chloride. The white crystalline solid was removed by filtration, washed with cold 70% acetone and dried, 53.2 g. (86% yield), m.p. 230°.

Anal. Calcd. for $C_{18}H_{30}ClNO$: Cl, 11.37. Found: Cl, 11.47, 11.30.

The free base was prepared by dissolving 42.0 g. of the hydrochloride in methanol and adding sodium bicarbonate. The white crystals which separated were recrystallized three times with 80% methanol and once from 80% ethanol, m.p. 69–70°.

Anal. Calcd. for $C_{18}H_{29}NO$: C, 78.49; H, 10.61. Found: C, 77.71; H, 10.63.

Reduction of N-(5-*t*-Butyl-2-hydroxy-3-methylbenzylidene)-cyclohexylamine (IVb).—Three grams of N-(5-*t*-butyl - 2 - hydroxy - 3 - methylbenzylidene) - cyclohexylamine (0.011 mole) in 75 ml. of dry ether was added dropwise with stirring to 0.41 g. of lithium aluminum hydride (0.044 equiv.) dissolved in 100 ml. of dry ether. After the reaction mixture was stirred for three hours and kept overnight at room temperature, the excess hydride was destroyed with water. The reaction mixture was poured into 15% hydrochloric acid at 2°. After adjusting the acidity of the aqueous layer to *p*H 6 with sodium bicarbonate, the ether layer was separated, washed with water and dried over sodium sulfate. The oil left after removing the ether was dissolved in 100 ml. of acetone. Addition of dry hydrogen chloride and cooling resulted in the precipitation of a hydrochloride (3.31 g., 97.4%).

Anal. Calcd. for $C_{18}H_{30}ClNO$: Cl, 11.37. Found: Cl, 11.33, 11.28.

After two recrystallizations from dilute ethanol the free base melted at 68.5–69° and did not depress the m.p. of 4-*t*-butyl-2-cyclohexylaminomethyl-6-methylphenol, prepared as described above.

Reduction of N-(5-*t*-Butyl-2-hydroxy-3-methylbenzylidene)-cyclohexylamine (IVb) in the Presence of *p*-Cresol Trimer.—N - (5 - *t* - Butyl - 2 - hydroxy - 3 - methylbenzylidene)-cyclohexylamine (2.50 g.) and 10.5 g. of 2,6-bis-(2-hydroxy-5-methylbenzyl)-4-methylphenol in 650 ml. of absolute ether was added with stirring to 2.50 g. of lithium aluminum hydride in 500 ml. of dry ether. After stirring six hours the reaction mixture was allowed to stand at room temperature overnight. The excess hydride was destroyed by the cautious addition of water and the resulting slurry was poured into 15% hydrochloric acid at 2°. After adjusting the *p*H to 6 with sodium bicarbonate the ether layer was removed, washed with water and dried over anhydrous sodium sulfate and then over anhydrous calcium sulfate. Dry hydrogen chloride was added and the solid removed by filtration, washed with ether and air-dried, 2.50 g., 88.5%.

Anal. Calcd. for $C_{18}H_{30}ClNO$: Cl, 11.37. Found: Cl, 11.32, 11.42.

The free base melted at 69–70°. The m.p. was not depressed by admixture with 4-*t*-butyl-2-cyclohexylaminomethyl-6-methylphenol.

Preparation of N-(5-*t*-Butyl-2-hydroxy-3-methylbenzylidene)-cyclohexylamine (IVb).—To 5.8 g. of 5-*t*-butyl-3-methylsalicylaldehyde (0.03 mole) in 35 ml. of dry benzene was added 3.0 g. of cyclohexylamine (0.03 mole) in 20 ml. of dry benzene. The solution was kept at room temperature for 15 hours. After removal of the benzene under reduced pressure the product was distilled. A yellow liquid (8.2 g.) boiling at 151–153° at 0.3 mm. was recovered. The infrared spectrum showed a prominent band at 6.10 μ.

Anal. Calcd. for $C_{18}H_{27}NO$: C, 79.07; H, 9.96. Found: C, 78.95; H, 9.88.

Preparation of N-(5-*t*-Butyl-2-hydroxy-3-methylbenzylidene)-aniline.—To 5.8 g. of 5-*t*-butyl-3-methylsalicylaldehyde (0.03 mole) in 40 ml. of dry benzene was added 3.1 g. of aniline (0.033 mole) in 40 ml. of dry benzene. The solution was heated at reflux for 30 minutes. After removal of the benzene under reduced pressure the bright orange oil was dissolved in 150 ml. of ether and the solution extracted three times with 75 ml. of saturated citric acid solution to remove the excess amine. After drying over sodium sulfate the ether was removed under reduced pressure and the material distilled at 140–143° at 0.45 mm. The resulting dark orange crystals (8.0 g.) melted at 60–61°. The product absorbed strongly at 6.17 μ.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92. Found: C, 80.55; H, 7.82.

Infrared Absorption Spectra.—A Perkin–Elmer model 21 spectrophotometer equipped with a sodium chloride prism was used.

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SALT LAKE CITY, UTAH

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

The Rearrangement of Isoquinoline-N-Oxides. II. Observations with N-Hydroxyisocarbostyrils and Other Substituted Derivatives[1]

BY MICHAEL M. ROBISON AND BONNIE L. ROBISON

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Rearrangement of 3-chloroisoquinoline-N-oxide with acetic anhydride produces mainly 3-chloro-4-acetoxyisoquinoline and very little 3-chloroisocarbostyril. Other oxides studied included derivatives of N-hydroxyisocarbostyril, which was synthesized by cyclization of *o*-carboxyphenylacetaldoxime. N-Tosyloxyisocarbostyril rearranges readily under various conditions at about 90° to yield mainly 4-substituted isocarbostyrils, though in one reaction in an aqueous medium substitution at the 3-position also was observed. The products and conditions of these transformations, together with observations on other substituted N-oxides, are considered in connection with possible mechanisms for the rearrangements.

Treatment of isoquinoline-N-oxide with refluxing acetic anhydride and hydrolysis of the resulting acetates produces isocarbostyril, the expected rearrangement product, in approximately 60% yield, along with 4-hydroxyisoquinoline in yields averaging 9%.[2] Similar results have been observed with 3-methylisoquinoline-N-oxide, and no products of substitution at the 3-position have been isolated from either reaction.[2] On treatment of isoquinoline-N-oxide with *p*-toluenesulfonyl chloride, however, substitution at the 4-position is predominant, only relatively small quantities of isocarbostyril being formed.[3] Several possible mechanisms have been considered for the rearrangement to the 4-position[2,3] but little evidence has been offered for any of them. In an effort to learn more about the detailed course of the transformation, the rearrangements of various substituted isoquinoline-N-oxides were investigated to determine the effects of substituent groups on the course of the reaction. Although the investigations have not provided any

(1) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

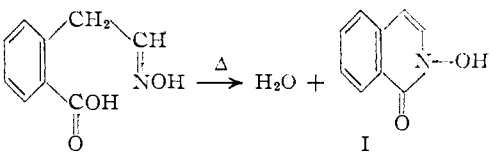
(2) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).

(3) E. Ochiai and M. Ikehara, *Pharm. Bull. Japan*, **3**, 454 (1955).

conclusive evidence as to the mechanism of the transformations, a number of the results are novel and unexpected. Indeed, the paths of rearrangement under various conditions and with different compounds are so diverse as to raise some question as to the applicability of one single mechanism-type to all cases.

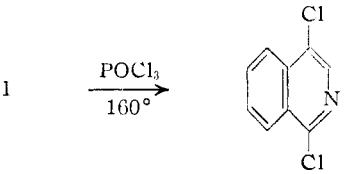
When 3-chloroisoquinoline-N-oxide was treated with refluxing acetic anhydride and the anhydride removed by vacuum distillation, there was left a mixture of products. Unlike isocarbostyril, 3-chloroisocarbostyril is soluble in aqueous sodium hydroxide,[4] and since the other expected product, 3-chloro-4-hydroxyisoquinoline, is also soluble in strong base, the easy chemical separation of products employed in the isoquinoline-N-oxide rearrangement[2] was not applicable. Further, attempts to hydrolyze the crude residues from the anhydride distillations with either acid or base led to considerable decomposition with the formation of highly colored, polymeric products. The most successful, though still unsatisfactory, method of separation depended on the crystallization of the predominant product, 3-chloro-4-acetoxyisoquinoline, from the residual oil. The crude material separated in 61% yield. Saponification of the purified acetate afforded 3-chloro-4-hydroxyisoquinoline, which was identified by analysis and by hydrogenolysis to 4-hydroxyisoquinoline. After crystallization of the acetate, the residual oils deposited 3-chloroisocarbostyril on prolonged standing. This was identified by mixture-melting point with an authentic sample prepared by the method of Gabriel.[4] The yield was only about 1%, and none of the extremely easily hydrolyzed acetyl derivative was isolated from the mixture. The remainder of the reaction product was an intractable mixture from which several minor products were obtained, but in insufficient quantity for identification.

Early attempts to prepare N-hydroxyisocarbostyril (I) involved the attempted oxidation of 1-methoxyisoquinoline, which was prepared by reaction of 1-chloroisoquinoline with sodium methoxide. The only identifiable product obtained from the oxidation was phthalimide. The desired cyclic hydroxamic acid was easily obtained, however, from the known[5] *o*-carboxyphenylacetaldehyde, whose oxime undergoes cyclization to the desired product on heating to 130°. Evidence for the constitution of the product, which is acidic and whose alcohol solution assumes a deep magenta color on treatment with ferric chloride, included its reduction to isocarbostyril by phosphorus and iodine.[6] The substance is formulated as N-hydroxyisocarbostyril, rather than 1-hydroxyisoquinoline-N-oxide, by analogy to the case of N-hydroxy-2-pyridone[6] and on the basis of a carbonyl absorption band at 1630 cm.$^{-1}$ in the infrared. This absorption is in the general region characteristic for other isocarbostyril derivatives.[2] It is probable that Gottlieb[7] has prepared the corresponding 3-methyl homolog by a similar cyclization, though this author described the product only as the "anhydro derivative" of *o*-carboxybenzyl methyl ketoxime and mentioned neither its acidity nor any other properties which make possible a clear decision as to its constitution.



I

The oxide was found to undergo rearrangement to 4-substituted isoquinolines under a variety of conditions. When it was heated with phosphorus oxychloride at 160°, 1,4-dichloroisoquinoline[8] was obtained in 43% yield, while a reaction at 107° left one-half of the starting material unchanged, although no other pure substance could be isolated.

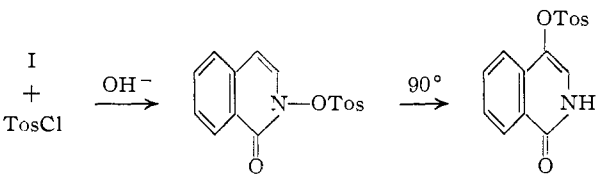


Treatment of the amine oxide with benzoyl chloride and aqueous sodium carbonate at room temperature produced N-benzoxyisocarbostyril in high yield. This ester reverted to N-hydroxyisocarbostyril on saponification. When the hydroxy compound was heated with benzoyl chloride at 180°, only the ester was isolated, though in considerably lower yield, and no other pure compounds were detected in the mixture. Further, when the ester was heated alone to 180°, some decomposition occurred, but 62% of the starting material and, after saponification, 59% of the theoretical N-hydroxyisocarbostyril could be recovered.

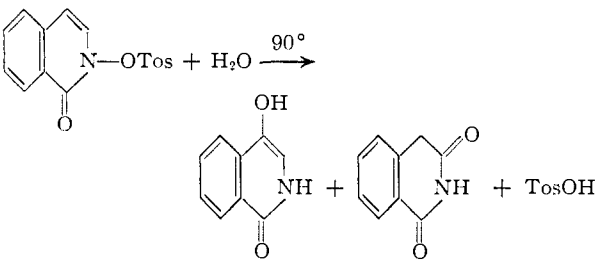
Reaction of the cyclic hydroxamic acid with *p*-toluenesulfonyl chloride under Schotten–Baumann conditions yielded N-tosyloxyisocarbostyril. This derivative also could be saponified to re-form N-hydroxyisocarbostyril. Of the several derivatives of the oxide studied, the tosylate was found to undergo the most facile rearrangements. Thus when it was heated to 90° it rearranged to the known[3] 4-tosyloxyisocarbostyril in high yield. The latter substance was prepared for comparison by treatment of 4-hydroxyisocarbostyril[8] with *p*-toluenesulfonyl chloride. Since the rearrangement of the dry tosylate on heating in large quantities was highly exothermic and vigorous, several reactions were conducted in inert solvents. When the intermediate was heated in toluene for 1 hour at 90°, 72% of the starting material could be recovered in a relatively pure state, and the rearrangement product was produced only to the extent of 18%. When the substance was heated under identical conditions in the more polar nitromethane, however, a 91% yield of fairly pure 4-tosyloxyisocarbostyril was obtained. It also was found that the 4-tosyloxy compound could be obtained directly from N-hydroxyisocarbostyril either by heating with *p*-toluenesulfonyl chloride alone at 95° or

(4) S. Gabriel, *Ber.*, **19**, 2354 (1886).
(5) C. Schöpf and R. Kühne, *Chem. Ber.*, **83**, 390 (1950).
(6) E. Shaw, THIS JOURNAL, **71**, 67 (1949).
(7) J. Gottlieb, *Ber.*, **32**, 958 (1899).
(8) S. Gabriel and J. Colman, *ibid.*, **33**, 980 (1900).

by heating with excess tosyl chloride and aqueous sodium carbonate on the steam-bath.



The above experiments in the different solvents suggested an acceleration of the rearrangement in more polar media, and several experiments were carried out with a 2:1 acetonitrile–water solvent, under the same conditions. By titration with base it was shown that at least 96% of the theoretical *p*-toluenesulfonic acid was liberated in this reaction, and the resulting dihydroxyisoquinoline, which contained little or no N-hydroxyisocarbostyril as shown by a negative ferric chloride test, was obtained in 88% yield. This product gave negative qualitative tests for sulfur.[9] The formation of the dihydroxyisoquinoline, which was originally thought to be pure 4-hydroxyisocarbostryil, did not involve 4-tosyloxyisocarbostyril as an intermediate, for that material is stable to the reaction conditions. When it was heated in acetonitrile–water containing approximately one-third of an equivalent of hydrochloric acid, it was recovered virtually quantitatively. For identification, however, it was necessary to convert the dihydroxy compound to a derivative, for 4-hydroxyisocarbostyril has an indefinite melting point above 250°.[8] Initially an attempt was made to convert the product to 1-chloro-4-hydroxyisoquinoline by reaction with phosphorus oxychloride. The monochloro compound is the chief product of the reaction by Gabriel's method.[8] The substance was obtained, in low yield, but in addition a steam-volatile material was isolated which was not the expected 1,4-dichloroisoquinoline. This second product, although impure, was later found to be mainly 1,3-dichloroisoquinoline. The hydroxyisocarbostyril was treated, in another experiment, with phenylphosphonic dichloride, a reagent whose action in chlorodehydroxylation reactions is similar to that of phosphorus oxychloride, but which is considerably more convenient because of its higher boiling point.[10] From this reaction 1-chloro-4-hydroxyisoquinoline again was obtained, in 23% yield, but 1,3-dichloroisoquinoline was the only steam-volatile product. Its identity was demonstrated by mixture-melting point with an authentic sample of the material and by the complete identity of the infrared spectra of samples prepared as above and by the usual procedure.[4] No method was found to separate the crude dihydroxy product into its supposed two components, for 4-hydroxyisocarbostyril and homophthalimide have the same solubilities and are both sufficiently volatile to be sublimed. Since the yield of 1,3-dichloroisoquinoline was only 9% from the mixture of dihydroxy compounds, the over-all recovery was unsatisfactory. In experiments with phenylphosphonic dichloride,[10] homophthalimide has been converted to the 1,3-dichloro compound in 88% yield under these conditions, while from 4-hydroxyisocarbostyril only a 33% yield of 1-chloro-4-hydroxyisoquinoline has been obtained, this unaccompanied by any of the 1,4-dichloro compound. However, *no* rearrangement to 1,3-dichloroisoquinoline has been observed in the reaction with 4-hydroxyisocarbostyril. Thus, al-



though the mode of analysis of the crude rearrangement product was far from satisfactory, it may be inferred that it contained a larger proportion of 4-hydroxyisocarbostyril than of homophthalimide.

The migration of the tosyloxy group to the 4-position could be formulated as a "quasi-six-membered-ring" mechanism, and examination of Fisher–Hirschfelder models indicates that the steric requirements of such a reaction could be met. The apparent marked influence of the solvent, however, would appear to militate against such a process,[11] and the ready substitution of the hydroxyl group at the 4-position when the reaction is run in an aqueous medium indicates that this is at least not the exclusive mode of rearrangement. No matter how the substitution at the 4-position may be formulated, however, no simple, satisfactory mechanism for substitution at the 3-position is obvious. It is apparent that considerably more information is required for profitable speculation on the exact courses of these diverse rearrangements.

Two 4-substituted isoquinoline-N-oxides were also included in this study. 4-Chloroisoquinoline was prepared by the reaction of 4-hydroxyisoquinoline with phosphorus oxychloride, and was converted to the oxide in the usual manner. On attempted rearrangement with acetic anhydride, however, intractable tars were formed and no identifiable products were isolated. A similar situation obtained on attempted rearrangement of 4-methylisoquinoline-N-oxide. In this case too it was not possible to separate any discrete chemical individuals from the very forbidding polymeric mass which was produced. Such results are not uncommon in these acetic anhydride rearrangements and even in such cases as isoquinoline-N-oxide itself, where the yield of mixed products is relatively high, the pure compounds are always accompanied by much colored, resinous material. Because of the particularly discouraging nature of the products in these two cases, work thereon was discontinued.

(9) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 53.

(10) M. M. Robison, results to be published.

(11) *Cf.* J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 453.

Experimental[12,13]

3-Chloroisoquinoline-N-oxide.—In early experiments the oxidation of 3-chloroisoquinoline[14] was attempted using acetic acid and 30% hydrogen peroxide as with other members of this series.[2] It was found, however, that by this method yields were low and considerable starting material was recovered. More effectively a mixture of 9.58 g. of 3-chloroisoquinoline and 17.6 g. of 40% peracetic acid[15] was warmed to 50° over a 45-minute period. At the initial stages the exothermic reaction required occasional moderation by cooling. After the orange-brown mixture had been maintained at 50° for 23 hours, it was evaporated to dryness *in vacuo*, water was added, the evaporation was repeated and 150 ml. of chloroform was added to the residue. Solid potassium carbonate and sufficient water to form a thick paste were added and the mixture was kept for 45 minutes, after which the chloroform layer was separated, dried over potassium carbonate and evaporated. Trituration of the residue with low-boiling petroleum ether and evaporation allowed recovery of 5.5% of the starting material. The oxide, after one recrystallization from ethyl acetate (Darco) and drying at 110° (20 mm.), weighed 5.53 g. (53%). The melting point was 152–155°. The analytical sample was recrystallized from water, from ethyl acetate and from benzene–cyclohexane as white needles, m.p. 153.5–155.5°.

Anal. Calcd. for C_9H_6NOCl: C, 60.18; H, 3.37. Found: C, 60.57; H, 3.01.

Rearrangement of 3-Chloroisoquinoline-N-oxide.—A mixture of 3.06 g. of the oxide and 29 ml. of acetic anhydride was heated to the reflux temperature over a 50-minute period and maintained at this temperature for 5 hours. The acetic anhydride was evaporated *in vacuo* and the dark-brown oil was allowed to crystallize as completely as possible at low temperature. A 61% yield of crude 3-chloro-4-acetoxyisoquinoline, m.p. 103–112°, was separated from the oil by filtration and washing with a minimum quantity of ether. On some occasions 3-chloroisocarbostyril also crystallized at this stage, but since the acetate is very much more soluble in ether, a separation could be effected. Recrystallization of the ester from benzene–cyclohexane (Darco) produced pale-yellow plates, m.p. 111–115°, in 49% yield. The analytical sample was obtained in the form of colorless needles, m.p. 113.5–114.5°.

Anal. Calcd. for $C_{11}H_8NO_2Cl$: N, 6.32. Found: N, 6.31.

The infrared spectrum showed a >C=O absorption at 1760 cm.$^{-1}$ and a —C(|)—O— band at 1200 cm.$^{-1}$. In addition, the characteristic[2] bands apparently due to ring absorptions were found at 1625 and 1580 cm.$^{-1}$.

When 1.24 g. of the 4-acetate was heated 1 hour on the steam-bath with 15 ml. of 5% sodium hydroxide and the mixture acidified with acetic acid, 3-chloro-4-hydroxyisoquinoline was obtained. After one recrystallization from benzene (Darco) this melted at 168–169.5° dec. and weighed 0.78 g. (77%). The analytical sample was recrystallized from benzene–cyclohexane and from ethanol–water and sublimed at 100° (0.2 mm.). The colorless needles melted at 168.5–169.5° dec.

Anal. Calcd. for C_9H_6NOCl: C, 60.18; H, 3.37; N, 7.80. Found: C, 60.59; H, 3.52; N, 7.81.

The oily filtrate from the 3-chloro-4-acetoxyisoquinoline on further standing at low temperature deposited 3-chloroisocarbostyril, usually in several batches. From the various reactions the yields seldom exceeded 1%. Typically, the material was separated by filtration, washed with ether and recrystallized from ethanol–water and from benzene–cyclohexane. The small, white needles had m.p. 219–220.5° dec., undepressed on admixture with authentic 3-chloroisocarbostyril.[4]

Although no two rearrangement mixtures behaved exactly the same in all respects, in most cases two other solids crystallized from the residual oils at some stage. One of these was a pale-yellow solid, which after recrystallizations from ethyl acetate and from benzene–cyclohexane had m.p. 244–244.5°. The analysis of the apparently pure white material, however, corresponded to no simple empirical formula. The chlorine-containing compound showed strong absorption in the infrared at 1670 cm.$^{-1}$, indicating the probable presence of an isocarbostyril grouping. A second solid was obtained by dissolving the final residual oil in a minimum quantity of hot cyclohexane and allowing crystallization to proceed. This base-insoluble substance was obtained in insufficient quantity for preparation of an analytical sample, but after some purification it had m.p. 100.5–101.5°, indicating that it was not the acetyl derivative of 3-chloroisocarbostyril (*vide infra*).

N-Acetyl-3-chloroisocarbostyril.—It was originally thought that the low-melting unknown might be the acetyl derivative of 3-chloroisocarbostyril, and this was accordingly prepared for comparison. The compound, which is hydrolyzed with exceptional ease, was synthesized by heating a mixture of 0.4 g. of the chloroisocarbostyril with 3.3 ml. of acetic anhydride under reflux for 7 hours, evaporating to dryness *in vacuo* and drying. Recrystallization from dry, low-boiling petroleum ether separated 33% of the insoluble starting material and afforded a 41% yield of acetyl derivative, m.p. 78.5–82°. The analytical sample, prepared by further recrystallizations from the same solvent, was obtained as white needles, m.p. 80–81°.

Anal. Calcd. for $C_{11}H_8NO_2Cl$: N, 6.32. Found: N, 6.45.

Acetylation of isocarbostyril produces N-acetylisocarbostyril, rather than 1-acetoxyisoquinoline.[2] The infrared spectrum of the above product indicated that it too is probably the N-acetyl derivative. Thus a band ascribable to the ring >C=O was found in normal position at 1670 cm.$^{-1}$ and was accompanied by another absorption at 1760 cm.$^{-1}$, attributable to the acetyl carbonyl. Although the latter band was found at a higher frequency than in N-acetylisocarbostyril, and indeed was observed at a position more common for an ester carbonyl absorption, such a frequency increase is consistent with the electron-withdrawing nature of the ring substituent. A similar correlation has been reported for the N-acetyl derivatives of five-membered heterocycles[16]; indeed, the >C=O absorption in N-acetyltetrazole was found at 1779 cm.$^{-1}$. An additional strong band, which is considered to be due to the C–N single bond absorption, rather than an ester —C(|)—O—, was found at 1190 cm.$^{-1}$ also in agreement with the data reported by Otting.[16]

Hydrogenolysis of 3-Chloro-4-hydroxyisoquinoline.—A solution of 1 millimole of the chloro compound and 0.3 g. of potassium acetate in 20 ml. of 95% ethanol was mixed with 0.1 g. of 5% palladium-on-charcoal and the whole stirred with hydrogen at room temperature. When slightly more than one millimole of hydrogen had been absorbed, the hydrogenation was interrupted, the catalyst separated by filtration and the filtrate evaporated to dryness. The residue was washed thoroughly with water and recrystallized from acetonitrile (Darco) to yield 71 mg. (49%) of 4-hydroxyisoquinoline, m.p. 221–221.5° dec., undepressed on admixture with an authentic sample.

1-Methoxyisoquinoline.—A solution of 8.18 g. of 1-chloroisoquinoline and 5.7 g. of sodium in 80 ml. of methanol was heated 2 hours at 100°. The solvent was evaporated and the residue treated with water and extracted with ether. Drying and distillation of the extracts afforded 6.91 g. (87%) of colorless oil, b.p. 116° (9 mm.) to 119° (8 mm.). Similar replacements have been carried out with substituted 1-chloroisoquinolines[4,8] but apparently have not been reported with 1-chloroisoquinoline itself, though 1-methoxyisoquinoline has been synthesized by Fernau[17] by another method. 1-Methoxyisoquinoline picrate was prepared in benzene solution and recrystallized from benzene, from ethanol–water and from ethyl acetate; yellow needles, m.p. 163.5–165.5° dec., when heated from 150°.

Anal. Calcd. for $C_{10}H_9NO \cdot C_6H_3N_3O_7$: C, 49.49; H, 3.12. Found: C, 49.55; H, 3.42.

(12) Melting points are corrected, boiling points uncorrected.

(13) Analyses by Weiler and Strauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., except for some nitrogen determinations which were carried out by a semi-micro Kjeldahl technique in this Laboratory.

(14) R. D. Haworth and S. Robinson, *J. Chem. Soc.*, 777 (1948).

(15) We wish to thank the Becco Chemical Division, Food Machinery and Chemical Corp., for a generous gift of this material.

(16) W. Otting, *Chem. Ber.*, **89**, 1940 (1956).

(17) A. Fernau, *Monatsh.*, **14**, 59 (1893).

Attempted Oxidation of 1-Methoxyisoquinoline.—Oxidations attempted with hydrogen peroxide and acetic acid yielded no appreciable solid products when worked up by the usual method, and unchanged starting material was recovered. Reactions carried out with 40% peracetic acid, either at room temperature for a prolonged period or at 50°, yielded an oil on evaporation together with very small quantities of phthalimide, m.p. 228.5–230°, undepressed on admixture with authentic material.

Anal. Calcd. for $C_8H_5NO_2$: C, 65.61; H, 3.57; N, 9.67. Found: C, 65.30; H, 3.43; N, 9.52.

Unchanged starting material was also present in the peracetic acid reaction residues. It was identified as its picrate, m.p. 159–162°, undepressed on admixture with authentic material.

***o*-Carboxyphenylacetaldoxime.**—The aldehyde[5] (4.92 g.) was dissolved as completely as possible in 30 ml. of water on the steam-bath and 3 g. of hydroxylamine hydrochloride and 3.6 g. of anhydrous sodium acetate were added. Crystallization commenced almost at once, but the mixture was heated for 15 minutes, then cooled slowly. The white crystals, after washing with water and drying, weighed 4.73 g. (88%) and melted at 137.5–9.0° dec. The analytical sample was recrystallized from nitromethane, m.p. 139.5–140.5° dec.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.32; H, 5.07. Found: C, 60.47; H, 5.13.

N-Hydroxyisocarbostyril.—Optimum yields were obtained when this cyclization was conducted at about 130°. A mixture of 0.18 g. of oxime and 3 ml. of chlorobenzene was refluxed for 2.75 hours, then cooled to deposit 0.12 g. (75%) of gold needles, m.p. 179–184°. The compound was purified by dissolution in dilute aqueous ammonia, Darco treatment, and reprecipitation. Recrystallization from nitromethane and sublimation at 140° (0.2 mm.) produced white needles, m.p. 184–185.5°.

Anal. Calcd. for $C_9H_7NO_2$: C, 67.07; H, 4.39. Found: C, 66.86; H, 4.47.

Like its pyridine and quinoline analogs, the cyclic hydroxamic acid is soluble in aqueous sodium bicarbonate and gives a deep magenta color on treatment of its solutions with ferric chloride.[18] In addition to the carbonyl absorption at 1630 cm.$^{-1}$ in the infrared, absorptions were found at 1610 and 1590 cm.$^{-1}$.

Reduction of N-Hydroxyisocarbostyril.—A mixture of 164 mg. of the N-oxide, 0.03 g. of iodine, 0.07 g. of red phosphorus and 3 ml. of glacial acetic acid was refluxed for 6 hours, the insoluble solids were removed by hot-filtration and the filtrate was evaporated to dryness *in vacuo*. Water was added and the resulting black solid was triturated with aqueous sodium carbonate to remove starting material, dried and sublimed at 170° (0.2 mm.). Recrystallization of the 103 mg. of isocarbostyril from water–ethanol afforded a product with m.p. 207–209°, both alone and on admixture with isocarbostyril.

Reaction of N-Hydroxyisocarbostyril with Phosphorus Oxychloride.—A mixture of 0.80 g. of the oxide and 8 ml. of phosphorus oxychloride was heated in a Carius tube at 160° for 3 hours. The mixture was poured onto 60 g. of ice and water, the solid separated by filtration and triturated with alkali. Recrystallization from ethanol–water (Darco) afforded 0.43 g. of pure needles of 1,4-dichloroisoquinoline (44%). These melted at 90.5–92.0°, both alone and on admixture with material prepared in the usual manner.[8]

Reaction of N-Hydroxyisocarbostyril with Benzoyl Chloride.—A solution of 0.24 g. of the oxide in 4 ml. of 10% sodium carbonate was stirred with 0.43 g. of benzoyl chloride at room temperature for 3.6 hours. The solid was separated by filtration and washed with water and with ethanol. The yield of essentially pure ester, m.p. 140–143°, was 0.32 g. (80%). The analytical sample was recrystallized from cyclohexane as white filaments, m.p. 142–143°.

Anal. Calcd. for $C_{16}H_{11}NO_2$: C, 72.44; H, 4.18. Found: C, 72.79; H, 4.18.

The infrared spectrum showed carbonyl bands at 1770 and 1660 cm.$^{-1}$ and ring absorptions at 1610 and 1600 cm.$^{-1}$. Two other strong bands, presumably due to —C(=O)—O— stretching vibrations,[19] were found at 1240 and 1175 cm.$^{-1}$.

For saponification, a solution of 0.1 g. of sodium hydroxide and 0.13 g. of the benzoate in 4 ml. of 95% ethanol was refluxed 1.75 hours, evaporated *in vacuo* to dryness and the solid dissolved in 7 ml. of water. The solution was acidified with hydrochloric acid and the precipitate was filtered, dried and washed with ether to remove benzoic acid. The yield of white needles of N-oxide was 87%, m.p. 183.5–185.5°, undepressed on admixture with authentic N-oxide. The substance gave a positive ferric chloride test.

When the hydroxyisocarbostyril was heated with 8 equivalents of benzoyl chloride for 2.5 hours at 175–185°, only the ester was obtained, though in lower yield. The mixture was cooled, poured into excess aqueous sodium hydroxide containing a few drops of pyridine and stirred to decompose excess benzoyl chloride. The thick oil was extracted into ether and the solution dried, treated with Darco and evaporated. The resulting oil was kept *in vacuo* over sulfuric acid to remove pyridine, then extracted with hot, low-boiling petroleum ether to remove benzoic anhydride. After recrystallization from cyclohexane (Darco), the product melted at 141.5–142.5°, yield 28%.

When 84 mg. of the benzoate was heated under nitrogen for 1 hour, then cooled, a tan solid, m.p. 124–156°, was obtained. Recrystallization from benzene–cyclohexane and washing of the product with dilute aqueous sodium hydroxide and with water afforded the crude benzoate, m.p. 135–138.5°. The recovery of product, whose melting point was undepressed on admixture with starting material, was 62%. It was saponified with ethanolic sodium hydroxide as above to yield 32 mg. (59% over-all) of N-hydroxyisocarbostyril, m.p. 180–182.5°, undepressed on admixture with that material. Saponification of the residue from the benzene mother liquors afforded 4.5 mg. of less pure N-oxide.

N-Tosyloxyisocarbostyril.—To a solution of 0.24 g. of the oxide in 4 ml. of 10% sodium carbonate was added 0.59 g. of *p*-toluenesulfonyl chloride, and the suspension was stirred for 9 hours at room temperature. The solid was separated, washed with water, dried and triturated thoroughly with ether to remove unreacted tosyl chloride. The yield of cream-colored precipitate was 87%. The material was recrystallized from ethyl formate (Darco) by addition of hexane to the cloud-point; cream-colored needles, 68% yield. The analytical sample was also recrystallized from acetone by addition of water to the cloud-point. The melting point of the compound is indefinite. When placed in a 130° bath it decomposes violently with formation of a brown liquid. When heated from room temperature the material sinters and turns orange at about 110°, then gradually darkens and finally melts with decomposition in the range 187–197°. The infrared spectrum shows a carbonyl band at 1675 cm.$^{-1}$, ring absorption at 1610 and 1595 cm.$^{-1}$ and bands probably ascribable to the sulfonate ester group[20] at 1380 and 1195 cm.$^{-1}$. Unlike 4-tosyloxyisocarbostyril (*vide infra*) the compound exhibits no blue fluorescence under ultraviolet light.

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.15. Found: C, 60.82; H, 4.38.

Seven milligrams of the material was heated with 1 ml. of 10% sodium hydroxide solution for 4 hours at 59°, during which period it dissolved almost completely. Acidification with concentrated hydrochloric acid produced a tan solid which gave a positive ferric chloride test and which had m.p. 179.5–183°, undepressed on admixture with N-hydroxyisocarbostyril.

Rearrangements of N-Tosyloxyisocarbostyril.—The intermediate (0.05 g.) was warmed slowly to 90–95° and maintained at this temperature for 45 minutes, during which time it darkened slightly. After washing with benzene the 90% yield of crude material melted at 193.5–202° dec. Recrystallization from benzene (Darco) afforded a 52% yield of product, m.p. 206–207.5° dec. The melting point was undepressed on admixture with an authentic sample of 4-tosyloxyisocarbostyril (*vide infra*). Further, the product showed no change on placing the capillary in the melting point bath at 130°. An attempted rearrangement of the dry compound on a slightly larger scale was so exothermic that much of the material was decomposed.

When 110 mg. of the intermediate and 3 ml. of toluene

(18) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948).

(19) *Cf.* L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 163.

(20) Reference 19, p. 300.

were heated slowly to 90°, then maintained at this temperature for 1 hour, the solution on cooling deposited white needles of 4-tosyloxyisocarbostyril, m.p. 206.5–207° dec. The yield of this pure rearrangement product, whose melting point was undepressed on admixture with authentic material, was 18%. Filtration of the toluene mother liquors through Darco and evaporation *in vacuo* left a 72% yield of apparently pure intermediate. The non-fluorescent solid exhibited the melting-point behavior described above.

When a rearrangement was carried out under exactly the same conditions in nitromethane and the solvent evaporated and the residue washed with benzene, a 91% yield of slightly impure 4-tosyloxyisocarbostyril, m.p. 200.5–205° dec., was obtained. Recrystallization from acetone (Darco) afforded material which melted at 207–208.5° dec. in 64% yield.

A rearrangement using 220 mg. of intermediate in a mixture of 4 ml. of acetonitrile and 2 ml. of water was carried out in a sealed tube as above. The solution, which turned pink and deposited red crystals during heating, was evaporated to dryness *in vacuo* and the resulting pink solid was triturated thoroughly with water. The water washings were titrated with sodium hydroxide using brom thymol blue indicator, but the end-point was not satisfactory, apparently because of the presence of small quantities of dissolved 4-hydroxyisocarbostyril. This substance not only buffered the solution but also obscured the color-change by its oxidation to the red "carbindigo"[21] as the mixture became alkaline. Alkali equivalent to 96% of the theoretical *p*-toluenesulfonic acid was added, however, before any color-change was observed. The dried pink precipitate weighed 99 mg. or 88.5% on the basis of a dihydroxyisoquinoline, and gave negative qualitative tests for sulfur.[9] The melting point was above 240°, both alone and on admixture with 4-hydroxyisocarbostyril.

In an experiment designed to determine whether 4-tosyloxyisocarbostyril might undergo hydrolysis in the acetonitrile–water medium, 0.11 g. of the pure compound was heated under the same conditions in a mixture of 2 ml. of acetonitrile and 1 ml. of 0.1 *N* hydrochloric acid. The solution remained colorless throughout the heating period. Addition of excess sodium bicarbonate and evaporation left, after water washing, 0.10 g. of unchanged starting material, m.p. 206–207°, both alone and on admixture with 4-tosyloxy compound.

For identification, 93 mg. of the crude dihydroxyisoquinoline was heated at 165° for 4.5 hours with 0.5 ml. of phosphorus oxychloride. The mixture was poured into 3 ml. of water and steam was passed through to produce a fluffy precipitate in the distillate. This product had m.p. 117–119° (very cloudy melt to 140°) alone and m.p. 120–121° on admixture with 1,3-dichloroisoquinoline. The residue from the steam distillation was decanted from tarry material, cooled and partially neutralized with ammonia. The resulting brown precipitate was only partially soluble in aqueous ammonium hydroxide. An ammonia solution was filtered through Darco and reacidified to produce 9 mg. (8%) of 1-chloro-4-hydroxyisoquinoline, m.p. 192.5–194° dec. alone and m.p. 194–195° dec. on admixture with the known substance.

In a more effective chlorination, 91 mg. of dihydroxy compound was heated with 0.55 g. of phenylphosphonic dichloride at 130° until bubbling slowed, then at 200° for 6 hours. Decomposition of the cooled mixture was effected by adding 25 ml. of water and distillation to a volume of about 3 ml. Filaments of slightly impure 1,3-dichloroisoquinoline were collected from the distillate in 9% yield, m.p. 116.5–118.5°. After recrystallization from ethanol–water this product melted at 121.5–122° and the melting point was undepressed on admixture with known material. Further, the infrared spectra of the two samples were identical. From the steam distillation residue 1-chloro-4-hydroxyisoquinoline was isolated as described above by partial neutralization. The yield of crude material, m.p. 191–191.5° dec., was 23%. After recrystallization from acetic acid–water the substance melted at 193.5–194° dec. and the melting point was not depressed on admixture with 1-chloro-4-hydroxyisoquinoline, while it was distinctly depressed on admixture with 1-chloro-3-hydroxyisoquinoline.[4]

4-Tosyloxyisocarbostyril was prepared directly from N-hydroxyisocarbostyril by heating 0.12 g. of the oxide with 0.3 g. of tosyl chloride for 1.5 hours at 75–85°, then for 1 hour at 95°. The cooled mixture was washed well with ether to yield a tan solid, m.p. 199–204° dec., in 43% yield. Recrystallization from benzene afforded a 30% yield of product, m.p. 205.5–207° dec.

Ochiai and Ikehara[3] prepared 4-tosyloxyisocarbostyril by rearrangement of 4-tosyloxyisoquinoline-N-oxide. Their reported melting point was 205°. It was prepared independently in this Laboratory by refluxing a mixture of 1.28 g. of 4-hydroxyisoquinoline, 3.20 g. of *p*-toluenesulfonyl chloride and 20 ml. of pyridine for 1 hour. The solution was added to 250 ml. of water, the aqueous layer was discarded and the oil layer was extracted with benzene to remove unreacted tosyl chloride. The tarry residue was extracted with chloroform and the dried extract was filtered through Darco and evaporated. The residual solid was washed with acetone; yield 14%, m.p. 206–208° dec. Recrystallizations from benzene and from acetone produced a white solid, m.p. 207–208° dec.

4-Chloroisoquinoline.—A mixture of 2.90 g. of 4-hydroxyisoquinoline and 12 ml. of phosphorus oxychloride was heated in a Carius tube at 180° for 22 hours. The mixture was poured onto 50 g. of ice and the tarry solution neutralized. Steam distillation followed by extraction of the distillate with ether and evaporation of the dried extracts afforded a yellow oil, b.p. 132° (10 mm.) to 130° (8 mm.). The yield was 2.39 g. (73%). The compound was redistilled for analysis; b.p. 130–132° (9 mm.), $n^{19}D$ 1.6372, d^{21}_4 1.225. A drop was chilled to a white solid in a capillary and on warming was found to have m.p. 27.5–29.5°.

Anal. Calcd. for C_9H_6NCl: C, 66.06; H, 3.70. Found: C, 65.94; H, 3.66.

4-Chloroisoquinoline-N-oxide.—A mixture of 1.71 g. of 4-chloroisoquinoline, 3 ml. of acetic acid and 1 ml. of 30% hydrogen peroxide was heated at 65° for 12 hours, 0.8 ml. more peroxide being added after 3 hours. The pale-yellow solution was evaporated and worked up by the method described for the 3-chloro derivative. The yield of crude product, m.p. 174–177.5°, was 93%. Washing with ethyl acetate and recrystallizations from benzene produced the analytical sample, m.p. 180.5–181.5°.

Anal. Calcd. for C_9H_6NOCl: C, 60.18; H, 3.37. Found: C, 60.41; H, 3.08.

4-Methylisoquinoline.—This compound was prepared by the method of Späth, *et al.*,[22] except that the cyclization of the N-formyl-1-amino-2-phenylpropane was run in polyphosphoric acid.[23] A mixture of 40.8 g. of the amide and 408 g. of PPA was heated with stirring at 180° for 2 hours. The mixture was added to about 350 g. of ice and water and decomposed with external cooling. The solution was extracted with 400 ml. of ether in three portions and the extracts discarded. The aqueous layer was then basified with ammonium hydroxide while cooling, the brown oil was taken up in ether and the water layer was extracted with 1 liter of ether in three portions. The combined ether solutions were dried, evaporated and distilled at 111–116° (12 mm.). The colorless oil, whose weight corresponded to a yield of 86% on the basis of pure cyclization product (reported[22] yield 37% using phosphorus pentoxide) probably contained 1-amino-2-phenylpropane as shown by analysis, but because of the greatly increased yield it appears that polyphosphoric acid is still advantageous in this cyclization. After several distillations the mid-fraction of the 4-methyl-3,4-dihydroisoquinoline had b.p. 111–112° (12 mm.), $n^{20.5}D$ 1.5686 and d^{25}_4 1.020.

Anal. Calcd. for $C_{10}H_{11}N$: C, 82.71; H, 7.63; N, 9.65. Found: C, 82.23; H, 7.67; N, 10.20.

A sample of the material from the first distillation was converted to its picrate in benzene solution and recrystallized from benzene–cyclohexane. The melting point was 134–136° (reported[22] m.p. 132–133°).

The dihydro compound was dehydrogenated to 4-methylisoquinoline as in the reference except that only 1.25 g. of 5% Pd-on-charcoal was used for 25 g. of base. The amine, b.p. 126–132° (13 mm.), was obtained in 92% yield. The picrate, after two recrystallizations from ethanol, had m.p. 202–203.5° (reported[22] m.p. 202–203°).

(21) S. Gabriel and J. Colman, *Ber.*, **33**, 996 (1900).

(22) E. Späth, F. Burger and W. Kuntara, *ibid.*, **63**, 134 (1930).

(23) *Cf.* H. R. Snyder and F. X. Werber, THIS JOURNAL, **72**, 2962 (1950).

4-Methylisoquinoline-N-oxide.—The oxide was prepared by the method employed for the 4-chloro compound. The material from the chloroform extracts was obtained as a hygroscopic solid of wide melting range. From 14.32 g. of 4-methylisoquinoline 14.62 g. of crude oxide was obtained. The analytical sample was recrystallized from chloroform (Darco) by adding hexane to the hot solution to the cloud point, and from toluene–hexane by the same procedure. The analytical sample was dried for 9 days *in vacuo* to constant melting point, m.p. 129–131°.

Anal. Calcd. for $C_{10}H_9NO$: C, 75.44; H, 5.71; N, 8.80. Found: C, 75.76; H, 5.62; N, 8.78.

Infrared Spectra.—All spectra were measured from KBr disks on either a Perkin–Elmer spectrophotometer or a Baird instrument by Dr. S. M. Nagy and associates at the Microchemical Laboratory, Massachusetts Institute of Technology.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. XIX. A New Synthesis of Pyrido[2,3-d]pyrimidines. The Condensation of 1,3-Diketones and 3-Ketoaldehydes with 4-Aminopyrimidines

BY ROLAND K. ROBINS AND GEORGE H. HITCHINGS

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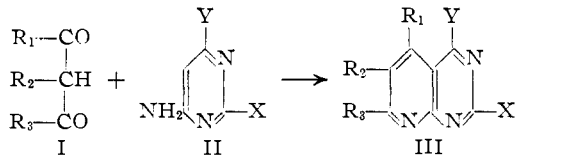
A number of 2,4-dihydroxy-, 2,4-diamino-, 2-amino-4-hydroxy- and 2-mercapto-4-hydroxypyrido[2,3-d]pyrimidines substituted in the pyridine ring has been prepared by the condensation of various 1,3-diketones and β-ketoaldehydes with the appropriate 4-aminopyrimidines in the presence of 85% phosphoric acid. The structures of representative compounds have been established by independent synthesis. When a β-ketoaldehyde is employed, the resulting condensation product is a 7-substituted pyrido[2,3-d]pyrimidine, indicating that the aldehyde group has condensed with the 5-position of the pyrimidine ring. Several 4-hydroxypyrido[2,3-d]pyrimidines have been prepared by treatment of the corresponding 2-mercapto-4-hydroxyl derivatives with Raney nickel.

Studies in this Laboratory of pyrimidines,[1] condensed pyrimidine systems[2,3] and related substances[4,5] as inhibitors of nucleic acid biosynthesis[6,7] have been in progress for a number of years. Recently two series of carbocondensed pyridopyrimidines[8,9] were developed primarily to provide derivatives with a diversity of functional groups in the pyrimidine moiety. The investigations of Rydon and co-workers[10,11] followed similar lines. The previously reported synthetic methods employed pyridines as starting materials and were restricted in scope not only by the unavailability of many substituted pyridines but also by the limitations of the methods available for the formation of the pyrimidine moiety. The present method employs the condensation of a 4-aminopyrimidine with a β-diketone or β-ketoaldehyde to form pyrido[2,3-d]-pyrimidines. Since the pyrimidine and particularly the dicarbonyl reagent may be modified independently within rather wide limits, the synthesis of a considerable number of new substances has been possible.

The reaction takes the form



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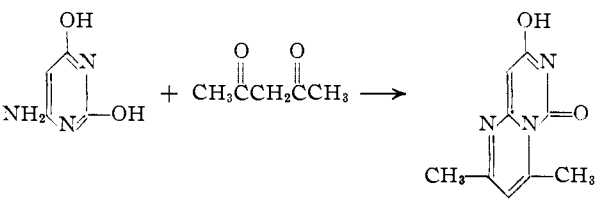
It might be anticipated that the course of the reaction would be affected by the nature of the substituents R_1, R_2 and R_3 of the dicarbonyl reagent and the nature of the functional groups X and Y of the pyrimidine. In preliminary experiments acetylacetone (I, R_1, R_3 = CH_3, R_2 = H) was heated with a solution of the pyrimidine in sirupy phosphoric acid. Products analyzing correctly for pyrido[2,3-d]pyrimidines were obtained with pyrimidines bearing hydroxyl, amino or mercapto groups in both the 2- and 4-position, but no product was obtained with either 2,4-diamino-6-methyl- or 6-amino-4-hydroxy-2-methylpyrimidine. Thus, the reactive pyrimidines appear to be those which have active 5-positions as judged by studies of nitrosation and coupling reactions.[12] Although the most probable course of the reaction was that formulated above, the possibility existed that the condensation might have occurred through the nitrogen of the pyrimidine ring to give a pyrimido-[1,2-c]pyrimidine derivative as



This possibility was eliminated and the structure

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