[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J.]

A Facile Pyrimidine Ring Cleavage[1,2]

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The reaction of 4-mercapto-6,7-diphenylpteridine (I) with chloroacetic acid and potassium carbonate has been shown to give 2-amino-3-cyano-5,6-diphenylpyrazine (V) and thioglycolic acid. Under similar conditions, 4-mercaptopteridine (VIII) yields 2-amino-3-cyanopyrazine (IX), 4-mercaptopyrimido[4,5-d]pyrimidine (XV) yields 4-amino-5-cyanopyrimidine (XVI), 4-mercaptopyrido[2,3-d]pyrimidine (XVIII) yields 2-aminonicotinonitrile, and 4-mercaptopyrido[4,3-d]pyrimidine (XX) yields 4-aminonicotinonitrile. Similar results are obtained with methyl iodide and alkali. By contrast, 6-mercaptopurine, 6-mercapto-9-methylpurine and 4-mercaptopyrido[3,4-d]pyrimidine (XIX) give alkali-stable carboxymethylthio derivatives. Furthermore, it has been found that treatment of 4-mercapto-6-nitroquinazoline (XXII, R = -H) and 4-mercapto-8-nitroquinazoline (XXIII, R = -H) with chloroacetic acid and potassium carbonate yields 5-nitroanthranilonitrile and 3-nitroanthranilonitrile, respectively. No nitrile was obtained with 4-mercapto-7-nitroquinazoline under similar conditions. 4-Methylthio-5-nitroquinazoline was recovered unchanged under mild alkaline conditions which converted 4-methylthio-6-nitroquinazoline to 5-nitroanthranilonitrile. It is concluded that heterocyclic systems containing a fused 4-substituted pyrimidine ring undergo a base-catalyzed cleavage to an *o*-aminonitrile provided (a) that the anion formed by attack of base at C_2 of the fused pyrimidine ring be capable of stabilization by appropriate structural features in the remainder of the molecule, and (b) that the substituent group attached to C_4 be capable of departure with its bonding pair of electrons in an irreversible cleavage step. These results underscore a fundamental chemical difference between purines and pteridines.

The intermediacy of alkylthio substituents for reductive desulfurization and nucleophilic displacement reactions is well-known and well documented in heterocyclic chemistry. In the purine series, for example, 6-alkylthiopurines have often been used as intermediates for the synthesis of 6-substituted adenines (6-aminopurines),[4] and for the preparation of purine itself by reductive desulfurization.[5] The nature of the alkyl group does not appear to be particularly significant, but it has been reported[6] that 6-carboxymethylthiopurine may be converted to adenine derivatives with considerable ease. Because of the known lability of certain pteridines to ring cleavage with basic reagents[7,8] it was thought that the analogous 4-carboxymethylthiopteridine derivatives might undergo displacement reactions with amines under relatively mild conditions and thus minimize competing cleavage reactions. Furthermore, the ready hydrolytic cleavage of pteridine itself[7] by alkali raised the question of whether attempts to subject 4-mercapto- or 4-allylthiopteridines to Raney nickel desulfurization might not be vitiated by cleavage of the resulting pteridine by residual alkali in the Raney nickel. A 4-carboxymethylthio derivative would thus have been an attractive intermediate for desulfurization attempts in this series.

For these reasons, 4-mercapto-6,7-diphenylpteridine (I)[9] was treated with chloroacetic acid and sodium bicarbonate under conditions which were similar to those reported[6] to yield 6-carboxymethylthiopurine from 6-mercaptopurine. To our surprise, the only products isolated were a yellow solid, $C_{17}H_{12}N_4$, and thioglycolic acid. The yellow solid was conclusively shown to be 2-amino-3-cyano-5,6-diphenylpyrazine (V) by (a) conversion to 2-amino-5,6-diphenylpyrazine-3-carboxamide (VI) by treatment with alkaline hydrogen peroxide, (b) conversion to 2-amino-5,6-diphenylpyrazine-3-thiocarboxamide (VII) with hydrogen sulfide, and (c) examination of its infrared spectrum, which revealed the presence of a strong nitrile band. The reaction apparently proceeds by initial formation of the expected 4-carboxymethylthio-6,7-diphenylpteridine (II), which then adds hydroxide ion at C_2 to give a resonance-stabilized anion III. The ability of the pteridine ring to add anionic reagents is becoming well established[10,11] and reversible addition of hydroxide ion to the other C=N bonds of the pteridine nucleus undoubtedly takes place. However, only the anion formed by addition at C_2 is capable of undergoing an irreversible cleavage, and elimination of thioglycolic acid as shown (see following chart) leads to V *via* the alkali-labile 2-formyl derivative IV.

The facility with which this reaction takes place appears to be the result of two factors: (1) the ability of the bicyclic system to stabilize the intermediate anion III, and (2) the irreversible nature of the subsequent cleavage. Although it is possible that 6-carboxymethylthiopurine fails to undergo cleavage in basic solution because of preliminary anion formation through loss of the acidic 9-hydrogen, we have shown that 9-methyl-6-carboxymethylthiopurine is likewise stable to alkali. Clearly, the pyrimidine ring cleavage observed with the pteridines fails to take place with the purines because factor 1 is not operating. This ready hydrolytic pyrimidine ring cleavage thus emphasizes in a striking way a fundamental chemical difference between pteridines and purines. It is important to underscore this difference, for the pteridines and the purines are two closely related heterocyclic systems. They are, for example, biochemically interdependent, pteridines being required for purine biosynthesis and *vice versa;*

(1) This investigation was supported in part by a grant to Princeton University from the American Cancer Society.

(2) This paper is Part XXIII of a series dealing with pteridine chemistry; for the preceding paper, see W. Pfleiderer and E. C. Taylor, THIS JOURNAL, **82**, 3765 (1960).

(3) Parke, Davis and Co. Pre-doctoral Fellow in Chemistry, 1956-1957.

(4) See E. C. Taylor, O. Vogl and C. C. Cheng, THIS JOURNAL, **81**, 2442 (1959), for pertinent references.

(5) A. G. Beaman, *ibid.*, **76**, 5633 (1954).

(6) G. Huber, *Angew. Chem.*, **68**, 706 (1956).

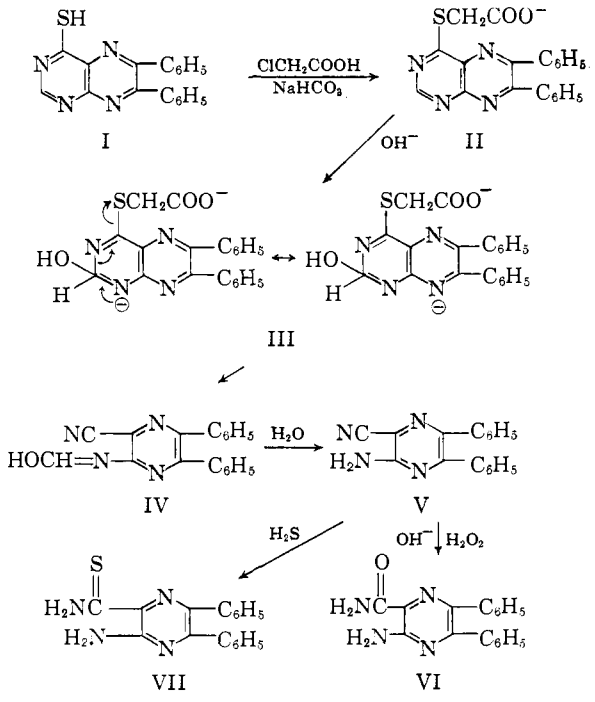
(7) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952).

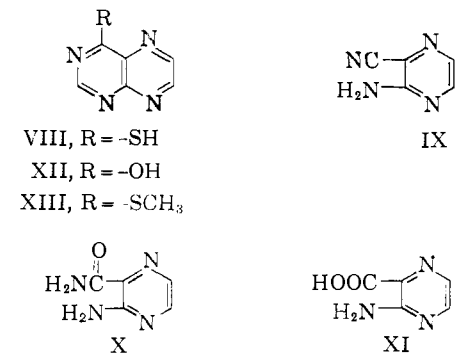
(8) E. C. Taylor in "The Chemistry and Biology of Pteridines," ed. by G. E. W. Wolstenholme and M. P. Cameron, J. and A. Churchill, Ltd., London, 1954, p. 2.

(9) E. C. Taylor, J. A. Carbon and D. R. Hoff, THIS JOURNAL, **75**, 1904 (1953).

(10) A. Albert, *J. Chem. Soc.*, 2690 (1955).

(11) D. J. Brown and S. F. Mason, *ibid.*, 3443 (1956).





both *in vitro* and *in vivo* conversion of purines into pteridines have been demonstrated, and both ring systems can be synthesized from common intermediates and, in many respects exhibit a common chemistry.[12] Recent emphasis on these relationships have tended to focus attention on the similarities of the two ring systems, but it is clear from the above reaction that this similarity is not profound.

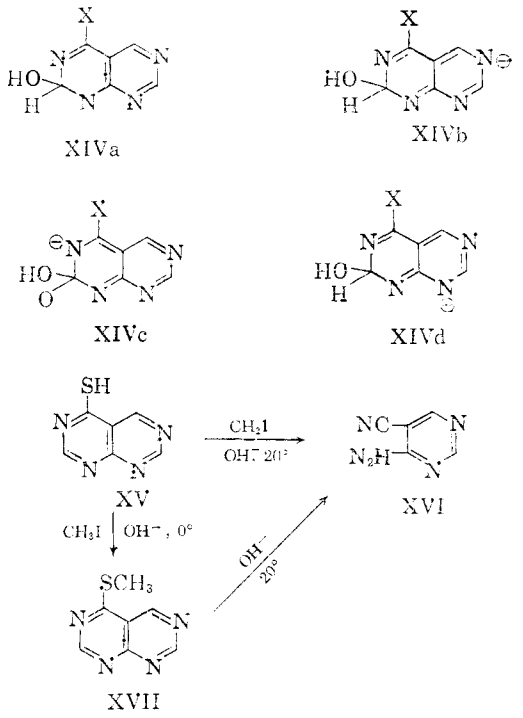
It was important to know whether the two phenyl groups present in I were responsible in any way for the remarkable facility of the cleavage reaction. We therefore prepared 4-mercaptopteridine (VIII) itself and subjected it to the action of chloroacetic acid and sodium carbonate. Under very mild conditions, the only product isolated, in addition to unchanged starting material, was 2-amino-3-cyanopyrazine (IX). Under more strenuous conditions, hydrolysis products of the rather soluble cyanopyrazine (IX) were formed (X-XII), and it was clear that the presence of the phenyl group in I, although playing no role in the cleavage reaction itself, decreased the water solubility of V sufficiently so that subsequent further hydrolysis was minimized.

If the interpretation of the course of the cleavage of I to V (*vide infra*), and of VIII to IX (*vide infra*), is correct, the only essential function of the chloroacetic acid is to convert the 4-mercapto group into an alkylthio substituent which can subsequently depart with its bonding electron pair in the cleavage step. This conclusion was confirmed by examination of the behavior of 4-methylthiopteridine (XIII, R = $-SCH_3$) toward dilute alkali. Depending upon the severity of the reaction conditions (see Experimental), varying amounts of 2-amino-3-cyanopyrazine (IX), 2-aminopyrazine-3-carboxamide (X), 2-aminopyrazine-3-carboxylic acid (XI) and 4-hydroxypteridine (XII) were formed. It is not clear whether X and XI arise by cleavage of XII or by subsequent hydrolysis of IX, for XII is known to be labile to base, and hydrolysis of IX to X under the reaction conditions was readily demonstrated. However, it is important to note that the formation of the aminonitrile IX occurs only in alkaline medium; hydrolysis of VIII in dilute acetic acid gave only 4-hydroxypteridine (XII), and VIII was recovered unchanged from boiling water.

On the basis of the above observations on the cleavage of 4-mercaptopteridines, and the contrasting stability to cleavage of the corresponding purines, one is led to the prediction that heterocyclic systems containing a fused 4-substituted pyrimidine ring may undergo base-catalyzed hydrolytic cleavage to an *o*-aminonitrile provided (a) that the anion formed by attack of hydroxide ion at C_2 be capable of stabilization by appropriate structural features in the remainder of the molecule, and (b) that the substituent in the 4-position be capable of ejection with its bonding pair of electrons. Confirmation of this generalization was provided as follows:

Consideration of the possible resonance contributors to the postulated anionic intermediate III reveals that no resonance form is possible in which the negative charge is localized on N_5. In the isomeric pyrimido[4,5-d]pyrimidine series, on the other hand, analogous resonance contributors (XIVa-d) can be written involving participation by each of the four heterocyclic nitrogen atoms, and one would thus predict that appropriate derivations of such a system should be even more labile to alkaline hydrolysis than the corresponding pteridine. This has been found to be the case. Not only is 4-mercaptopyrimido[4,5-d]pyrimidine (XV) rapidly converted to 4-amino-5-cyanopyrimidine (XVI) with chloroacetic acid and sodium bicarbonate, but treatment of XV with methyl iodide and sodium carbonate (following chart) for only a few minutes at room temperature also gave XVI as the sole product. The intermediate 4-methylthiopyrimido[4,5-d]pyrimidine (XVII) could be isolated by employing an equivalent amount of alkali and operating at 0°, but it was rapidly converted to XVI with sodium carbonate at 20° (following chart 9).

(12) For complete discussions of these points and for extensive bibliographies, see (a) "The Chemistry and Biology of Pteridines," ed. by G. E. W. Wolstenholme and M. P. Cameron, J. and A. Churchill, Ltd., London, 1954, and (b) "The Chemistry and Biology of Purines," ed. by G. E. W. Wolstenholme and C. M. O'Connor, J. and A. Churchill, Ltd., London, 1956.

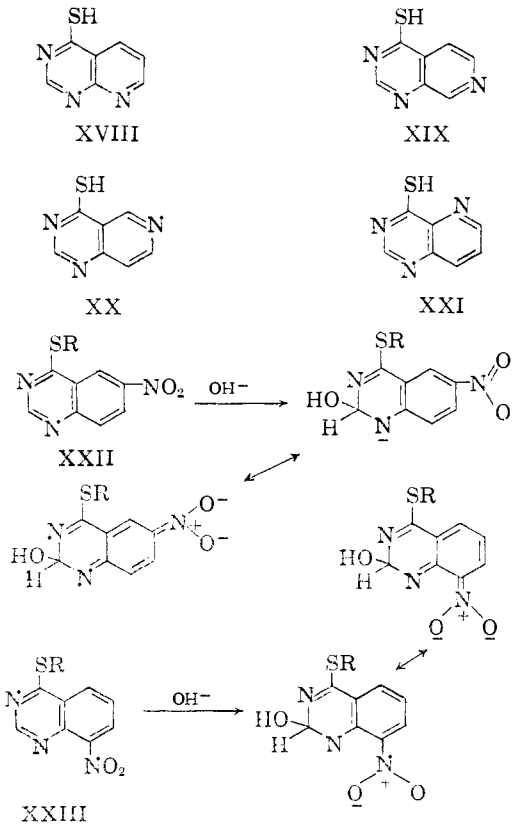


Furthermore, since N_5 of the pteridine ring cannot participate in localization of the negative charge in the anion III, the course of the reaction should not be changed if a molecule were constructed (*e.g.*, 4-mercaptopyrido[2,3-d]pyrimidine, XVIII) in which this hetero-nitrogen were omitted. Similarly, one would further predict that retention of the non-participating nitrogen in position 5 and elimination of the stabilizing nitrogen in position 8 (*e.g.*, 4-mercaptopyrido[3,2-d]pyrimidine, XXI) would result in stability toward ring cleavage. Using the same argument, one would further predict that 4-mercaptopyrido[4,3-d]pyrimidine (XX) should undergo cleavage with the same facility as 4-mercaptopteridine itself, and that the isomeric 4-mercaptopyrido[3,4-d]pyrimidine (XIX) should again be stable to cleavage.

Our results are completely in accord with these predictions. 4-Mercaptopyrido[2,3-d]pyrimidine (XVIII), prepared by the action of phosphorus pentasulfide in pyridine on 4-hydroxypyrido[2,3-d]-pyrimidine, was treated with chloroacetic acid and sodium carbonate to give a mixture of starting material, 2-aminonicotinonitrile, 2-aminonicotinamide and some 4-hydroxypyrido[2,3-d]pyrimidine. Similarly, 4-mercaptopyrido[4,3-d]pyrimidine (XX) under the same conditions gave starting material, 4-aminonicotinonitrile and some 4-hydroxypyrido[4,3-d]pyrimidine. By contrast, 4-mercaptopyrido[3,4-d]pyrimidine (XIX) yielded only the 4-carboxymethylthio derivative and a small amount of 4-hydroxypyrido[3,4-d]pyrimidine. Unfortunately, all attempts to prepare the fourth isomer, 4-mercaptopyrido[3,2-d]pyrimidine (XXI), were unsuccessful. Previous attempts to prepare 4-chloropyrido[3,2-d]pyrimidine were also reported to be unsuccessful.[13]

(13) C. C. Price and D. Y. Curtin, THIS JOURNAL, 68, 914 (1946).

The validity of the above arguments relating the stability of fused 4-substituted pyrimidine rings to (a) structural features capable of stabilizing the anion formed by attack of hydroxide ion at C_2 and (b) the ability of the 4-substituent to depart with its bonding pair of electrons in the irreversible cleavage step, has been further demonstrated by a study of the isomeric bz-nitro-4-mercaptoquinazolines. Since 4-mercaptoquinazoline itself is converted by chloroacetic acid and alkali to 4-carboxymethylthioquinazoline, which in turn is stable to base, any decrease in stability resulting from the introduction of a bz-nitro group may be attributed to factor a above. Here again, as with the isomeric pyridopyrimidines XVIII-XXI, in only two of the four isomers is the anionic intermediate capable of stabilization, in this instance by an appropriately situated nitro group. One would therefore predict that ring cleavage should be observed only with the 6- and 8-nitro isomers XXII and XXIII, respectively.

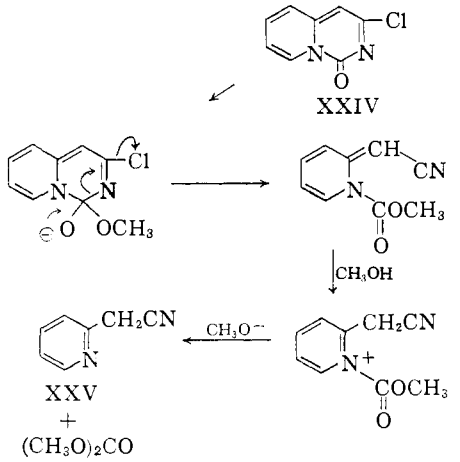


Once again, results are entirely in accord with prediction. 4-Mercapto-6-nitroquinazoline was prepared by thiation of 6-nitro-4-quinazolone; in agreement with observations in other series, we have found that pyridine is preferable to xylene as a solvent for the thiation. 4-Mercapto-7-nitro- and 4-mercapto-8-nitroquinazoline were similarly prepared from the corresponding bz-nitro-4-quinazolones. 4-Mercapto-5-nitroquinazoline, however, could not be prepared from 5-nitro-4-quinazolone in this manner because of its extreme sensitivity to base. It was successfully prepared by treatment of 4-chloro-5-nitroquinazoline with

potassium hydrosulfide, but attempted recrystallization yielded only an amorphous green solid. The crude product could, however, be successfully converted to 4-methylthio-5-nitroquinazoline, which was used as described below in the hydrolysis experiment.

Treatment of 4-mercapto-6-nitroquinazoline with chloroacetic acid and potassium carbonate yielded, as the only isolable product, 5-nitroanthranilonitrile. Similar treatment of 4-mercapto-8-nitroquinazoline gave 3-nitroanthranilonitrile, although in poor yield. Only amorphous material could be obtained from the reaction of 4-mercapto-7-nitroquinazoline with chloroacetic acid and potassium carbonate, but a careful examination of the infrared spectra of all solids recovered from the reaction mixture failed to reveal the presence of a nitrile group. Finally, although 4-mercapto-5-nitroquinazoline could not be investigated because of its instability, 4-methylthio-5-nitroquinazoline was recovered unchanged under conditions which converted 4-methylthio-6-nitroquinazoline to 5-nitroanthranilonitrile.

Considerable effort has been expended in recent years in the synthesis of potential antimetabolites of the naturally occurring purines and pteridines. For the most part, these hopeful synthetic forays into pharmaceutical chemistry have been guided by principles of structural analogy[14] which have been liberally interpreted and, *inter alia*, suggest by common usage that the replacement of an aromatic —CH= by a heterocyclic —N=, or *vice versa*, may lead to a structural analog of possible antimetabolic activity. The experiments outlined above indicate without question that a rearrangement of heteroatoms in any given heterocyclic system may result in compounds with vastly different chemical properties. In principle, of course, this has long been recognized, but in view of the extent of current efforts in this field, it seems advisable to re-emphasize this point.



The closest analogous pyrimidine ring cleavage to our knowledge is the conversion of 1*H*-3-chloro-4-phenylpyrido[1,2-c]pyrimidone-1 (XXIV) to phenyl-2-pyridylacetonitrile (XXV) with sodium methoxide in methanol.[15] This reaction differs from the cleavages discussed above in that a normal carbonyl group rather than an aromatic ring is the site of the initial nucleophilic attack and, as a consequence, the additional structural features required for stabilization of the anionic intermediate are not necessary. Both cleavages bear a formal similarity to the C–N bond scission commonly observed in the "abnormal" Beckmann rearrangement.

Experimental[16]

2-Amino-3-cyano-5,6-diphenylpyrazine (V). Method A.—A solution of 0.2 g. of 4-mercapto-6,7-diphenylpteridine[9] and 0.1 g. of chloroacetic acid in 15 ml. of 1 *N* sodium bicarbonate was heated under reflux for 30 minutes. The red color of the initial solution slowly lightened to yellow and a yellow solid started to separate as heating continued. The hot mixture was filtered and the collected solid was washed with water and dried; yield 0.12 g. (70%), m.p. 160–163°.

Anal. Calcd. for $C_{17}H_{12}N_4$: C, 75.0; H, 4.4; N, 20.6. Found: C, 74.7; H, 4.4; N, 20.5.

In a separate experiment, in which a little less than the theoretical amount of sodium carbonate had been added, addition of silver nitrate to the filtrate (after separation of 2-amino-3-cyano-5,6-diphenylpyrazine) resulted in the formation of the insoluble silver salt of thioglycolic acid, which was identified by comparison of its infrared spectrum with the spectrum of an authentic sample.

2-Amino-5,6-diphenylpyrazine-3-carboxamide (VI).—A mixture of 0.54 g. of 2-amino-3-cyano-5,6-diphenylpyrazine, 0.16 g. of sodium hydroxide and 2 ml. of 30% hydrogen peroxide in 25 ml. of 40% aqueous ethanol was heated under reflux for 3 hours, cooled and filtered to give 0.40 g. (70%) of fine yellow needles, m.p. 202–205°, identical in all respects with an authentic sample of 2-amino-5,6-diphenylpyrazine-3-carboxamide.[9]

2-Amino-5,6-diphenylpyrazine-3-thiocarboxamide (VII).—A slow stream of hydrogen sulfide was passed for 3 hours through a solution (maintained at 50–55°) of 1.4 g. of 2-amino-3-cyano-5,6-diphenylpyrazine in 100 ml. of 95% ethanol containing a few drops of triethanolamine. The reaction mixture was cooled and filtered and the collected yellow needles washed with cold ethanol; yield 1.3 g. (83%), m.p. 158–160°. The product was identical in all respects with an authentic sample of 2-amino-5,6-diphenylpyrazine-3-thiocarboxamide.

Action of Chloroacetic Acid and Sodium Carbonate on 4-Mercaptopteridine (VIII).—A solution of 0.5 g. of 4-mercaptopteridine,[17] 0.45 g. of chloroacetic acid and 0.81 g. of sodium carbonate in 30 ml. of water was heated under reflux for 6 minutes. During this time the initial light orange color changed to dark red. The hot reaction mixture was immediately chilled to 0° by immersion in an ice-bath. Filtration after 12 hours at 0° yielded 0.12 g. of colorless needles, m.p. 192°. Evaporation of the filtrate to dryness and sublimation of the residue at 185–190° (0.5 mm.) gave an additional 0.04 g. of 2-amino-3-cyanopyrazine as a colorless sublimate, m.p. 192°. The residue in the sublimation tube proved to be unchanged starting material. Comparison of the cleavage product with an authentic sample of 2-amino-3-cyanopyrazine[18] showed them to be identical.

Action of Sodium Bicarbonate on 4-Methylthiopteridine (XIII). Method A.—A mixture of 0.54 g. of 4-methylthiopteridine and 20 ml. of 1 *N* sodium bicarbonate was heated under reflux for 6 minutes and then filtered to remove a small amount of insoluble material. Paper chromatography showed that this solution contained 2-amino-3-cyanopyrazine, 2-aminopyrazine-3-carboxamide and 4-hydroxypteridine. It was evaporated to dryness and the residual solid sublimed at 150° (0.5 mm.) to give 0.20 g. of a colorless

(14) D. W. Woolley, "A Study of Antimetabolites," John Wiley and Sons, Inc., New York, N. Y., 1952.

(15) A. Hunger and K. Hoffmann, *Helv. Chim. Acta*, **40**, 1319 (1957).

(16) We are indebted for the microanalyses to Dr. Joseph F. Alicino, Metuchen, N. J., and to Drs. G. Weiler and F. R. Strauss, Oxford, England. All melting points are uncorrected.

(17) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(18) R. C. Ellingson, R. L. Henry and F. G. McDonald, THIS JOURNAL, **67**, 1711 (1945).

sublimate, m.p. 165–225°. Extraction of this solid with ether yielded an ether-insoluble solid which was recrystallized from water to give 0.07 g. of colorless needles, m.p. 235°, identical with an authentic sample of 2-aminopyrazine-3-carboxamide.[19] Evaporation of the ether extracts to dryness and recrystallization of the residue from water gave 0.09 g. of colorless needles, m.p. 188–190°, identical with an authentic sample of 2-amino-3-cyanopyrazine. Recrystallization of the sublimation residue from water yielded a small amount of 4-hydroxypteridine.

Method B.—Using milder conditions, a mixture of 0.18 g. of 4-methylthiopteridine and 10 ml. of 1 *N* sodium bicarbonate was heated under reflux for 2 minutes, filtered hot to remove a small amount of insoluble material and chilled to give 0.1 g. of unchanged 4-methylthiopteridine, m.p. 194°. Examination of the filtrate by paper chromatography showed the presence of 2-amino-3-cyanopyrazine, 2-aminopyrazine-3-carboxamide and 4-hydroxypteridine.

Method C.—A mixture of 0.16 g. of 4-methylthiopteridine and 10 ml. of 1 *N* sodium bicarbonate was heated under reflux for 45 minutes. The color of the solution changed from colorless to dark blue-gray to yellow. Paper chromatography showed the presence of 4-hydroxypteridine, 2-aminopyrazine-3-carboxylic acid and 2-aminopyrazine-3-carboxamide. The latter compound was readily isolated by evaporation of the reaction mixture to dryness and sublimation of the residue at 150° (0.5 mm.); yield 0.07 g., m.p. 230°.

Hydrolysis of 4-Methylthiopteridine (XIII) with Acetic Acid.—A mixture of 0.16 g. of 4-methylthiopteridine and 10 ml. of 1 *N* acetic acid was heated under reflux for 1 hour. Methylmercaptan was evolved and the color of the solution darkened to red-brown. The hot solution was treated with charcoal, filtered and the filtrate chilled to 0° to give 0.1 g. of 4-hydroxypteridine, identical with an authentic sample.[7] Paper chromatography of the filtrate showed that no other hydrolysis products had been formed.

4-Hydroxypyrimido(4,5-d)pyrimidine.—A mixture of 60 ml. of ethyl orthoformate, 60 ml. of acetic anhydride and 8.0 g. of 4-aminopyrimidine-5-carboxamide[20] was heated under reflux for 3 hours and then evaporated to approximately one-third of its volume under reduced pressure. Addition of 150 ml. of anhydrous ether resulted in the separation of a light yellow solid. The mixture was chilled at 0° for several hours and filtered to give 6.30 g. (73%), m.p. 246–251° dec. Recrystallization from water with the use of charcoal gave fine white needles, m.p. 253–255° dec.; $\lambda_{max}^{0.1\ N\ NaOH}$ 229, 310 mμ; log ε 3.99, 3.75; $\lambda_{max}^{0.1\ N\ HCl}$ 227, 285 mμ; log ε 3.82, 3.47.

This compound has been prepared previously by a similar method[21] but was described as "glittering, faintly cream-colored crystals decomposing over a range of 220–250°," with λ_{max}^{pH10} 231, 312 mμ; log ε 4.08, 3.81.

4-Mercaptopyrimido(4,5-d)pyrimidine (XV).—To an intimately powdered mixture of 3.70 g. of 4-hydroxypyrimido(4,5-d)pyrimidine and 5.55 g. of phosphorus pentasulfide was added 20 ml. of dry pyridine and the mixture was heated gently to boiling. The solids dissolved rapidly to give a deep red solution which was heated under reflux for 45 minutes. After standing for 15 minutes, the reaction solution was poured into a well-stirred mixture of 50 ml. of water and 50 g. of crushed ice. A bright orange solid separated immediately. After 30 minutes of stirring and 12 hours of standing at 0°, the mixture was filtered and the collected solid washed well with water and ethanol and dried to give 3.80 g. of crude 4-mercaptopyrimido(4,5-d)pyrimidine. A suitable solvent for recrystallization could not be found, but vacuum sublimation at 230° (0.1 mm.) afforded 2.05 g. (49%) of a bright yellow solid which had no definite melting point, but which darkened rapidly above 300°. Several additional vacuum sublimations in the same manner yielded the analytical sample.

Anal. Calcd. for $C_6H_6N_4S$: C, 43.9; H, 2.4; N, 34.1. Found: C, 44.0; H, 2.5; N, 34.0.

This compound has been incorrectly reported to melt at 260–275°dec.[21] This melting point was presumably taken on an impure sample of 4-mercaptopyrimido(4,5-d)pyrimidine which contained significant amounts of 4-aminopyrimidine-5-carboxamide (m.p. 257–259°) and/or 4-hydroxypyrimido(4,5-d)pyrimidine (m.p. 253–255°dec. pure, 220–250° dec. impure[21]).

4-Methylthiopyrimido(4,5-d)pyrimidine (XVII).—A well-stirred suspension of 0.66 g. of 4-mercaptopyrimido(4,5-d)-pyrimidine in 16 ml. of 1% sodium hydroxide was cooled to 0–5° in an ice-bath and treated with 0.20 ml. of methyl iodide. Stirring was continued for 1.5 hours and the mixture was filtered by gravity to remove a very small quantity of suspended solid. The clear filtrate was refrigerated overnight and the lustrous yellow plates which had separated were collected by filtration, washed with a small amount of cold ethanol and dried; yield 0.40 g. (56%), m.p. 154–157°. Sublimation at 130° (0.05 mm.) yielded colorless crystals, m.p. 159–160°.

Anal. Calcd. for $C_7H_6N_4S$: C, 47.2; H, 3.4. Found: C, 47.1; H, 3.2.

4-Amino-5-cyanopryimidine (XVI).—To a solution of 0.75 g. of sodium hydroxide in 12 ml. of water was added 0.70 g. of 4-mercaptopyrimido (4,5-d)-pyrimidine and the suspension was stirred at room temperature until solution was complete. To this solution was then added 1.0 g. of methyl iodide and stirring was continued for 2 hours. Chilling and filtering gave 0.25 g. (49%) of a colorless solid, m.p. 248–251°. Recrystallization from water yielded silky white needles, m.p. 250–252°, identical with an authentic sample of 4-amino-5-cyanopyrimidine.[22]

The same product was obtained in 82% yield when 4-methylthiopyrimido(4,5-d)pyrimidine was stirred at room temperature in dilute sodium hydroxide solution.

4-Mercaptopyrido(2,3-d)pyrimidine (XVIII) was prepared by the procedure described by Robins and Hitchings.[23]

4-Mercaptopyrido(3,4-d)pyrimidine (XIX).—A mixture of 10 g. of 4-hydroxypyrido(3,4-d)pyrimidine[24] and 59 g. of phosphorus pentasulfide in 250 ml. of dry pyridine was heated in an oil-bath under reflux for 2 hours and then evaporated to dryness under reduced pressure. To the residue was added 500 ml. of water and, after 12 hours, the resulting suspension was boiled for 20 minutes and filtered. The collected solid (10.5 g.) was dissolved in a mixture of 15 ml. of water and 20 ml. of concentrated ammonium hydroxide, charcoal added, filtered and the filtrate added dropwise to a boiling mixture of 300 ml. of water and 50 ml. of glacial acetic acid. The yellow precipitate which separated was collected by filtration, washed well with water and dried; yield 9.0 g. (81%), m.p. 325° dec. The analytical sample was prepared by recrystallization of 2 g. form 1 l. of ethanol.

Anal. Calcd. for $C_7H_5N_3S$: C, 51.5; H, 3.1; N, 25.8. Found: C, 52.0; H, 2.95; N, 25.5.

4-Methylthiopyrido(3,4-d)pyrimidine.—To a solution of 2.0 g. of 4-mercaptopyrido(3,4-d)pyrimidine in a mixture of 20 ml. of 1 *N* sodium hydroxide and 10 ml. of water was added 1.5 ml. of dimethyl sulfate, and the mixture was shaken for 5 minutes. Filtration gave 1.5 g. (69%) of colorless needles, m.p. 126–128°. Recrystallization from water then gave 1.2 g. of fine colorless needles, m.p. 132°.

Anal. Calcd. for $C_8H_7N_3S$: C, 54.2; H, 4.0; N, 23.7. Found: C, 54.2; H, 3.9; N, 23.7.

Ethyl **4-aminonicotinate** was prepared by a variation of the procedure given by Fox. A mixture of 36 g. of 4-aminonicotinic acid,[25] 500 ml. of absolute ethanol and 36 ml. of concentrated sulfuric acid was heated under reflux on a steam-bath for 70 hours. The ethanol was removed by distillation under reduced pressure and the residue was poured over ice. The resulting solution was neutralized with sodium carbonate, extracted several times with chloroform and the combined extracts dried over anhydrous sodium sulfate and evaporated to dryness to give 31 g. of crude ethyl 4-aminonicotinate, m.p. 100–105°. The reported[25] melting point for the pure material is 109–111°.

4-Hydroxypyrido(4,3-d)pyrimidine.—A mixture of 25 g. of crude ethyl 4-aminonicotinate and 50 ml. of formamide was heated in an oil-bath at 160° for 1 hour and then under reflux at 200–210° for 3 hours. Cooling and filtering gave 10 g. of a colorless solid, m.p. 280–285°; an additional 3.5

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g. of product, m.p. 280°, was obtained by chilling the filtrate for 2 days. The total yield was 13.5 g. (61%). Recrystallization from water gave 10.5 g. of colorless crystals, m.p. 293°.

Anal. Calcd. for $C_7H_5N_3O$: C, 57.1; H, 3.4; N, 28.6. Found: C, 57.1; H, 3.5; N, 28.2.

4-Mercaptopyrido(4,3-d)pyrimidine (XX) was prepared from 4-hydroxypyrido(4,3-d)pyrimidine by the method described above for 4-mercaptopyrido(3,4-d)pyrimidine. Recrystallization of the crude product from ethanol gave yellow crystals, m.p. 323–325° dec.

Anal. Calcd. for $C_7H_5N_3S$: C, 51.4; H, 3.1; N, 25.8. Found: C, 52.0; H, 3.3; N, 26.1.

Action of Chloroacetic Acid and Sodium Carbonate on 4-Mercaptopyrido(2,3-d)-pyrimidine (XVIII).—A mixture of 1 g. of 4-mercaptopyrido(2,3-d)pyrimidine, 0.9 g. of chloroacetic acid, 1.8 g. of sodium carbonate and 30 ml. of water was heated under reflux for 20 minutes. The clear solution was treated with charcoal, filtered and the filtrate chilled to give 0.15 g. of colorless crystals, m.p. 131°, identical with an authentic sample of 2-aminonicotinonitrile.[26] Evaporation of the filtrate to dryness and sublimation of the residue at 120° (0.5 mm.) gave an additional 0.05 g. of 2-aminonicotinonitrile, m.p. 131°. Raising the temperature of the sublimation furnace to 200° resulted in the subsequent sublimation of 0.1 g. of 2-aminonicotinamide, m.p. 199°, identical with an authentic sample.

Paper chromatography of the reaction mixture revealed the presence of unchanged starting material and 4-hydroxypyrido(2,3-d)pyrimidine in addition to the two cleavage products isolated.

Action of Chloroacetic Acid and Sodium Carbonate on 4-Mercaptopyrido-(3,4-d)pyrimidine (XIX).—A mixture of 1 g. of 4-mercaptopyrido(3,4-d)pyrimidine, 0.9 g. of chloroacetic acid, 1.8 g. of sodium carbonate and 30 ml. of water was heated under reflux for 20 minutes, treated with charcoal and filtered. Nothing separated from the filtrate on chilling. Addition of dilute hydrochloric acid to *p*H 2 and filtration then yielded 0.7 g. (52%) of light tan crystals, m.p. 220°dec. Recrystallization from water gave 0.6 g. of almost colorless needles, m.p. 221° dec.

Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.9; H, 3.2; N, 19.0. Found: C, 49.1; H, 3.2; N, 18.6.

Chilling of the filtrate for 4 days resulted in the further separation of 0.12 g. of a colorless solid, m.p. 305°, which was identical with an authentic sample of 4-hydroxypyrido-(3,4-d)pyrimidine.

Action of Chloroacetic Acid and Sodium Carbonate on 4-Mercaptopyrido(4,3-d)pyrimidine (XX).—A mixture of 1 g. of 4-mercaptopyrido(4,3-d)pyrimidine, 0.9 g. of chloroacetic acid, 1.8 g. of sodium carbonate and 30 ml. of water was heated under reflux for 20 minutes, treated with charcoal and filtered. Cooling and filtering gave 0.3 g. of 4-aminonicotinonitrile, m.p. 170°, which was readily purified by vacuum sublimation to give 0.25 g., m.p. 173°. An additional 0.2 g. of this material, m.p. 173°, was obtained by evaporation of the filtrate above to dryness and vacuum sublimation of the residue.

Anal. Calcd. for $C_6H_5N_3$: C, 60.5; H, 4.2; N, 35.3. Found: C, 60.9; H, 4.5; N, 35.0.

Examination of the reaction mixture by paper chromatography revealed the presence of unchanged starting material and 4-hydroxypyrido(4,3-d)pyrimidine in addition to 4-aminonicotinonitrile.

9-Methyl-6-carboxymethylthiopurine.—A suspension of 1.0 g. of 9-methyl-6-mercaptopurine[27] in 10 ml. of water containing 0.9 g. of chloroacetic acid and 1.8 g. of sodium carbonate was heated under reflux for 35 minutes. The resulting clear solution was cooled to room temperature and acidified with dilute hydrochloric acid until separation of a white, crystalline solid commenced. Chilling and filtering then gave 1.25 g. (93%) of colorless crystals, m.p. 216–219°. Recrystallization from boiling 30% aqueous ethanol raised the melting point to 225–226°.

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.9; H, 3.6; N, 25.0. Found: C, 42.95; H, 3.8; N, 24.8.

4-Mercapto-6-nitroquinazoline (XXII, R = -H).—A mixture of 1.0 g. of 6-nitro-4-quinazolone,[28] 1.5 g. of phosphorus pentasulfide and 15 ml. of dry pyridine was heated under reflux for 30 minutes, cooled and poured over crushed ice. After 2 hours of occasional stirring, the mixture was filtered and the collected solid was dissolved in dilute sodium hydroxide and the solution treated with charcoal. Acidification of the filtrate to *p*H 4 with acetic acid and chilling resulted in the separation of 0.93 g. of a yellow powder, m.p. 249–255°dec. Recrystallization from aqueous pyridine gave bright yellow needles, which became opaque on drying; yield 0.75 g. (69%), m.p. 261–263° dec.

Anal. Calcd. for $C_8H_5N_3O_2S$: C, 46.4; H, 2.4. Found: C, 46.2; H, 2.3.

4-Mercapto-7-nitroquinazoline was prepared in 67% yield from 7-nitro-4-quinazolone[28] by the procedure described above. Recrystallization from aqueous pyridine gave bright yellow needles, m.p. 270–271°dec.

Anal. Calcd. for $C_8H_5N_3O_2S$: C, 45.4; H, 2.4; N, 20.3; S, 15.5. Found: C, 45.9; H, 2.4; N, 20.7; S, 15.5.

4-Mercapto-8-nitroquinazoline (XXIII, R=-H) was prepared in 46% yield from 8-nitro-4-quinazolone[29] by the method described above. The product was obtained in the form of fibrous yellow needles, m.p. 266–267°dec., upon recrystallization from aqueous pyridine.

Anal. Calcd. for $C_8H_5N_3O_2S$: C, 45.4; H, 2.4; N, 20.3; S, 15.5. Found: C, 45.3; H, 2.6; N, 20.2; S, 15.3.

4-Chloro-5-nitroquinazoline.—An intimate mixture of 6 g. of 5-nitro-4-quinazolone[30] and 10.5 g. of phosphorus pentachloride was heated under reflux for 3 hours at 150°. The reaction mixture was then cooled, 150 ml. of petroleum ether (60–70°) added and the suspension chilled to 0° for 1 hour. Filtration yielded a tan solid which was added to a cold, stirred solution of dilute sodium hydroxide, ice and methylene chloride. After 10 minutes, the organic layer was drawn off, the aqueous layer extracted twice with methylene chloride, and the combined extracts dried and evaporated to dryness *in vacuo*. Sublimation of the residue at 130° (0.1 mm.) gave 4.7 g. (71%) of nearly colorless needles, m.p. 146–147°.

Anal. Calcd. for $C_8H_4N_3O_2Cl$: C, 45.8; H, 1.9; N, 20.1. Found: C, 45.5; H, 2.0; N, 20.7.

4-Methylthio-5-nitroquinazoline.—A solution of 1 g. of 4-chloro-5-nitroquinazoline in 20 ml. of purified dioxane was stirred at room temperature and treated with a solution of potassium hydrosulfide prepared by saturating a solution of 0.3 g. of potassium hydroxide in 20 ml. of absolute methanol with hydrogen sulfide. After 1 hour, 20 ml. of ether was added and the precipitated solid was collected by filtration and washed with a little dilute acetic acid. This crude product was added to a rapidly stirred mixture of 10 ml. of water, 0.25 g. of sodium hydroxide and 0.4 ml. of methyl iodide. Filtration after 20 minutes gave 0.55 g. (52%) of a tan solid, m.p. 130–135°. Two recrystallizations from petroleum ether (60–70°) gave pale yellow flakes, m.p. 146–147°.

Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.8; H, 3.2; N, 19.0. Found: C, 49.05; H, 3.3; N, 18.8.

This material appeared to be stable to mild alkali and could be recovered unchanged from a mixture of dilute potassium hydroxide and dioxane after several hours standing at room temperature.

4-Methylthio-6-nitroquinazoline (XXII, R=-CH_3).—A solution of 7.35 g. of 4-mercapto-6-nitroquinazoline, 400 ml. of water, 6.8 g. of potassium hydroxide and 8.4 g. of methyl iodide was stoppered and stirred at room temperature for 4 hours. Filtration then gave 7.2 g. (92%) of a light yellow solid, m.p. 160–162°. Recrystallization from absolute ethanol raised the melting point to 162–163°.

Anal. Calcd. for $C_9H_7N_3O_2S$: C, 48.9; H, 3.2. Found: C, 48.7; H, 3.2.

Action of Chloroacetic Acid and Potassium Carbonate on 4-Mercapto-6-nitroquinazoline.—A solution of 1 g. of 4-mercapto-6-nitroquinazoline, 2 g. of potassium carbonate and 0.5 g. of chloroacetic acid in 20 ml. of water was heated

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(27) We are indebted to Professor Roland K. Robins, Department of Chemistry, Arizona State University, for a generous gift of this material.

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under reflux for 30 minutes. During this time the original deep red color had changed to dark brown. Chilling to 0° and filtering gave 0.43 g. (55%) of 5-nitroanthranilonitrile, m.p. 208–210°. Sublimation at 140° (0.05 mm.) raised the melting point to 210–211°. The reported[31] melting point for this compound is 210°.

Action of Potassium Hydroxide on 4-Methylthio-6-nitroquinazoline.—A solution of 0.5 g. of 4-methylthio-6-nitroquinazoline, 1.24 g. of potassium hydroxide, 40 ml. of water and 60 ml. of purified dioxane was stirred at room temperature for 2 hours and then evaporated under reduced pressure to a small volume. Chilling and filtering gave a brown solid which was purified by sublimation at 140° (0.02 mm.) to give 0.032 g. (9%) of 5-nitroanthranilonitrile, m.p. 210°.

Action of Chloroacetic Acid and Potassium Carbonate on 4-Mercapto-8-nitroquinazoline.—Treatment of 1 g. of 4-mercapto-8-nitroquinazoline with chloroacetic acid and potassium carbonate as described above for the 6-nitro isomer gave 0.085 g. (11%) of 3-nitroanthranilonitrile in the form of yellow needles, m.p. 125–128°. Vacuum sublimation at 100° (0.01 mm.) raised the melting point to 137–138°.

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.5; H, 3.1; N, 25.8. Found: C, 51.6; H, 3.3; N, 26.15.

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[CONTRIBUTION FROM THE PIONEERING RESEARCH DIVISION OF THE QUARTERMASTER RESEARCH AND ENGINEERING CENTER, NATICK, MASS.]

Base Strengths of *p*-Substituted Benzalanilines[1]

BY JULIUS WEINSTEIN AND EDWARD MCININCH

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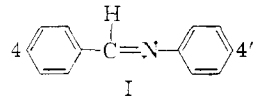
Using infrared absorbance measurements, values of K are determined at three temperatures for complex formation, through hydrogen bonding, between *p*-nitrophenol and three series of *p*-substituted benzalaniline derivatives. Values of $\Delta H°$ and $\Delta S°$ for the reaction are also calculated. For the series of compounds substituted in the aniline ring, log K values are linearly proportional to the Hammett σ-constants. For the compounds with a substituent in the benzaldehyde ring, a straight line is obtained when log K values are plotted against σ^+-constants. The correlation with σ^+-values suggests the stabilization of the hydrogen bond by resonance interaction with the *p*-substituent. In the case of the disubstituted compounds, the data are discussed in terms of an extended form of the Hammett equation.

Introduction

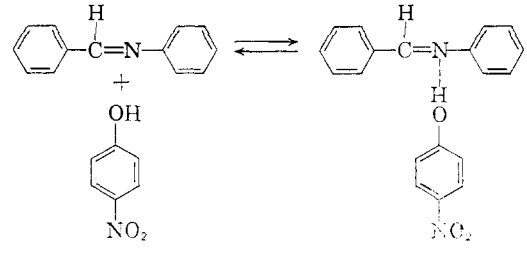
This investigation was undertaken in order to determine the effect of substituents on the base strengths of *p*-substituted benzalanilines (I).



I

Specifically, information was sought concerning the inductive and resonance effects of the substituents on the availability of the non-bonded electrons on the central nitrogen atom for hydrogen bond formation. Substituent effects may depend, for example, on whether the substituent is in the 4- or 4′-position, since structures involving resonance interaction with the nitrogen atom can be drawn with a negative charge on the nitrogen when the substituent is in the 4- but not the 4′-position.

Other workers[2–6] have shown that infrared absorption measurements of the stretching vibration band of the X-H group taking part in the intermolecular bond X—H---Y are suitable for detecting changes in the electron density at Y. Our study employed this means of detecting electron density changes at the nitrogen atom in the three series of compounds, 4- and 4′-monosubstituted and 4,4′-disubstituted benzalanilines. *p*-Nitrophenol served as the proton donor. The solvent was carbon tetrachloride. Formation of the O—H---N bond produced a decrease in the intensity of the free O-H infrared absorption band of the proton donor. Measurements of the absorbance of the free O-H band, therefore, permitted the calculation of K for the equilibrium



In addition, values of $\Delta H°$ and $\Delta S°$ for the reaction were calculated from the dependence of K upon the temperature.

Experimental

***p*-Substituted Benzalanilines.**—The compounds were prepared for the most part by heating together equimolar amounts of the appropriate benzaldehyde and aniline derivatives for 1 hour on a steam-bath. The procedure of Miller and Plöchl[7] was used to prepare N-benzylidine-*p*-nitroaniline. N-*p*-Chlorobenzylidine-*p*-chloroaniline was prepared by refluxing an ethanolic solution of equimolar quantities of the reactants for 1 hour. The product precipitated on cooling.

Compounds were purified by recrystallization from ethanol or another suitable solvent. The products were characterized by comparison of their melting points with reported values. Two new compounds were prepared, N-*p*-bromobenzilidineaniline (m.p. 72.5–73.0°: *Anal.* Calcd. for $C_{13}H_{10}NBr$: C, 60.02; H, 3.88; N, 5.38; Br, 30.72. Found: C, 59.90; H, 3.76; N, 5.33; Br, 30.56) and N-*p*-dimethylaminobenzilidine - *p* - chloroaniline (m.p. 149.5–150.5°: *Anal.* Calcd. for $C_{15}H_{15}N_2Cl$: C, 69.62; H, 5.84; N, 10.83; Cl, 13.70. Found: C, 69.42; H, 5.70; N, 10.78; Cl, 13.59).

Method and Calculations.—The concentration of *p*-nitrophenol in CCl_4 was always 0.001 M. The concentration of the benzalaniline derivative was usually 0.008 M. In

(1) Presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959.

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