crystallized from 1-propanol; m.p. 174–174.5° (lit.[23] m.p. 174°).

*Anal.* Calcd. for $C_{21}H_{20}N_4$: N, 16.57. Found: N, 16.79.

*1-Methyl-4-carbostyrilcarboxaldehyde-p-phenylazoanilineanil.*[24] Attempts to recrystallize the product from either ethanol or propanol resulted in a resin. The product was dissolved in benzene and the solution was poured into a large excess of petroleum ether (b.p.; 60–75°) m.p. 91–99° (lit.[24] m.p. 93–99°).

*Anal.* Calcd. for $C_{23}H_{18}N_4O$: N, 15.30. Found: N, 15.52.

*N,N'-Dienabzal-1,4-diaminobenzene*[25] was recrystallized from 1-propanol; m.p. 138-139° (lit.[25] m.p. 139°).

*Anal.* Calcd. for $C_{20}H_{16}N_2$: N, 9.85. Found: N, 9.78.

*N-(p-Dimethylaminobenzal) aniline*[26] was recrystallized from ethanol; m.p. 100–100.5° (lit.[26] m.p. 100°).

*Anal.* Calcd. for $C_{15}H_{16}N_2$: N, 12.50. Found: N, 12.56.

The ultraviolet and visible spectra in ethanol of the molecules in the range 220 to 600 mμ were determined with the Beckmann DU Spectrophotometer using matched silica cells. The cell compartment was thermostated to 24.9 ± 0.2°. In the case of the aqueous ethanol solutions of various acid strengths the spectral range covered was from 300 to 600 mμ. The range of acidities covered was from *p*H 7 through concentrated sulfuric acid. The *p*H of the buffer solutions, *p*H 1 through 7, was determined using the Beckman Model G *p*H meter. The *p*H values of the various sulfuric acid solutions were computed using the extended scale of Michaelis and Granick.[27] The infrared spectra of the molecules were determined in $CCl_4$ solution using the Perkin-Elmer Infracord.

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(24) D. Cook, *Proc. Ind. Acad. Sci.*, 60, 138 (1950).
(25) A. Landenburg, *Ber.*, 11, 599 (1878).
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## 3-Aminopiperidones. I. The Cyanoethylation of 2-(*N,N*-Diethylamino)-2-phenylacetonitrile and the Synthesis of an Enaminonitrile[1]

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The cyanoethylation of 2-disubstituted amino-2-phenylacetonitriles has been studied in this laboratory in the interest of developing a synthetic route to appropriate dinitriles which, in turn, could be hydrolyzed and cyclized to yield a series of 3-disubstituted amino-3-phenyl (and substituted phenyl)-2,6-piperidinediones. Studies directed toward the synthesis of this series, as well as of corresponding basically-substituted 2-piperidones, has been undertaken to provide compounds for use in experiments designed to correlate the biological activity of these structurally-modified compounds with the activity of 3-alkyl-3-phenyl (and substituted phenyl)-2,6-piperidinediones (*e.g.*, Doriden[2] and Elipten[3]).

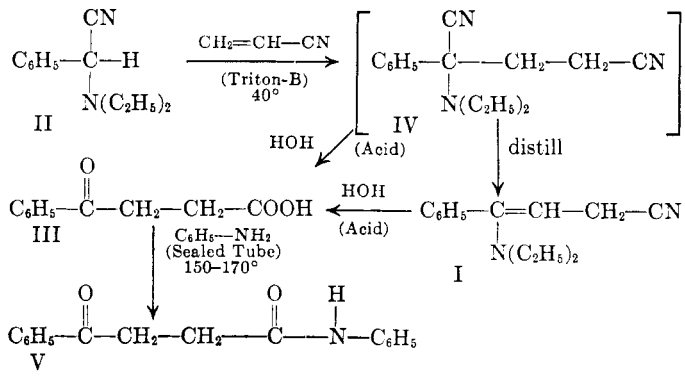
During the course of a part of this investigation, the authors discovered that the product which was isolated from a reaction involving the cyanoethylation of 2-(*N,N*-diethylamino)-2-phenylacetonitrile displayed (as evidenced by its infrared spectrum and elemental analysis) the characteristics of an enaminonitrile. Supportive evidence for the formation of this compound is found in a recent report by Hauser *et al.*[4] concerning the synthesis of enamines from alkyl derivatives of 2-(*N,N*-dimethylamino)-2-phenylacetonitrile. A description of the method involved in the formation of the enaminonitrile (I) and the details of its identification are presented herewith.

The literature does not record previous work on the cyanoethylation of α-aminonitriles. Therefore, the conditions of the reaction, specifically as applied to 2-(*N,N*-diethylamino)-2-phenylacetonitrile (II), were studied with reference to those usually employed in the Michael addition. The reaction in the present instance was accomplished only in the absence of solvent and by using, as a catalyst, benzyltrimethylammonium hydroxide[5] (35% solution in methanol). Furthermore, it was exothermic and a blue color which changed rapidly to brown was observed when the catalyst was added to II. The difficulty experienced in this case, compared to the relative ease with which the cyanoethylation of α-alkylphenylacetonitriles is accomplished, may be attributed to the decrease in acidity of the α-hydrogen due to the electron-donating tendency of the amino nitrogen.

Distillation of the residue obtained after ether extraction of the cyanoethylation reaction mixture yielded a compound which, according to its infrared absorption spectrum, contained a cyano group other than that attached to the α-carbon atom of the starting material. It was possible to make this observation because the characteristic infrared absorption band for CN, noted in the spectrum of 2-phenylacetonitrile (5% solution in carbon tetrachloride) at 2250 cm.$^{-1}$, was "quenched" in 2 - (*N,N*-diethylamino) - 2 - phenylacetonitrile apparently by the diethylamino group. The so-called "quenching" of nitrile absorption intensity has been noted previously in compounds bearing oxygen functions on the same carbon atom as that carrying the CN group.[6] Analysis of the

(1) This investigation was supported in part by funds provided for biological and medical research by the State of Washington Initiative Measure No. 171.

(2) Brand name of Ciba Pharmaceutical Products, Incorporated for α-ethyl-α-phenylglutarimide.
(3) Brand name of Ciba Pharmaceutical Products, Incorporated for α-(*p*-aminophenyl)-α-ethylglutarimide.
(4) C. R. Hauser, H. M. Taylor, and T. G. Ledford, *J. Am. Chem. Soc.*, 82, 1786 (1960).
(5) Commonly referred to in the literature as "Triton-B," a Rohm & Haas Company brand name.



infrared spectrum of the cyanoethylated product also indicated the presence of a double bond conjugated with the aromatic ring (strong bands from 1580 to 1600 cm.$^{-1}$).[7] Elemental analysis of the compound provided further evidence in support of its identification as the structure represented by I, as did hydrolysis of the freshly-distilled product in 6*M* hydrochloric acid. The hydrolysis reaction yielded 3-benzoylpropionic acid (III), which was identified by its analysis and comparison with an authentic sample of the compound synthesized by an alternate route.

In order to determine whether dehydrocyanation of the addition product had occurred during the Michael addition or had resulted during distillation of the crude reaction product, the reaction mixture was examined at appropriate stages for the evolution of hydrogen cyanide, using the sensitive benzidine acetate–copper acetate test.[8] There was no evidence that hydrogen cyanide was evolved during the cyanoethylation reaction, but a positive test was obtained during distillation. Acid hydrolysis of the crude reaction product, employing conditions identical to those used in the hydrolysis of the purified product, also yielded 3-benzoylpropionic acid (IV→III), but it was noted in this case that hydrogen cyanide was evolved during the reaction. This result pointed to the intermediate formation of the enaminonitrile during the heating process. The elimination of the cyano group and a β-hydrogen, which resulted in the formation of the enaminonitrile, was assisted by the presence of the lone pair of electrons on the amino nitrogen. In the elimination, furthermore, the driving force for dehydrocyanation was provided by: 1. an attempt to gain resonance energy (alkene conjugation with the aromatic ring), and 2. an attempt to relieve steric strain.

Attempts to isolate diethylaminophenylglutaronitrile (IV) as its hydrochloride from a cold, anhydrous ethereal solution of the crude reaction product led instead to the isolation of diethylamine hydrochloride. The same result was obtained in an attempt to prepare 4-(*N*,*N*-diethylamino)-4-phenyl-3-butenenitrile hydrochloride. Attempts to prepare a stable picrate of the enaminonitrile were also unsuccessful.

## EXPERIMENTAL[9]

*2-(N,N-Diethylamino)-2-phenylacetonitrile* (II). This compound was prepared by a modification of the method described by Knoevenagel and Mercklin.[10] A 2-l., three-necked flask fitted with a mechanical stirrer and an addition funnel was assembled in the fume chamber. Benzaldehyde, 145 g., (1.5 moles), was introduced, and, with efficient stirring, 380 cc. of 40% aqueous sodium bisulfite solution (representing 1.5 moles of sodium bisulfite) was added all at once. The slurry which formed was stirred for 15 min. after the last of the bisulfite solution had been added, and the mixture was allowed to cool to room temperature. Diethylamine, 110 g. (1.5 moles), was added slowly, whereupon the bisulfite addition compound liquified. This was followed by the slow addition of 73.5 g. (1.5 moles) of sodium cyanide dissolved in 150 cc. of water. The mixture was diluted with 200 cc. of water and transferred to a separatory funnel. The yellow oil which separated was dried over anhydrous sodium sulfate overnight and distilled to yield 203 g. (72%) of II, b.p. 128°/9.0 mm. and 132°/11.0 mm. A sample was redistilled for greater purity, b.p. 92°/0.9 mm., $n_D^{25}$ 1.5028. Boiling points reported[10] for this compound are 130–131°/11.0 mm. and 142°/16.0 mm.

The infrared spectrum of II (5% solution in carbon tetrachloride) did not show the characteristic nitrile band at 2250 cm.$^{-1}$.

*Anal.* Calcd. for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.29; H, 8.66; N, 14.45.

*4-(N,N-Diethylamino)-4-phenyl-3-butenenitrile* (I). A 300-cc. four-necked flask fitted with a mechanical stirrer, a nitrogen inlet tube, an addition funnel, and a thermometer, which was arranged to record the temperature of the reaction mixture, was assembled in the fume chamber. The apparatus was flooded with dry nitrogen for 15 min. prior to the introduction of the reactants and this atmosphere was maintained in the apparatus throughout the reaction. Compound

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 266.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 72.

(8) F. Feigl, *Spot Tests*, Vol. 2, 4th ed., Elsevier Publishing Co., New York, N. Y., 1954, p. 74

(9) Elemental analyses were done by the Dr. G. Weiler, Dr. F. B. Strauss Microanalytical Laboratory, 164 Banbury Road, Oxford, England. Melting points are uncorrected. Infrared spectra were recorded on solutions of the compounds in spectro grade carbon tetrachloride or in chloroform, as noted in the text, using the Beckman IR-5 Infrared Spectrophotometer.

(10) E. Knoevenagel and Ernst Mercklin, *Ber.*, **37**, 4090 (1904).

II, 47 g. (0.25 mole), was placed in the flask and 4 cc. of 35% methanolic benzyltrimethylammonium hydroxide (Chemlab Inc., Chicago) was added with stirring. A blue color which changed to brown was observed immediately after this addition. Recently-distilled acrylonitrile, 15 g. (0.28 mole), was added at such a rate that the temperature of the stirred reaction mixture was maintained at 38 to 40° (1.5 hr.). After the addition was completed, the mixture was stirred and warmed for an additional 2 hr., during which the temperature was maintained at 38 to 42°. The apparatus was flooded with dry nitrogen, sealed and allowed to stand at room temperature overnight. The mixture was treated with an equal volume of water, transferred to a separatory funnel, and extracted with three 100-cc. portions of ether. The extracts were combined, washed with three 150-cc. portions of water, and dried over anhydrous sodium sulfate. The ether was evaporated under reduced pressure and the residue was distilled *in vacuo* twice to yield 31.1 g. (58%)[11] of I, a pale-liquid, b.p. 112–114°/0.5 mm., $n_D^{25}$ 1.5160.

The infrared spectrum of I (5% solution in carbon tetrachloride) showed the characteristic nitrile peak at 2250 cm.$^{-1}$ and an alkene-aromatic ring conjugation at 1580–1600 cm.$^{-1}$.

*Anal.* Calcd. for $C_{14}H_{18}N_2$: C, 78.50; H, 8.41; N, 13.09. Found: C, 78.61; H, 8.62; N, 13.00.

The compound was unstable when stored under ordinary conditions. A sample which had been stored in a stoppered flask exposed to diffused light for 1 week developed a strong ammoniacal odor and a dark brown color. Its infrared spectrum showed a strong conjugated carbonyl band at 1690 cm.$^{-1}$ indicating that hydrolytic changes had occurred. It was determined that the stability of the compound could be improved by storing it under dry nitrogen in a tightly-stoppered container and protecting it from light.

*Hydrolysis of* I. To 300 cc. of 6*M* hydrochloric acid was added 21.4 g. (0.1 mole) of the enaminonitrile (I), and the solution was warmed on the steam bath for 45 min. During this period, a white, crystalline solid which separated in the early stages of the heating process redissolved in the hot reaction mixture, and after 30 min. of heating, a white, crystalline solid separated again from the hot solution. The reaction mixture was cooled and the crystals were collected, yielding 10.9 g. (61.4%) of III, m.p. 116° after purification and drying to constant weight according to the method of Somerville and Allen.[12] The melting point was undepressed upon admixture with an authentic sample of 3-benzoylpropionic acid[12] and the infrared spectra of the two specimens (5% solution in chloroform) were identical.

*Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.65. Found: C, 67.33; H, 5.54.

*Anilide of* III. The product of the hydrolysis of I was treated with freshly-distilled aniline according to the method of Klobb.[13] From this reaction, in which 6.25 g. of III and 4.0 g. of aniline were used, 2.6 g. (29.5%) of 3-benzoylpropionanilide (V) was obtained, m.p. 149–150° after recrystallization from benzene and drying to constant weight *in vacuo*.

The melting point of the anilide obtained in this case showed no depression when it was mixed with a sample of the anilide prepared from an authentic sample of 3-benzoylpropionic acid. The infrared spectra of the two specimens (5% solution in chloroform) were identical.

*Anal.* Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.96; N, 5.53. Found: C, 75.96; H, 6.18; N, 5.75.

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(11) This yield is based upon the quantity of 2-(*N*,*N*-yellow diethylamino)-2-phenylacetonitrile employed in the cyanoethylation reaction.

(12) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, **Coll. Vol. II**, 81 (1950).

(13) T. Klobb, *Bull. soc. chim. Paris*, **19**, 391 (1898).

## Pteridine Chemistry. V. The Methylation of 2-Amino-4-hydroxy-6,7-dimethylpteridine

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Although several investigators have reported on the alkylation of a number of mono- and polyhydroxypteridines[1,2] there is very little information available on the alkylation of aminohydroxypteridines. Leucopterin (2-amino-4,6,7-trihydroxypteridine) has been treated with diazomethane to give two trimethyl derivatives of unknown structure.[3] More recently we disclosed that 2-amino-4-hydroxypteridines, when treated with acrylonitrile, gave 8,9-dihydro-11H-pyrimido(2,1-b)pteridine-7-(6H),11-diones.[4] The latter reaction involved an alkylation of the 3-nitrogen of the pteridine ring and no isomeric compounds were detected.

It was of interest to determine whether the methylation of 2-amino-4-hydroxypteridines would give a single product, as occurred with acrylonitrile,[4] or several isomeric monomethyl derivatives as might be expected in this type of alkylation. 2-Amino-4-hydroxy-6,7-dimethylpteridine (I) was therefore methylated using four moles of dimethyl sulfate[5] and four moles of sodium hydroxide to give a 70% yield of a light yellow product. Chromatographic comparison with authentic compounds[6] showed that the crude product was a mixture[7] of the 1-methyl (II) and 3-methyl (III) derivatives of I, along with a very small amount of starting material. Due to the difference in the basicities of II and III (see Table I) the mixture was readily separated by crystallization from dilute acid. The yields of the products indicated that this methylation of I gave the two monomethyl derivatives in a ratio of approximately three parts of the 3-methyl derivative (III) to two parts of the 1-methyl derivative (II).

(1) H. C. S. Wood, *Chemistry and Biology of Pteridines*, Ciba Foundation Symposium, Little Brown and Co., Boston, Mass., 1954, p. 35.

(2) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956); W. Pfleiderer, *Chem. Ber.*, **90**, 2582, 2588, 2605, 2631 (1957); G. P. G. Dick, H. C. S. Wood, and W. B. Logan, *J. Chem. Soc.*, 2131 (1956).

(3) H. Wieland and P. Decker, *Ann.*, **547**, 180 (1941).

(4) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 5650 (1959).

(5) This large excess of dimethyl sulfate was necessary. Smaller quantities of alkylating agent always left considerable starting material in the crude product.

(6) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958).

(7) The chromatographic examination of this mixture had to be done carefully since the 1-methyl derivative (II) was much less fluorescent than the 3-methyl derivative (III). In practice, the former compound (II) was best detected as an absorption spot using a zinc silicate plate coated with Dupont phosphor No. 609235.