259.5	12307
p-BrC_6H_4	. . .	. . .	235	9471
	251.5	15424	260.5	13376
p-$NO_2C_6H_4$	219	9481	230	8798
	293	13931	317	11095

Acknowledgment.—The authors are indebted to Dr. J. M. Vandenbelt of Parke, Davis and Co. for ultraviolet absorption measurements.

Experimental[26,27]

1-Aryl-5(4H)tetrazolinones (III).—The general procedure and amounts of reactants are based on the method described by Behringer and Kohl[7] for the conversion of nitriles to 5-substituted tetrazoles.

To a suspension of 19.5 g. of sodium azide in 50 ml. of tetrahydrofuran, containing 0.1 mole of aryl isocyanate II,

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[21] E. Lieber, D. R. Levering and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

[22] D. B. Murphy and J. P. Picard, *J. Org. Chem.*, **19**, 1807 (1954).

[23] An absorption in the form of a shoulder in the region of 3.10 to 3.20 μ was detected for each of the 1-aryl-5-hydroxytetrazoles. However, the close proximity of a peak at 3.25 μ due to Ar–H (stretching) coupled with a background peak (Nujol) at 3.45 μ precluded any possibility of assignment.

[24] R. A. Henry, W. G. Finnegan and E. Lieber, THIS JOURNAL, **76**, 88 (1954).

[25] L. Daub and J. M. Vandenbelt, *ibid.*, **69**, 2714 (1947); **71**, 2414 (1949).

[26] All reactions involving the generation of aluminum azide were carried out with anhydrous aluminum chloride and sodium hydride-dried tetrahydrofuran.

[27] All melting points are uncorrected. Analyses by Micro-Tech Laboratories, Skokie, Ill.

was added, all at once and with mechanical stirring, a solution of 14.7 g. of aluminum chloride (0.11 mole) in 150 ml. of tetrahydrofuran. The reaction mixture was stirred under reflux for 24 hours, cooled externally with an ice-water-bath and acidified with 20 ml. of 6 *N* hydrochloric acid. The two-phase mixture was then evaporated to dryness *in vacuo*.

Digestion of the dry residue with three 100-ml. portions of acetone effected a separation of IIIa, b and e from inorganic salts. The residue obtained after removal of the acetone was dissolved in hot 95% ethanol and treated with Norit. Dilution of the alcohol filtrate with water induced the crystallization of a colorless solid in each case. Two recrystallizations from aqueous alcohol provided analytical samples of IIIa, b and e.

The separation of IIIc, d and f from inorganic salts was accomplished by stirring the dry residue with 200 ml. of 6-N hydrochloric acid at room temperature for 1 hour. The product was collected, washed with generous quantities of water and sucked dry. The filter cake was then stirred into 200 ml. of 5% sodium hydroxide and a small quantity (0.5 to 1.0 g.) of the corresponding *sym*-diarylurea removed by filtration. Acidification of the filtrate gave, in each case, a colorless solid which was recrystallized from aqueous ethanol.

1-Phenyl-5(4H)tetrazolinone (IIIa). (a) **Benzoyl Cyanide**.—To a suspension of 19.5 g. of sodium azide (0.3 mole) in 50 ml. of tetrahydrofuran, containing 13.1 g. of benzoyl cyanide[28] (0.1 mole), was added, all at once with mechanical stirring, a solution of 14.7 g. of aluminum chloride (0.11 mole) in 150 ml. of tetrahydrofuran. The mixture was stirred under reflux for 24 hours, chilled and acidified by dropwise addition of 20 ml. of 6 *N* hydrochloric acid. The acidified mixture was then evaporated to dryness *in vacuo* and the dry residue digested with three 100-ml. portions of acetone. Removal of the acetone gave a brown solid which was dissolved in hot 95% ethanol and heated with Norit. Dilution of the alcohol filtrate with water gave a colorless solid (5.0 g., 30% yield), m.p. 180–186° dec. Recrystallization from aqueous ethanol gave IIIa in the form of white needles, m.p. 189–190° dec. (lit.[9,10] 187°, 188°).

(b) **Benzoyl Chloride**.—To a solution of 26.6 g. (0.2 mole) of aluminum chloride in 100 ml. of anhydrous tetrahydrofuran was added 39 g. of sodium azide and the mixture stirred under reflux for 2.5 hours. To the cool solution was added a solution of 14.1 g. of benzoyl chloride (0.1 mole) in 100 ml. of tetrahydrofuran and the mixture refluxed for 21 hours. The reaction mixture was cooled externally by an ice–water-bath and acidified with 100 ml. of 6 *N* hydrochloric acid. The two-phase mixture was then evaporated to dryness *in vacuo* and the residue extracted with 500 ml. of hot acetone and the extract evaporated to dryness under reduced pressure. The solid residue was twice recrystallized from 95% ethanol to give 7.0 g. (43% yield) of IIIa, m.p. 186–188°.

1-*p*-Aminophenyl-5(4H)tetrazolinone.—A solution of 2.07 g. of IIIf (0.01 mole) in 150 ml. of 95% ethanol was shaken with platinum oxide and hydrogen (17 lb.) at room temperature. The catalyst was removed by filtration, the filtrate evaporated to dryness *in vacuo* and the residue crystallized from water to give 1.42 g. (80% yield) of white needles, m.p. 167–169°. Recrystallization from benzene gave short white needles, which appeared to darken on standing, m.p. 173–174° (see Table I for analysis).

Formation of *sym*-Diphenylurea (Phenyl Isocyanate).—A mixture of benzoyl cyanide (4 g., 0.03 mole), sodium azide (4 g., 0.06 mole) and glacial acetic acid (30 ml.) was heated quickly to reflux. A copious evolution of gas(es) developed, and after refluxing for 3 minutes, the mixture was diluted with 100 ml. of water. The crystalline material was filtered from the cooled reaction mixture and recrystallized from ethyl acetate. The yield of colorless needles, m.p. 239–240°, was 1.0 g. (31%); mixture melting point with authentic *sym*-diphenylurea, 239–240°.

Formation of *n*-Butyl Benzoate.—A mixture of benzoyl cyanide (33 g., 0.25 mole), sodium azide (22 g., 0.33 mole), glacial acetic acid (20 g., 0.33 mole) and *n*-butyl alcohol (100 ml.) was refluxed for 5 days. At the end of this period, sodium azide (5 g.) and *n*-butyl alcohol (10 ml.) were added, and heating continued for an additional 24 hours. Water (300 ml.) was added and the mixture was concentrated to approximately 100 ml. by distillation under reduced pressure. The residue was extracted with ether. Distillation of the ether extract at atmospheric pressure gave 24.6 g. (56% yield) of *n*-butyl benzoate as a colorless liquid, b.p. 248–249°, $n^{25}\mathrm{D}$ 1.4940. A small portion of the ester was saponified and the product identified as benzoic acid. A small amount of crystalline material, *ca.* 150 mg., obtained from the aqueous phase has been tentatively identified as 5-phenyltetrazole.

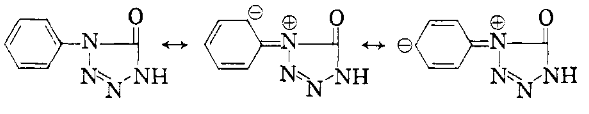

Fig. 2.

1-Methyl-5(4H)tetrazolinone.—To a suspension of 19.5 g. of sodium azide (0.3 mole) in 50 ml. of anhydrous tetrahydrofuran was added, all at once, a solution of 14.7 g. of aluminum chloride (0.11 mole) in 150 ml. of tetrahydrofuran. The mixture was stirred under reflux for 1 hour, then cooled to room temperature whereupon a solution of 3.90 g. of acetyl chloride (0.05 mole) in 50 ml. of tetrahydrofuran was introduced. The reaction mixture was stirred under gentle reflux for 24 hours, cooled externally by an ice-water-bath and acidified by dropwise addition of 20 ml. of 6 *N* hydrochloric acid. The mixture was evaporated to dryness *in vacuo* and the residue digested with three 100-ml. portions of acetone. The acetone was evaporated to dryness and the residue crystallized from ether to give 1.5 g. (30% yield) of a tan solid, m.p. 110–116°. The crude product was dissolved in benzene, treated with Norit, and the filtrate, on cooling, deposited transparent white plates, m.p. 121–122° (lit.[10,11] 122°, 122–124°); calcd. neut. equiv. 100, found 101.

Spectra.—Ultraviolet absorption spectra were determined with a Cary model 11 spectrophotometer. Infrared absorption measurements were determined in Nujol using a Perkin–Elmer model 21 recording spectrophotometer fitted with sodium chloride optics.

Apparent Acidic Dissociation Constants.—Approximately 0.01 *N* solutions of III in 50% aqueous ethanol were titrated potentiometrically with 0.1 *N* sodium hydroxide at 27°. The *p*H at the half neutralization point was taken as the $p'K_a$.

DETROIT 1, MICH.

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[28] E. Horning, "Organic Syntheses," Coll. Vol. III, John Wiley and Son, Inc., New York, N. Y., 1955, p. 112.