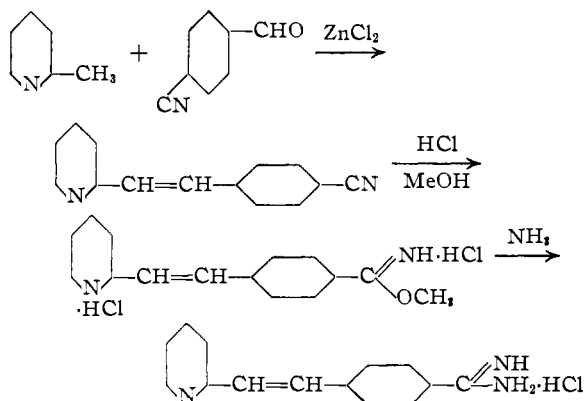


Benzamidine Derivatives

BY ELLIS K. FIELDS

In conjunction with the Survey of Antimalarial Drugs this Laboratory synthesized a number of benzamidines containing pyridine, quinoline or phenanthridine rings in the molecules. In general these were prepared by the reaction of *p*-cyanobenzaldehyde with a nitrogen ring compound containing an active methyl group. The resulting cyano compound was converted to the imido-ether hydrochloride and then to the amidine, according to the scheme for α -picoline.



The compounds prepared in this work are listed in Table I. They have not been previously reported in the literature.

TABLE I

R	R-CH=CH-C ₆ H ₄ -CN				R-CH=CH-C ₆ H ₄ -CNHNH ₂ HCl			
	M. p., ^a °C.	Yield, %	Nitrogen, % Calcd.	Found	M. p., ^b °C.	Yield, %	Nitrogen, % Calcd.	Found
α -Pyridyl	123-124	41	13.60	13.25	95 ^c	60	16.18	15.93
γ -Pyridyl	125-127	45	13.60	13.98	335	63	16.18	16.25
2-Quinoly	154	92	10.94	11.29	154 ^d	73	13.57	13.55
4-Quinoly	169-170	94	10.94	11.01	240-241	78	13.57	13.63
6-Ethoxy-2-quinoly	173	65	9.33	10.20	271	65	11.89	11.99
6-Methoxy-4-chloro-2-quinoly	190-192	64	8.75	9.20				
9-Phenanthridyl	200-201	40	9.15	9.10	174-175 ^e	60	11.67	11.54

^a Melting point uncorrected. ^b All decomposed. ^c Decomposed at 138°. ^d Higher melting form, m. p. 254°, yield 86%, N, 13.49. ^e Higher melting form, m. p. 282° (dec.), yield 68, N, 11.61.

Passing dry hydrogen chloride into solutions of the cyano compounds caused immediate precipitation of the corresponding hydrochlorides. The insolubility of the cyano hydrochlorides in benzene, ether, benzene plus methanol and other combinations of solvents was a stumbling block in the preparation of the amidines. The problem was solved by the discovery that dry chloroform was an excellent solvent for the cyano hydrochlorides, but dissolved practically none of the imido-ether dihydrochlorides.

1-(2-Quinoly)-2-(*p*-amidinophenyl)-ethene hydrochloride and 1-(9-phenanthridyl)-2-(*p*-amidinophenyl)-ethene hydrochloride were obtained in two forms that had different melting points and presumably were *cis-trans* isomers. The higher melting isomer was obtained in each case when a

large excess of alcoholic ammonia reacted with the imido-ether hydrochloride and the resulting clear solution, after 2-3 days at room temperature, was evaporated on a steam-bath. The lower melting isomer resulted when a slight excess of alcoholic ammonia was used and the amidine filtered from solution without heating. There were no separations involved; the pure *trans* or *cis* form was obtained.

α -Propylquinoline was heated with *p*-cyanopropiophenone and zinc chloride in an attempt to prepare 3-(2-quinoly)-4-(*p*-cyanophenyl)-hexene-3. At a temperature sufficient to cause the expected reaction, the mixture resinified.

Procedures

Cyano Compounds.—*p*-Cyanobenzaldehyde¹ was condensed with the various methyl heterocyclic compound, according to Wallach and Wusten.² Quinaldine, lepidines 9-methylphenanthridine and 6-ethoxy-4-chloroquinaldine condensed readily at 100-130° in two to four hours. α -Picoline and γ -picoline required six to eight hours in sealed tubes at 180°, even in the presence of larger quantities of zinc chloride.

Amidines.—The preparation of the amidine from the condensation product of *p*-cyanobenzaldehyde and quinaldine is described as typical. When dry hydrogen chloride was passed into a solution of 1-(2-quinoly)-2-(*p*-cyanophenyl)-ethene in dry benzene or ether containing the calculated amount of methanol, the hydrochloride of the unchanged cyano compound precipitated. No reaction occurred after hours of vigorous stirring or shaking. The cyano compound (4.7 g.) was dissolved in 350 cc. of dry chloroform containing a 10% excess of methanol. The solution was cooled in ice-salt and a vigorous stream of dry hydrogen chloride introduced. A white precipitate formed after twenty-five minutes. The mixture was kept

at room temperature for twenty-four hours under a slight pressure of hydrogen chloride. The white solid was filtered, washed with chloroform, and shaken with 50 cc. of dry methanol containing 2 g. of ammonia. Most of the solid dissolved. The mixture was kept twenty-four hours at room temperature, filtered from a little ammonium chloride, evaporated to a small volume and chilled. The amidine hydrochloride crystallized in white plates, melting at 154° dec., soluble in methanol, hot water and acetone and slightly soluble in cold water.

α -Propylquinoline.—This compound was prepared by the method of Tschitchibabin³ for γ -propylquinoline. By this synthesis was obtained a 60% yield of α -propylquinoline boiling at 274-275°.

α -Propylquinoline (5.13 g.), 4.77 g. of *p*-cyanopropiophenone,⁴ and 0.5 g. of anhydrous zinc chloride were

(1) Moses, *Ber.*, **33**, 2624 (1900).(2) Wallach and Wusten, *ibid.*, **16**, 2007 (1883).(3) Tschitchibabin, *Bull. soc. chim.*, [5] **3**, 1618 (1940).(4) Hellberger and von Reboj, *Ann.*, **531**, 284 (1937).

heated ten hours at 210–230°. There was no perceptible reaction. The mixture was refluxed twenty minutes at 280°, at which temperature it completely resinified.

These amidines were tested on ducks and proved to be extremely toxic.

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The Oxidation of Certain Ketones to Acids by Alkaline Hypochlorite Solution

BY MARTIN W. FARRAR AND ROBERT LEVINE

The advantages of hypohalite oxidation of methyl ketones^{1,2} are well recognized, yet apparently little is known of the behavior of higher alkyl ketones under similar conditions.³ We have found that higher alkylaryl and alkylheterocyclic ketones may likewise be cleaved in good yields to carboxylic acids by hypohalite oxidation. A detailed study on the stoichiometry and mechanism of this reaction is now in progress in this Laboratory.

Procedure.—A solution of sodium hypochlorite is prepared from 50 g. of "HTH" following the directions in the literature.¹ The solution is heated to 55°, and 0.1 mole of the ketone to be oxidized is added dropwise to the rapidly stirred solution, keeping the temperature at 60–70°. After the addition of the ketone is completed (about fifteen minutes), the reaction mixture is stirred at 70° for thirty minutes. Any unreacted sodium hypochlorite is then destroyed with sodium bisulfite solution. The contents of the flask is then heated to 100°, stirred and heated for fifteen minutes longer and then cooled to room temperature. The reaction mixture is then extracted with ether to remove any unreacted ketone, and the phases separated. The aqueous phase is acidified with concentrated hydrochloric acid. The crude acid is filtered on a Büchner funnel and recrystallized from hot water. In this way the following acids were obtained: benzoic, m. p. 121–122°⁴ (64%) from propiophenone, 2-thiophenic, m. p. 129–130°⁵ from *n*-propyl 2-thienyl ketone, and 5-methyl-2-thiophenic, m. p. 137–138°⁶ (67%) from 5-methyl-2-propionylthiophene.

In the preparation of 2-furoic acid (59%) from ethyl 2-furyl ketone the procedure followed is similar to that described above except that the temperature of the reaction mixture is never allowed to rise above 65° during the addition of the ketone and the reaction is then completed by stirring the contents of the flask at 65° for fifteen minutes after the addition of the ketone is completed. The reaction mixture is then acidified, extracted with ether, and the solvent distilled. The residue solidified. Recrystallization of this solid gave 2-furoic acid, m. p. 131–132°⁶ (59%).

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(1) Newman and Holmes, "Organic Syntheses," 2nd Coll. Vol., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 428.

(2) Fuson and Bull, *Chem. Revs.*, **15**, 275 (1934).

(3) Although Schmidt (*Arch. Pharm.*, **252**, 96 (1914)) reported that the interaction of propiophenone with alkaline hypiodite solution gives iodoform as one of the oxidation products, he did not report the isolation of any other compounds. In repeating his work, we have isolated benzoic acid as well as iodoform.

(4) Riessert, *Ber.*, **23**, 2244 (1890).

(5) Hartough and Conley, *THIS JOURNAL*, **69**, 3097 (1947).

(6) Heintzelmann, *Ann.*, **193**, 192 (1878).

Extrapolation of Conductance Data for Weak Electrolytes

BY RAYMOND M. FUOSS AND THEODORE SHEDLOVSKY

Unambiguous extrapolations of conductance data, in order to determine Λ_0 , the limiting conductance, and K , the dissociation constant for weak electrolytes, are possible in aqueous systems by synthesizing a hypothetical conductance curve for the completely dissociated portion of the weak electrolyte from conductance data on the corresponding strong electrolytes,¹ e.g.

$$\Lambda^*_{(\text{HAc})} = \Lambda(\text{HCl}) - \Lambda(\text{NaCl}) + \Lambda(\text{NaAc}) \quad (1)$$

in which the Λ values refer, of course, to the same ion concentration. The degree of dissociation is then given by Λ/Λ^* , since $\Lambda = 1000\kappa/c$ and $\Lambda^* = 1000\kappa/c_i$, κ being the specific conductance, c the equivalent electrolyte concentration, and c_i the corresponding free ion concentration.

In non-aqueous systems, where the dielectric constant of the solvent is about 40 or less, this procedure cannot be employed since no strong electrolytes exist in such solvents. It therefore becomes necessary to evaluate Λ_0 and K from the conductance data for the electrolyte itself. Two extrapolation methods have been proposed.

Fuoss and Kraus² wrote for 1-1 electrolytes

$$\Lambda = \gamma(\Lambda_0 - \alpha\sqrt{c}\gamma) \quad (2)$$

where γ is the degree of dissociation defined as the ratio of the concentration of free ions to the stoichiometric concentration c and α is the Onsager coefficient

$$\alpha = 8.2 \times 10^6 \Lambda_0 / (DT)^{3/2} + 82/\eta(DT)^{1/2} \quad (3)$$

where D is the dielectric constant, η the viscosity of the solvent, and T the absolute temperature. Equation (2) was solved for γ in terms of a function³ $F(z)$ where

$$z = \alpha\sqrt{c}\Lambda_0/\Lambda_0^{3/2} \quad (4)$$

and

$$\gamma = \Lambda/\Lambda_0 F(z) \quad (5)$$

Substituting Eq. (5) in the mass action equation and rearranging, one obtains

$$F/\Lambda = 1/\Lambda_0 + c\Lambda f^2/FK_F\Lambda_0^2 \quad (6)$$

where f is the activity coefficient which is computed from $(-\log f) = \beta\sqrt{c_i}$. A plot of F/Λ against $c\Lambda f^2/F$ is linear at low concentrations and extrapolates to the reciprocal of the limiting equivalent conductance, with slope $1/K_F\Lambda_0^2$.

Shedlovsky⁴ later proposed the equation

$$\Lambda = \Theta\Lambda_0 - \alpha(\Lambda/\Lambda_0)\sqrt{c\Theta} \quad (7)$$

where Θ is the degree of dissociation. Equation (7) is a quadratic in $\Theta^{1/2}$ and is therefore much simpler to solve than Eq. (2), which is a cubic in

(1) D. A. MacInnes, *THIS JOURNAL*, **48**, 2068 (1926); M. S. Sherrill and A. A. Noyes, *ibid.*, **48**, 1861 (1926); D. A. MacInnes and T. Shedlovsky, *ibid.*, **54**, 1430 (1932).

(2) R. M. Fuoss and C. A. Kraus, *ibid.*, **55**, 476 (1933).

(3) R. M. Fuoss, *ibid.*, **57**, 488 (1935).

(4) T. Shedlovsky, *Jour. Franklin Inst.*, **225**, 739 (1938).