Anderson,[9] to give more certain resolution of hydroxylysine from histidine.

(9) P. B. Hamilton and R. A. Anderson, *J. Biol. Chem.*, **211**, 95 (1954).

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The Stability of Metal Chelates of 5-Sulfo-anthranilic Acid

BY WILLIAM F. HARRIS AND THOMAS R. SWEET

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During an investigation of the analytical properties of derivatives of anthranilic acid, the stability constants of 5-sulfo-anthranilic acid with several transition metals were determined. The Bjerrum[1] titration method as modified by Calvin and Wilson[2] was adapted to the present work.

Experimental

Materials.—The 5-sulfo-anthranilic acid was prepared by a modification of the procedure suggested by Moser.[3] Thirty-four grams of anthranilic acid and 25 g. of sulfuric acid were thoroughly mixed in a beaker that was cooled in an ice-bath. The mixture was then ground in a mortar until it was a fine powder. The powder was heated in an oven at 150° for about 5 hours and was mixed. This was followed by heating at 180° for 9 hours. The product was crystallized 3 times from a 50% acetic acid solution, washed with acetone, and dried at 110°.

The metal solutions were prepared from the nitrate salts of the metals. The nickel, copper and zinc solutions were standardized by direct titration with a 0.015 *N* solution of disodium dihydrogen ethylenediaminetetraacetate. The cadmium and cobalt solutions were standardized by the addition of a known excess of a 0.015 *N* solution of disodium dihydrogen ethylenediaminetetraacetate and titration with a 0.015 *N* solution of zinc.

Procedure.—The titration vessel contained the metal ion in 100 ml. of aqueous solution. The 5-sulfo-anthranilic acid was added as a solid because it decomposed on standing in aqueous solution. The standard carbonate-free NaOH solution was added from a 10-ml. buret in which volume measurements could be estimated to within ±0.002 ml. After each addition of NaOH, the *p*H was measured with a Beckman model G *p*H meter that was standardized with Beckman buffer solutions at *p*H values of 4 and 7. During the titration the temperature was maintained at 35 ± 0.2°, carbon dioxide was excluded from the solution, and constant stirring was provided.

Calculation.—The calculations were made by adapting the method of Calvin–Bjerrum to the present situation.

H_2R represents the reagent, 5-sulfo-anthranilic acid

K represents the acid dissociation constant of the carboxyl group

T_M represents the total added metal concentration

T_{H_2R} represents the total added reagent concentration

From the equations for the conservation of species, charge balance and dissociation constant

$$T_M = [M^{++}] + [MR] + [MR_2^-]$$

$$T_{H_2R} = [HR^-] + [R^=] + 2[MR_2^-] + [MR]$$

$$[NO_3^-] = 2T_M$$

$$2T_{H_2R} + [OH^-] - [Na^+] = [H^+] + [HR^-]$$

$$K = [H^+][R^=]/[HR^-]$$

$$2[M^{++}] + [H^+] + [Na^+] = [NO_3^-] + 2[R^=] + [OH^-] + 2[MR_2^-] + [HR^-]$$

(1) J. Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941.

(2) M. Calvin and K. W. Wilson, THIS JOURNAL, **67**, 2003 (1945).

(3) E. Moser, U. S. Patent 2,353,351.

the following expressions for $\bar{n}$ and $R^=$ were obtained

$$\bar{n} = \left([H^+] + [Na^+] - T_{H_2R} - \frac{K}{[H^+]}(2T_{H_2R} - [Na^+] - [H^+])\right) \Big/ T_M$$

$$[R^=] = \frac{K}{[H^+]}(2T_{H_2R} - [Na^+] - [H^+])$$

The ionization of the sulfonic acid group was considered complete in all the calculations. Since a titration of the reagent with NaOH showed that the pK value of the protonated nitrogen is less than 2, a consideration of this ionization constant was omitted from the calculations. The treatment was further simplified by the fact that it was not necessary to add an excess of mineral acid to the solution prior to the titration.

Results and Discussion

The dissociation constant of 5-sulfo-anthranilic acid was found to be 2.00×10^{-5}. The chelate formation constants that were determined are given in Table I. The concentrations of metal salts and the concentrations of 5-sulfo-anthranilic acid in the table represent the total concentrations of each of these substances before the addition of NaOH.

TABLE I

CHELATE FORMATION CONSTANTS IN WATER AT 35°

Metal	Metal concn. $\times 10^3$ M	Reagent concn. $\times 10^3$ M	$k_1 \times 10^{-2}$	$k_2 \times 10^{-2}$	$K_{av} \times 10^{-2}$
Cu	1.01	6.84	2.45[a]	5.75	1.19[b]
	1.01	9.12	2.29[a]	5.75	1.15[b]
Zn	1.05	9.12	8.33	2.76	4.79
	1.05	13.68	7.58	2.28	4.16
Ni	1.02	6.84	7.58	2.24	4.12
	1.02	11.40	7.58	2.24	4.12
Cd	1.05	11.40	6.90	2.40	4.07
	1.05	13.68	7.09	2.51	4.22
Co	1.09	9.12	6.62	2.14	3.76
	1.09	11.40	6.62	2.14	3.76

[a] $k_1 \times 10^{-3}$. [b] $K_{av} \times 10^{-3}$.

The order of stability of the metals with 5-sulfo-anthranilic acid was found to be Cu, Zn, Ni, Cd and Co. This order agrees with that found for *o*-amino-phenol by Charles and Freiser,[4] with the exception that Cd was not included in their work and the positions of Zn and Ni were reversed. However, the values for the stability constants of these two metals are so nearly alike in the present work that their relative positions could have been reversed by experimental errors.

(4) R. C. Charles and H. Freiser, THIS JOURNAL, **74**, 1385 (1952).

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Benzoylations of 2-Methoxylepidine and 4-Methoxyquinaldine by Means of Potassium Amide

BY CHARLES R. HAUSER AND JAMES G. MURRAY[1]

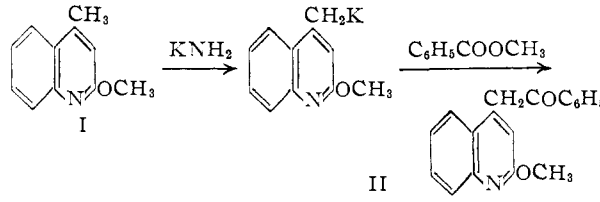
RECEIVED DECEMBER 23, 1954

Although 2-methoxyquinoline has been shown to react with potassium amide in liquid ammonia at room temperature to form 2-aminoquinoline,[2] it seemed possible to benzoylate the methyl group of 2-methoxylepidine (I) with methyl benzoate by

(1) Eli Lilly Fellow, 1952–1954.

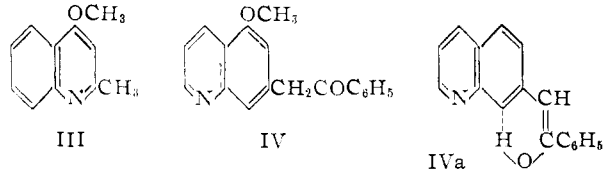
(2) F. W. Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

means of potassium amide without displacing the methoxy group to form II. This was accomplished employing essentially the conditions used previously with lepidine and quinaldine.[3]



I II

Similarly 4-methoxyquinaldine (III) was benzoylated to form IV. Whereas II is nearly colorless, IV is bright yellow. This suggests that the latter compound exists at least partly in the enol structure which would presumably be stabilized by hydrogen bonding (IVa). In agreement with this, the hydrochloride of IV is colorless. Levine[4] has proposed the corresponding structure for the copper chelate of 2-phenacylpyridine.



III IV IVa

The yields in these acylations were 37 and 48%, respectively, and are probably not the maximum obtainable. At least there was no indication that the methoxy group was displaced by the amide ion to form the corresponding amine under the conditions employed. Moreover, III was largely recovered after standing an hour with excess potassium amide in liquid ammonia. 4-Chloroquinaldine, on the other hand, produced tars under similar conditions.

Experimental[5]

2-Methoxy-4-phenacylquinoline (II).—2-Methoxylepidine[6] (I) (1.73 g., 0.01 mole) in dry ether was added to a solution of 0.026 mole of potassium amide in liquid ammonia prepared from 1.01 g. (0.026 mole) of potassium. Methyl benzoate (3.53 g., 0.026 mole) in ether was added, and the mixture stirred for an hour. After removing the ammonia on a water-bath, the resulting ether suspension was refluxed for 1 hour (5 hours refluxing did not improve the yield). Wet ether was added followed by water, and the ether layer extracted with 6 *N* hydrochloric acid. The acid solution, which sometimes contained a precipitate of the amine hydrochloride, was washed with ether, and then neutralized with sodium bicarbonate. The precipitated amine was extracted with ether. After drying, the ether was removed, and the residue recrystallized from ether yielding 0.82 g. of colorless needles of 2-methoxy-4-phenacylquinoline (II), m.p. 124–125.5°. More (0.20 g.) of this compound, m.p. 120–122°, was isolated from the filtrate; total yield 37%. A sample, recrystallized from ethanol, melted at 124.5–125.5°.

Anal. Calcd. for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.99; H, 5.60; N, 5.36.

2-Phenacyl-4-methoxyquinoline (IV).—4-Methoxyquinaldine[7] (III) was benzoylated as described above for 2-methoxylepidine. After the removal of the ammonia, the ether solution was refluxed for 6 hours, and the product recrystallized from ethanol giving 1.09 g. of bright yellow needles of 2-phenacyl-4-methoxyquinoline (IV), m.p. 129–131°. More (0.23 g.) of this product, m.p. 127–130°, was isolated from the filtrate; total yield 48%. A sample, recrystallized from ethanol, melted at 132–133°.

Anal. Calcd. for $C_{18}H_{15}O_2N$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.19; H, 5.24; N, 5.35.

The dinitrophenylhydrazone of IV (orange needles), recrystallized from ethanol, melted at 224°.

Anal. Calcd. for $C_{24}H_{19}N_5O_5$: N, 15.31. Found: N, 15.04.

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(3) M. J. Weiss and C. R. Hauser, THIS JOURNAL, **71**, 2023 (1949).

(4) N. N. Goldberg, L. B. Barkley and Robert Levine, *ibid.*, **73**, 4301 (1951).

(5) Melting points are uncorrected. Microanalyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(6) L. Knorr, *Ann.*, **236**, 100 (1886).

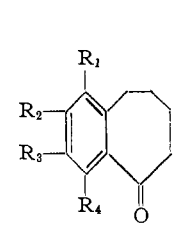
(7) M. Conrad and L. Limpach, *Ber.*, **20**, 954 (1887).

The Reaction of Hydrogen Bromide–Acetic Acid on *o*-Alkoxyacetophenones

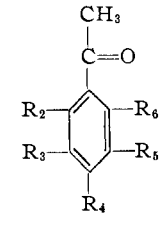
BY W. J. HORTON AND JACK T. SPENCE

RECEIVED DECEMBER 4, 1954

The cleavage of the 4-methoxy group of 2,3,4-trimethoxybenzosuberone[1] (Ia) in hydrogen bromide–acetic acid at room temperature has been extended to 1,4-dimethoxy- (Ib) and 1,2,3,4-tetramethoxybenzosuberone (Ic). Only Ic seemed to show the behavior of the original Ia. These exploratory experiments suggested that the adjacent 3-methoxy group in Ia and Ic was responsible for the high yield of cleavage product under these mild conditions.



Ia, R_2, R_3, R_4 = OCH_3
Ib, R_1, R_4 = OCH_3
Ic, R_1, R_2, R_3, R_4 = OCH_3
R otherwise = H



IIa, R_2, R_3 = OCH_3
IIb, R_2, R_3, R_4 = OCH_3
IIc, R_2, R_4, R_5 = OCH_3
IId, R_2, R_4, R_6 = OCH_3
IIe, R_2, R_4 = OCH_3
IIf, R_2, R_5 = OCH_3
IIg, R_3, R_4 = OCH_3
IIh, R_2 = OC_2H_5; R_3 = OCH_3
IIi, R_2 = OC_2H_5; R_3, R_4 = OCH_3

We have investigated this matter in the more easily available methoxy- and ethoxyacetophenones (Table I). Column 5 gives the yields of the corresponding 2-hydroxyacetophenones after 4.5 hours in *ca.* 6% hydrogen bromide–acetic acid at room temperature. Only those compounds (IIa, IIb, IIh, IIi) containing a *3-methoxy group* gave high yields. 2,4,6-Trimethoxyacetophenone (IId) apparently has the advantage of two methoxy groups *ortho* to the acetyl group. The case IIf indicates that a 5-methoxy (*para* to the cleavable group) is not as effective as the (*ortho*) 3-methoxy substituent. Hence the spacial position of the 3-methoxy group relative to the group cleaved, rather than an inductive effect due to salt formation, would seem to be responsible for the high rate of cleavage.

In columns 2 and 3, Table I, the yields of acetophenones from appropriate methoxybenzenes, ace-

(1) P. D. Gardner and W. J. Horton, *J. Org. Chem.*, **19**, 213 (1954).