2-Imino-3,3-diphenyl-5-methyltetrahydrofuran (XII) was obtained from the reaction of propylene oxide and diphenylacetonitrile.

A procedure for the preparation of diphenylacetonitrile through the bromination of benzyl cyanide followed by reaction with benzene and aluminum chloride is described.

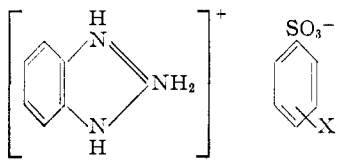
GLENOLDEN, PENNSYLVANIA RECEIVED MAY 15, 1947

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Sulfonate Salts of Substituted Benzimidazoles[1]

BY NELSON J. LEONARD, DAVID Y. CURTIN[2] AND KARL M. BECK

A generally satisfactory method for the preparation of "sulfa" drugs,[3] when applied to the synthesis of 2-sulfabenzimidazole, led to the formation of a product for which Price and Reitsema[4] have suggested a salt structure. 2-Aminobenzimidazole sulfanilate (I) has now been prepared by direct combination of 2-aminobenzimidazole and sulfanilic acid. This salt corresponds in physical properties to the "sulfabenzimidazole" of Raiziss, Clemence and Freifelder.

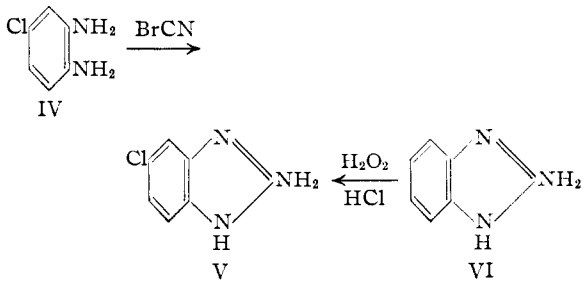


I X = *p*-NH_2
II X = *m*-NO_2
III X = *m*-NH_2

2-Aminobenzimidazole *m*-nitrobenzenesulfonate (II) and 2-aminobenzimidazole metanilate (III) have also been prepared by direct salt formation and have been shown to be identical with these sulfonate salts as obtained by Price and Reitsema by indirect methods. 2-Amino-5-chlorobenzimidazole *m*-nitrobenzenesulfonate has been formed by combination of *m*-nitrobenzenesulfonic acid with 2-amino-5-chlorobenzimidazole (V). Compound V has been shown to be the monochlorination product of 2-aminobenzimidazole and the condensation product of *p*-chloro-*o*-phenylenediamine with cyanogen bromide.

Salts of aromatic amines with *m*-nitrobenzenesulfonic acid were first made by Keyworth[5] for use as derivatives for the identification of certain amines. The salts were prepared by treating sodium or potassium *m*-nitrobenzenesulfonate with the arylamine hydrochloride in aqueous solution. The contrasting use of an organic base to isolate and identify arylsulfonic acids is illustrated by the reaction of S-benzylthiouronium chloride with sodium *m*-nitrobenzenesulfonate in aqueous solution.[6] Many other arylsulfonic acids have been used to identify amines and likewise have been identified by amines through salt formation. Occasionally amine arylsulfonates have been obtained in reactions from which one might be led to expect other products. Rouiller[7] obtained benzamidine benzenesulfonate when benzoic acid and benzenesulfonamide were heated at 225°. Clarke and Gillespie[8] obtained guanidine benzenesulfonate from guanidine carbonate and benzenesulfonyl chloride in aqueous potassium carbonate. Karrer and Epprecht[9] showed that guanidine *p*-nitrobenzenesulfonate was the product of the reaction of guanidine nitrate with *p*-nitrobenzenesulfonyl chloride in aqueous sodium hydroxide by its identity with the salt obtained directly from *p*-nitrobenzenesulfonic acid and guanidine carbonate. Guanidine *m*-nitrobenzenesulfonate was obtained by the same method.[4]

In the present investigation, 2-aminobenzimidazole sulfanilate (I), *m*-nitrobenzenesulfonate (II), and metanilate (III) have been prepared by combination of 2-aminobenzimidazole with the corresponding arylsulfonic acid in aqueous solution. The study initiated by Price and Reitsema on the condensation products of arylsulfonyl chlorides with 2-aminobenzimidazole in pyridine has been extended to chloro-substituted 2-aminobenzimidazole in order to determine the effect of rendering the ring-nitrogen less basic. The reaction of *p*-chloro-*o*-phenylenediamine (IV) with cyanogen bromide produced a compound which had the correct analysis for 2-amino-5-chlorobenzimidazole (V) and also for the substituted cyanamide in which the



IV V VI

(1) Presented before the Division of Organic Chemistry at the 111th meeting of the American Chemical Society, Atlantic City, New Jersey, April 16, 1947.

(2) Present address: Department of Chemistry, Columbia University, New York.

(3) Raiziss, Clemence and Freifelder, THIS JOURNAL, **63**, 2739 (1941).

(4) Price and Reitsema, *J. Org. Chem.*, **12**, 269 (1947).

(5) Keyworth, *J. Soc. Chem. Ind.*, **46**, 20T (1927).

(6) Donleavy, THIS JOURNAL, **58**, 1004 (1936); Chambers and Watt, *J. Org. Chem.*, **6**, 376 (1941).

(7) Rouiller, *Am. Chem. J.*, **47**, 475 (1912).

(8) Clarke and Gillespie, THIS JOURNAL, **54**, 1964 (1932).

(9) Karrer and Epprecht, *Helv. Chim. Acta*, **24**, 310 (1941).

TABLE I

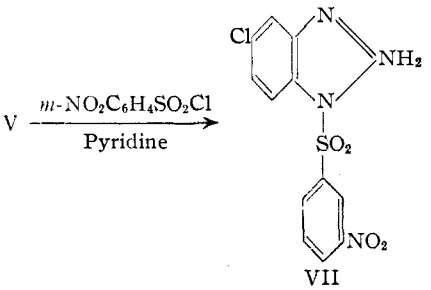
SULFONATE SALTS

Salt	M. p., °C.	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
2-Aminobenzimidazole sulfanilate (I)	223–224[a]	$C_{13}H_{14}N_4O_3S$[b]	50.94	50.90	4.61	4.57
2-Aminobenzimidazole *m*-nitrobenzenesulfonate (II)[c]	207–208	$C_{13}H_{12}N_4O_5S$	46.42	46.28	3.60	3.64
2-Aminobenzimidazole metanilate (III)	192–193[d]	$C_{13}H_{14}N_4O_3S$				
2-Amino-5-chlorobenzimidazole *m*-nitrobenzenesulfonate	167–171	$C_{13}H_{11}ClN_4O_5S$	42.11	42.13	2.99	2.93
2-Amino-4,6-dimethylpyrimidine di-*p*-nitrobenzenesulfonate	236–237	$C_{18}H_{19}N_5O_{10}S_2$	40.83	41.17	3.61	3.28

[a] Previously reported as 212°.[3] [b] Per cent. nitrogen; calcd. 18.29; found 18.40. [c] Crystallized in plates. [d] Erroneously reported[4] as 178–180°.

ring has not closed. Proof that ring closure had been effected was established by chlorination of 2-aminobenzimidazole (VI) with the formation of the identical product. The formation of V from the two sources likewise established the position of chlorine substitution in 2-aminobenzimidazole under the conditions employed.

When 2-amino-5-chlorobenzimidazole (V) was treated with *m*-nitrobenzenesulfonyl chloride in pyridine, 2-amino-5-chloro-1-(*m*-nitrobenzenesulfonyl)-benzimidazole (VII) was obtained. The assignment of structure is implicit in the observed insolubility of VII in alkali. Price and Reitsema showed that 2-amino-1-(*m*-nitrobenzenesulfonyl)-benzimidazole was formed from 2-aminobenzimidazole and *m*-nitrobenzenesulfonyl chloride by this method. The fact that both 2-aminobenzimidazole and 2-amino-5-chlorobenzimidazole undergo ring-nitrogen substitution indicates that the chlorine does not decrease the ring-nitrogen basicity sufficiently to encourage lateral-nitrogen substitution. When V was treated with *m*-nitrobenzenesulfonic acid in aqueous solution, 2-amino-5-chlorobenzimidazole *m*-nitrobenzenesulfonate was obtained.



VII

In an extension of the study of sulfonate salts to these of 2-aminopyrimidines, 2-amino-4,6-dimethylpyrimidine formed a di-*p*-nitrobenzenesulfonate salt but failed to yield a pure sulfanilate. The less basic 2-amino-5-bromo-4,6-dimethylpyrimidine[10] did not form a salt with *p*-nitrobenzenesulfonic acid.

Experimental[11]

Sulfonate Salts.—The salts listed in Table I were formed by combination of equimolar amounts of the base and the substituted benzenesulfonic acid in aqueous solution. Crystallization was induced by evaporation. Purification was effected by recrystallization from water. Unless otherwise indicated they crystallized as prisms.

Reaction of *p*-Chloro-*o*-phenylenediamine with Cyanogen Bromide.—Cyanogen bromide (35.5 g., 0.335 mole)[12] was added in small portions, with shaking, to a suspension of 56.3 g. (0.335 mole) of *p*-chloro-*o*-phenylenediamine in 400 ml. of water, following the directions for the preparation of 2-aminobenzimidazole.[13] The solution was filtered after standing overnight. Sodium hydroxide (13.4 g., 0.335 mole) in 30 ml. of water was then added and the solution was evaporated on a steam-bath. A dark oily layer separated on cooling and crystallized on standing. Recrystallization from water gave 41 g. (73%) of colorless needles, m. p. 167–168° (Compound A).

Anal. Calcd. for $C_7H_6ClN_3$: C, 50.16; H, 3.61; N, 25.07. Found: C, 50.06; H, 3.62; N, 25.13.

Since the analysis is correct for 2-amino-5-chlorobenzimidazole and also for the substituted cyanamide in which the ring has not closed, the properties of Compound A were carefully investigated. It was found to be soluble in dilute sodium hydroxide and in dilute hydrochloric acid. By contrast, 2-aminobenzimidazole is not appreciably soluble in dilute alkali. Compound A gave a red solid when it was diazotized and coupled with β-naphthol. 2-Aminobenzimidazole, under the same conditions, gave only tar. Compound A was recovered unchanged in at least 75% yield after refluxing with 6 *N* hydrochloric acid for one hour.

The **acetate** was prepared by dissolving 5.0 g. of A in 7 ml. of 5 *N* sodium hydroxide and making the solution acid with glacial acetic acid. The crude acetate (6.2 g.) thus obtained melted at 224–226°. The compound was purified for analysis by recrystallization from ethanol; m. p. 226–227°, with effervescence.

Anal. Calcd. for $C_7H_6ClN_3 \cdot C_2H_4O_2$: C, 47.47; H, 4.43; N, 18.45. Found: C, 47.81; H, 4.43; N, 18.75.

The **nitrate**, prepared in a similar manner, melted at 250° with sudden decomposition. Both nitrate and acetate could be reconverted to the free base, m. p. 168°, by warming in aqueous sodium bicarbonate solution.

Chlorination of 2-Aminobenzimidazole. 2-Amino-5-chlorobenzimidazole (V).—To 7.72 g. (0.058 mole) of 2-aminobenzimidazole dissolved in 50 ml. of water and 5 ml. of 12 *N* hydrochloric acid was added an additional 45 ml. of concentrated hydrochloric acid. The solution was stirred during the addition of 6 ml. of 30% hydrogen peroxide (sp. gr. 1.10) and for one-half hour following the addition. Evaporation to dryness on the steam-bath gave a brown solid. A solution of the solid in 50 ml. of water was made alkaline to litmus by the addition of 20 ml. of concentrated ammonium hydroxide. After the solution had been boiled and then cooled in an ice-bath, the solid which separated was collected by filtration and washed twice with water to remove ammonium chloride. The crude product (9.2 g., 95% yield) was recrystallized four times from water as colorless needles, m. p. 167–168°.

(10) Price, Leonard and Whittle, *J. Org. Chem.*, **10**, 327 (1945).

(11) The microanalyses were performed by Miss Theta Spoor. Melting points are uncorrected.

(12) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 150.

(13) Buttle, Dewing, Foster, Gray, Smith and Stephenson, *Biochem. J.*, **32**, 1101 (1938); British Patent 551,524.

The pure product gave no depression of melting point when mixed with Compound A. 2-Amino-5-chlorobenzimidazole is therefore the correct representation of the structure of the monochlorination product of 2-aminobenzimidazole and of the condensation product of *p*-chloro-*o*-phenylenediamine with cyanogen bromide.

2-Amino-5-chloro-1-(*m*-nitrobenzenesulfonyl)-benzimidazole (VII).—2-Amino-5-chlorobenzimidazole (28.5 g., 0.170 mole) and *m*-nitrobenzenesulfonyl chloride (39.0 g., 0.175 mole) were shaken overnight in 70 ml. of dry pyridine. The pasty mass was poured into 400 ml. of water, and 51.1 g. of yellow, alkali-insoluble solid was isolated following cooling, filtration and drying. The material was recrystallized from ethanol and methyl cellosolve repeatedly, with great loss. After seven recrystallizations, the platelets melted at 216–218°.

Anal. Calcd. for $C_{13}H_9ClN_4O_4S$: C, 44.29; H, 2.57. Found: C, 44.47; H, 2.70.

Summary

Some arylsulfonate salts of substituted benzimidazoles have been prepared by direct combination of the arylsulfonic acid and the amine.

2-Amino-5-chlorobenzimidazole has been identified as the monochlorination product of 2-aminobenzimidazole and the condensation product of *p*-chloro-*o*-phenylenediamine with cyanogen bromide.

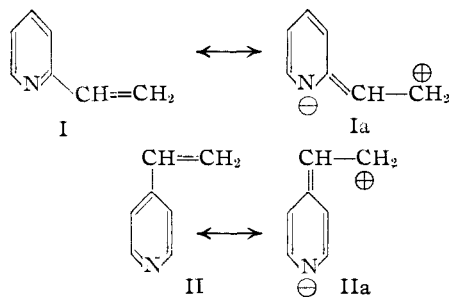
URBANA, ILLINOIS RECEIVED MAY 18, 1947

[CONTRIBUTION FROM CHANDLER LABORATORY, COLUMBIA UNIVERSITY]

Electrophilic Reactions of 2- and 4-Vinylpyridines

BY WILLIAM E. DOERING AND RUTH ALICE N. WEIL[1]

Theoretical consideration of the electronic interaction of the pyridine nucleus with a conjugated double bond leads to the conclusion that 2-vinylpyridine (I) and 4-vinylpyridine (II) should react with nucleophilic reagents more rapidly than 3-vinylpyridine (III). The electron deficiency imposed on the α- and γ-positions of pyridine by the electronegative nitrogen inhibits substitution by electrophilic reagents, facilitates reaction with nucleophilic reagents, and would be expected to extend electron deficiency to a double bond conjugated in the α- and γ-positions. Such resonance interaction is apparent in I and Ia, II and IIa, pertinent pairs of the six resonance



structures comprising I and II. Similar resonance interaction of the double bond in III is impossible, only slight activation comparable to that in styrene[2] and involving higher energy structures with carbon bearing a negative charge being possible.[3]

Accordingly the α- or γ-pyridyl group should be classed with the carbonyl, carboxyl, carbalkoxyl, cyano, nitro and sulfonyl groups among others which activate a conjugated double bond to attack by nucleophilic reagents.[4]

No example of the predicted reaction involving vinylpyridines has been found. However, it is apparent from Vorländer's failure to add sodiomalonic ester to benzalquinaldine[5] that he has tried to realize a similar reaction, a single example of which is reported in the reaction of phenylmagnesium bromide with benzalquinaldine to give 2-(β,β-diphenyl)-ethylquinoline (with structure unproved).[6]

Of the wide variety of nucleophilic reagents that react with carbonyl compounds and α,β-unsaturated carbonyl compounds[7] a representative group has been chosen to demonstrate the general validity of the predicted reactivity of I and II. The group of reagents which react to form carbon to carbon bonds is exemplified by sodiomalonic ester, sodioacetoacetic ester and hydrogen cyanide. Diethylamine and piperidine represent the class of reagents forming carbon–nitrogen bonds; sodium ethoxide furnishes an example of the formation of a carbon–oxygen bond; and finally, sodium bisulfite exemplifies the class of reactive nucleophilic reagents giving rise to carbon–sulfur bonds.

Sodiomalonic ester reacts with I to give diethyl β-(2-pyridyl)-ethylmalonate (IV) in moderate yield. The ester is hydrolyzed to β-(2-pyridyl)-ethylmalonic acid (V), which loses carbon dioxide on heating to give γ-(2-pyridyl)-butyric acid (VI).

(1) Submitted in partial fulfilment of the requirements for the Degree, Doctor of Philosophy, in the Department of Chemistry, Columbia University. Present address: Hickrill Chemical Research Foundation, Katonah, New York.

(2) Styrene does not react with sodiomalonic ester [Herrmann and Vorländer, *Chem. Zentr.*, **70**, I, 730 (1899)] nor with sodium bisulfite, a powerful electron donor [v. Miller, *Ann.*, **189**, 340 (1877)], although with peroxide catalysis a complicated reaction occurs [Kharasch, Schenck and Mayo, THIS JOURNAL, **61**, 3092 (1939)].

(3) In terms of the transition state theory, attack of a base at the end of the double bond in I and II leads to an activated state of lower energy, electronegative nitrogen bearing the negative charge, than is possible in similar intermediates derived from III or styrene in which carbon would bear a negative charge.

(4) Similar analysis of conjugated unsaturated quinolines, isoquinolines, acridines and other heterocycles of comparable electronic type leads to predictions analogous to those made for the vinylpyridines.

(5) Vorländer, *Ann.*, **320**, 66 (1902).

(6) Hoffmann, Farlow and Fuson, THIS JOURNAL, **55**, 2000 (1933).

(7) Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 1860.