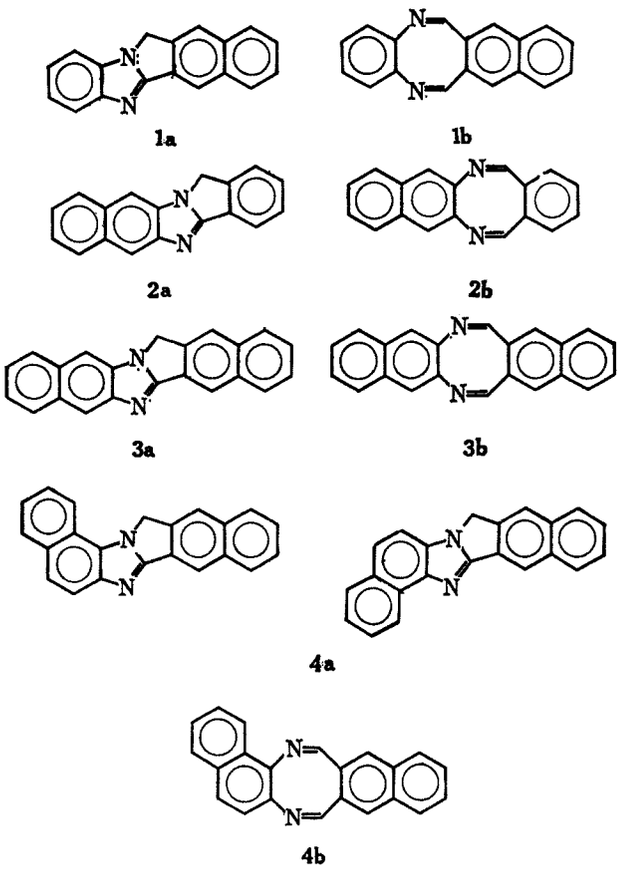
CHART I




diamine (**12**) was reported as the product using free amine **5** in cold ethanol, although **12** was unstable, rearranging readily to **13**.[6]

In view of this reservation, the condensations of Ried and co-workers were repeated. Free amines were used in all cases, and in addition, **5**·2HCl was used. The nmr spectra of the products were similar to those obtained by Amos and Gillis[4] for **10** and by Hawthorne and coworkers[7] for a similar adduct. Each compound evinced an aromatic multiplet centered at *ca.* $\tau$ 2.3 and a singlet at *ca.* 4.5. (Relative areas corresponded to theory.) The latter chemical shift contrasts with the value of $\tau$ 1.5 for the aldimine proton of benzylideneaniline. The aforementioned results certainly rule out diimine structures **1b–4b** and support the formation of **1a–4a**[8] under either acidic or nonacidic[9] conditions.

### Experimental Section[10]

**Chemicals.**—*o*-Phenylenediamine was Eastman Yellow Label material. *o*-Phthalaldehyde was from L. Light and Co., Ltd., England. 2,3-Naphthylenediamine was from Columbia Organic Chemicals, Columbia, S. C. 1,2-Naphthylenediamine was obtained from Aldrich Chemical Co. All the above materials were either sublimed or recrystallized and stored under nitrogen before use. *o*-Phenylenediamine dihydrochloride was Eastman White Label material and was used without further purification. 2,3-Naphthalenedicarboxaldehyde was prepared by the method of Ried and Bodem,[2] and was stored under nitrogen before use.

**Amine Hydrochloride–Aldehyde Condensation. General Method.**[5]—The stoichiometric amount of *o*-phenylenediaminedihydrochloride was dissolved in water and added to a solution of either *o*-phthalaldehyde in water or 2,3-naphthalenedicarboxaldehyde in water–ethanol. The solution was made neutral with alkali and the resulting solid was either recrystallized from the appropriate solvent or sublimed.

**Amine–Aldehyde Condensation. General Method.**[2]—The stoichiometric amount of aldehyde dissolved in absolute ethanol was added to a solution of diamine in ethanol under nitrogen. The product was isolated either by filtering off the precipitate or by evaporating the solution to dryness. The crude product was purified by recrystallization from the appropriate solvent or by sublimation.

All products showed melting points identical with literature[2,5] values. In the case of compounds **1a**, **2a**, and **10**, melting points, mixture melting points, and infrared spectra of products obtained using either free amine or amine hydrochloride methods were identical.

**Registry No.**—**1a**, 10561-93-0; **1b**, 258-91-3; **2a**, 248-53-3; **2b**, 258-92-4; **3a**, 10561-96-3; **3b**, 258-95-7; 14H-benz[*f*]isoindolo[2,1-*a*]naphth[2′,1′-*d*]imidazole, 10562-17-1; 8H-benz[*f*]isoindolo[2,1-*a*]naphth[1′,2′-*d*]-imidazole, 10562-18-2; **4b**, 227-06-5; **11**, 739-88-8.

**Acknowledgment.**—The authors wish to thank Messrs. M. Rozolsky and R. Borzelli for assistance in part of this work.

(7) J. O. Hawthorne, E. L. Mihelic, M. S. Morgan, and M. H. Wilt, *J. Org. Chem.*, **28**, 2831 (1963).

(8) Systematic names for these compounds are **1a**, 12H-benz[*f*]isoindolo-[2,1-*a*]benzimidazole; **2a**, 7H-isoindolo[2,1-*a*]naphth[3′,2′-*d*]imidazole; **3a**, 14H-benz[*f*]isoindolo[2,1-*a*]naphth[3′,2′-*d*]imidazole; **4a**, 8H-benz[*f*]isoindolo[2,1-*a*]naphth[1′,2′-*d*]imidazole and 14H-benz[*f*]isoindolo[2,1-*a*]-naphth[2′,1′-*d*]imidazole. *Cf.* A. M. Patterson, L. T. Cappell, and D. F. Walker, "The Ring Index," 2nd ed, American Chemical Society, Washington, D. C., 1960, RRI 2923, 4174, 5554, 5555, for model structures.

(9) Compound **10** was also formed under nonacidic conditions, using free amines **5** and **8**. See the Experimental Section.

(10) Nmr spectra were recorded on a Varian A-60A spectrometer equipped with a variable-temperature probe and a CAT (Computer of Average Transients), the latter being used for several of the spectra.

## A New Synthesis of 1-Methyl-1,6-dihydro-6-oxonicotinic Acid and 1-Methyl-1,4-dihydro-4-oxonicotinic Acid Derivatives[1a]

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In connection with an interest in 1-methyl-1,4-dihydro-4-oxonicotinamide (**1a**) as a niacin metabolite,[2-4] an attempt was made to synthesize the ester (**1b**) by the self-condensation of ethyl $\beta$-methylaminoacrylate (**2**). This method has been reported[5] to furnish 1-aryl-4-pyridones from $\beta$-arylaminoacrylic esters. On heating **2** at 145°, a crystalline product was obtained in 59% yield. Hydrolysis of this ester (**3**) gave 1-methyl-1,6-dihydro-6-oxonicotinic acid (**4**), showing that the condensation of the $\beta$-alkylamino ester occurs by 1,2-carbonyl addition. This reaction represents a convenient synthesis of **4** and its derivatives. An improved synthesis of **1a** resulted from N-methylation of 4-

(1) (a) This work was supported by a grant from the American Cancer Society and by Grant No. CA-07817 from the National Institutes of Health, U. S. Public Health Service. (b) Present address: Eisai Research Laboratories, Tokyo, Japan. (c) American Cancer Society, Charles S. Hayden Foundation Professor of Surgery in Cancer Research.

(2) M. L. Wu Chang and B. C. Johnson, *J. Biol. Chem.*, **234**, 1817 (1959).

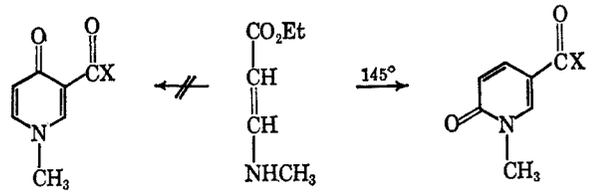
(3) M. L. Wu Chang and B. C. Johnson, *ibid.*, **236**, 2096 (1961).

(4) T. Wieland, C. Fest, and G. Pfleiderer, *Ann.*, **642**, 163 (1961).

(5) M. V. Rubtsov, *J. Gen. Chem. USSR*, **9**, 1517 (1939); *cf. Chem. Abstr.*, **34**, 2845 (1940).

hydroxynicotinic acid[6,7] in a sealed tube with methyl iodide in alcoholic potassium hydroxide followed by conversion of the product to the amide. (See Scheme I.)

SCHEME I



1a, X = $NH_2$
b, X = OEt
c, X = OH

2

3, X = OEt
4, X = OH
5, X = $NH_2$

### Experimental Section[8]

**Ethyl β-Methylaminoacrylate (2).**—Methylamine gas (8 g) was absorbed while passing through a solution of 25 g of commercial ethyl propiolate in 150 ml of benzene with cooling by ice water to keep the temperature below 25°. The benzene solution was stirred for 1 hr at room temperature and refluxed for 2 hr. After the solvent had been removed, the reaction mixture was distilled to yield **2**, bp 83–90° (15 mm), 24.8 g (74.6%). Repeating the distillation gave a boiling point of 85–86° (17 mm). *Anal.* Calcd for $C_5H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.07; H, 8.37; N, 10.99.

**Ethyl 1-Methyl-1,6-dihydro-6-oxonicotinate (3).**—Heating 7.8 g of **2** at 140–145° for 6 hr with stirring gave a solid product upon cooling. The reaction mixture was dissolved in 30 ml of 2-propanol, treated with active charcoal, and concentrated to 10 ml. The addition of *n*-hexane led to a good yield of colorless needles, mp 78–80° (lit.[9] mp 74°), 3.2 g (59%). *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.28; H, 5.82; N, 7.70.

**1-Methyl-1,6-dihydro-6-oxonicotinic Acid (4).**—Compound **3** (5.7 g) was hydrolyzed with potassium hydroxide in 95% ethanol. After the ethanol was removed *in vacuo* the residue was dissolved in 300 ml of water and passed through a column (17.8 × 3.2 cm) of Dowex 2 formate ion-exchange resin.[10] After the column was washed with 1 l. of water, **4** was eluted with 1 l. of 6 *N* formic acid. The eluate was concentrated *in vacuo* and the residue was recrystallized from water to yield 3.8 g (78%) of colorless needles, mp 241–243° (lit.[10,11] mp 240–240.5°, 238–239°). The melting point of a mixture with an authentic sample[10] (mp 243°) was 240–243°. *Anal.* Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.80; H, 4.75; N, 9.15.

**1-Methyl-1,6-dihydro-6-oxonicotinamide (5).**—To a solution of 1.5 g of **4** in 20 ml of chloroform, 10 ml of tetrahydrofuran, and 2 g of triethylamine was added, dropwise, 2 g of ethyl chloroformate at −5°. After stirring the solution for 1 hr, 30 ml of 15 *N* ammonium hydroxide was added to the solution which was then stirred for 2 hr more at room temperature. After the solvent was removed *in vacuo*, the residue was dissolved in 300 ml of water and applied to a column (12.7 × 3.2 cm) of Dowex 2 formate ion-exchange resin. The column was washed with 600 ml of water. From the combined effluent and wash water, 0.55 g (36.1%) of **5** was obtained, mp 211° (lit.[12] mp 212–215°). An admixture of **5** with an authentic sample (mp 208.5–210°) melted at 211–214°. Unreacted **4** (0.3 g) was recovered by elution of the column with 6 *N* formic acid.

**4-Hydroxynicotinic Acid.**—3-Iodo-4-hydroxypyridine (mp 290–293° dec, 4.4 g)[6] and 5.4 g of cuprous cyanide were stirred and heated in 100 ml of dimethylformamide at 140–145° for 5 hr. The reaction mixture was filtered and concentrated *in vacuo*. The residual oil was refluxed in a solution of 12 g of potassium hydroxide in 40 ml of water for 6 hr. The reaction mixture was then diluted to 400 ml and filtered. The filtrate was passed through a column (10 × 3.2 cm) of Dowex 2 formate ion-exchange resin. After washing the column with 800 ml of water, the acid was eluted with 800 ml of 6 *N* formic acid. The eluate was evaporated *in vacuo* and the residue was recrystallized from water, mp 246–250° (lit.[7] mp 249–251°), 1.23 g (45.5%). Repeating the recrystallization gave a melting point of 250–252°, with a change in the crystal form from plates to pillows at about 220–230°.

**1-Methyl-1,4-dihydro-4-oxonicotinic Acid (1c).**—The above acid (0.5 g), 20 ml of 90% methyl alcohol containing 0.6 g of potassium hydroxide, and 10 ml of methyl iodide were heated at 100° for 44 hr in a sealed tube. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in 25 ml of 10% potassium hydroxide solution and refluxed for 1 hr. The cooled solution was diluted to 400 ml and passed through a column (10 × 3.2 cm) of Dowex 2 formate ion-exchange resin. After the column was washed with 800 ml of water, the acid **1c** was eluted with 800 ml of 6 *N* formic acid. The solvent was removed *in vacuo* and the residual white powder was recrystallized from 95% ethanol to give colorless needles, mp 245–247°, 0.196 g (35.7%). *Anal.* Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.19; H, 4.56; N, 9.07. The ultraviolet spectrum showed $\lambda_{max}$ 251.5 mμ (ε 1.099 × $10^4$) in water, $\lambda_{max}$ 262.5 mμ (ε 1.288 × $10^4$) in 1 *N* NaOH, and $\lambda_{max}$ 241.5 mμ (ε 8.74 × $10^3$) in 1 *N* HCl.

**1-Methyl-1,4-dihydro-4-oxonicotinamide (1a).**—The acid **1c** (0.2 g) was converted to the amide by the procedure used to convert **4** to **5**. The residue obtained from the effluent of the Dowex 2 formate column was extracted twice with 100 ml of boiling acetone and two recrystallizations from acetone gave **1a** as colorless pillows, mp 183–184° (lit.[2,4] mp 181–182°, 179–181°), 0.092 g (43%). *Anal.* Calcd for $C_7H_8N_2O_2 \cdot 0.5H_2O$: C, 52.17; H, 5.63; N, 17.38. Found: C, 52.05; H, 5.80; N, 17.36. The ultraviolet spectrum[13] gave $\lambda_{max}$ (water) 257.5 mμ (lit.[2] 256 mμ) (ε 1.063 × $10^4$), 285 mμ (ε 4.36 × $10^3$); $\lambda_{max}$ (1 *N* NaOH) 258 mμ (ε 1.186 × $10^4$), 285 mμ (ε 4.98 × $10^3$); $\lambda_{max}$ (1 *N* HCl) 239.5 mμ (ε 7.48 × $10^3$). Elution of the column with 600 ml of 6 *N* formic acid recovered 0.02 g of **1c**.

**Registry No.**—**1a**, 769-49-3; **1c**, 10561-89-4; **2**, 10561-90-7; **3**, 10561-91-8; **4**, 3719-45-7; **5**, 701-44-0; 4-hydroxynicotinic acid, 609-70-1.

(6) F. W. Broekman and H. J. C. Tendeloo, *Rec. Trav. Chim.*, **81**, 107 (1962).

(7) F. W. Broekman, A. van Veldhuizen, and H. Janssen, *ibid.*, **81**, 792 (1962).

(8) All melting points were obtained with a Kofler micro hot stage apparatus. Elemental analyses were done by Huffman Microanalytical Laboratories, Wheatridge, Colo.

(9) C. Räth and F. Schiffmann, *Ann.*, **487**, 127 (1931).

(10) G. E. Lindenblad, M. Kaihara, and J. M. Price, *J. Biol. Chem.*, **219**, 893 (1956).

(11) H. Meyer, *Monatsh. Chem.*, **26**, 1311 (1905).

(12) W. E. Knox and W. I. Grossman, *J. Biol. Chem.*, **166**, 391 (1946).

(13) The ultraviolet spectra were identical with those reported in water, 0.1 *N* NaOH, and 1 *N* HCl.[4]

## Acid-Catalyzed Rearrangement of Cyclopropylphenylglycolic Acid[1a,b]

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*Received January 25, 1967*

In the course of a study of the ozonolysis of 3-cyclopropyl-3-phenyl-1-propyn-3-ol (**1**) in attempts to prepare cyclopropylphenylglycolic acid (**2**), it was observed that when a method of isolation of product was employed in which sulfuric acid was added to the ozonolysis mixture, a compound was isolated which was neither the starting material **1** nor the anticipated glycolic acid **2**. A communication from this labora-

(1) (a) A preliminary report of this work appeared in *Tetrahedron Letters*, 423 (1966). (b) The investigation was supported in part by Grant MH-07775 from the National Institutes of Health. Abstracted in part from a portion of a thesis submitted by L. L. D. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1966. (c) To whom all correspondence should be addressed.