added dropwise during 2 hr to a refluxing solution of dicyclohexylcarbodiimide (DCC, 1.3 g, 5.0 mmol) in dry pyridine. The solution was maintained at reflux for 2 hr after the addition was complete. The solution was concentrated to dryness under reduced pressure giving a gum. This gum was partitioned between water (100 ml) and ether (50 ml) with vigorous shaking. The insoluble urea was filtered and the aqueous layer was concentrated to a small volume (*ca.* 10 ml) after Darco-60 treatment. On standing the product crystallized as a colorless, highly crystalline solid. The product was filtered, washed with a small amount of water, and dried under vacuum to give 510 mg of product. A sample was recrystallized three times from water for analysis: mp 202.5–206.0°; $\lambda_{max}$ 258 mμ (18,000), 302 (10,800); $\nu_{max}$ 3560, 3460, 3200, 3100, 1700, 1650, and 1610 $cm^{-1}$.

*Anal.* Calcd for $C_{16}H_{16}O_8N_8P \cdot C_{17}H_{31}N_3O$: C, 56.5; H, 6.76; N, 11.98; P, 4.42. Found: C, 53.69;[17] H, 6.60; N, 11.70; P, 4.54.

***ara*-Cytidine 2′,5′ Cyclic Phosphate (3).**—A 400-mg sample of the above cyclic phosphate (2, 0.76 mmol) was dissolved in 20 ml of cold anhydrous ammonia saturated methanol and allowed to stand at room temperature overnight. The solution was taken to dryness under reduced pressure at 40° and the residue dissolved in 20 ml of distilled water and extracted with carbon tetrachloride (20 ml). The aqueous phase was separated, taken to dryness as above, and redissolved in 4.8 ml of water, filtered free of insoluble material, and then adjusted to pH 1 by the addition of concentrated hydrochloric acid, whereupon the product crystallized. After refrigeration the product was isolated (100 mg), washed with a small volume of 1 *N* HCl, then dried (*in vacuo*, 60°). A sample was recrystallized once for analysis, $\lambda_{max}^{pH\ 2.0}$ 210 mμ (ε10,220), 279 (14,060). This material was homogeneous by paper and thin layer chromatography (cellulose DF and silica gel G) employing solvent A and by high-voltage electrophoresis (HVE) at pH 6.8 and 3.5 and migrated as expected.

*Anal.* Calcd for $C_9H_{12}N_3O_7P$ (305.18): C, 35.42; H, 3.96; P, 9.54; N, 13.78. Found: C, 35.94; H, 4.07; P, 9.48; N, 14.08.

**$N^4$-Benzoyl-*ara*-cytidine 2′-Phosphate (5).**—*ara*-Cytidine 2′-phosphate[4] (4, 380 mg, 1.18 mmol) was dissolved in water (100 ml) containing a small amount of pyridine and lyophilized. The finely dispersed powder was taken up in 35 ml of dry pyridine containing 2.5 ml of benzoyl chloride and allowed to stand for 1 hr. Ice–water (100 ml) was added and after the solution had warmed to room temperature it was extracted with three 50-ml portions of chloroform. The combined extracts were backwashed with water, dried and evaporated to dryness. Two-thirds of this material was taken up in pyridine (20 ml) and water (10 ml) and the solution treated with 30 ml of 2 *M* sodium hydroxide. The heterogeneous solution was stirred vigorously for 4 min, then neutralized by the addition of pyridinium Dowex 50W-X8 resin (100 ml). After the pH had fallen to about 7 the resin was filtered and the filtrate taken to dryness (under reduced pressure at 40°) and then suspended in 100 ml of ether–water (1:1). The aqueous portion was separated, freed of ether and percolated through a column of 100 ml of the above resin (100–200 mesh) followed by elution with 250 ml of water. The total eluate was extracted four times with ether and the aqueous solution taken to dryness (*in vacuo*). The residue was taken up in pyridine and examined by tlc (cellulose, solvent B). This material appeared homogeneous and not contaminated with either nucleotide or benzoic acid and its mobility was very similar to that of the known compound 1. This material was employed for the next synthetic step without further purification.

***ara*-Cytidine 2′,5′ Cyclic Phosphate (3) from *ara*-Cytidine 2′-Phosphate.**—The $N^4$-benzoylated nucleotide above (5, *ca.* 0.68 mmol by uv) was dried by repeated evaporation in anhydrous pyridine. This material was cyclized as described for the 5′-phosphate (1) above giving a crystalline salt which was hydrolyzed in cold ammoniacal methanol as described for compound 2. The crystalline solid produced by acidification of the pyridinium salt was compared with the cyclic phosphate 3 described above and found to be identical by ir, nmr, uv, tlc (cellulose, solvent A) and HVE (6000 V, pH 6.8, 3 hr).

**Registry No.**—2, 15465-99-3; 3, 15466-01-0; 4, 14433-48-8; 5, 17955-19-0; 6, 147-94-4.

(17) Carbon values in nucleotide analysis are often low because carbon is trapped in the melt which remains in the combustion boat.

**Acknowledgment.**—The author wishes to express his appreciation to Mr. A. J. Taylor for technical assistance, to the Physical and Analytical Chemistry Department of The Upjohn Co. for elemental, uv, and ir determinations, and to Mr. J. F. Zieserl, Jr., for performing the nmr experiments. We are indebted as well to Drs. R. C. Kelly, F. Kagan, and S. S. Cohen for helpful discussion.

## Anomalous Reactions of 4-Methylnicotinic Acids

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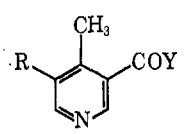
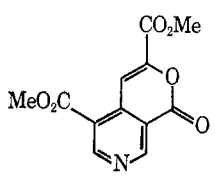
In connection with a problem of alkaloid synthesis, 4-methyl-5-carbomethoxynicotinyl chloride (**1a**) was needed. The dimethyl ester **1b** was prepared by the reported procedure leading to the diethyl ester[1] and was hydrolyzed partially to the acid ester **1c**. Exposure of the latter to oxalyl chloride and triethylamine yielded unexpectedly a mixture whose methanolysis gave the enol lactone **2** and, in trace quantity, the diester **1b**. Thus condensation on the methyl site by the oxalyl moiety appeared to be the preponderant reaction path which even variation of reaction conditions could not avoid.[2]

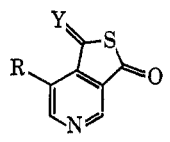




**1a**, R = $CO_2Me$; Y = Cl
**b**, R = $CO_2Me$; Y = OMe
**c**, R = $CO_2Me$; Y = OH
**d**, R = H; Y = OH

**2**

Interaction of the acid **1c** with thionyl chloride under a variety of conditions yielded exclusively an anomalous product containing sulfur and chlorine whose instability prevented its elemental analysis. Its facile hydrolysis, the major source of its lability, produced the thioanhydride **3b**. Its mode of formation, spectral properties and comparison with models (*vide infra*) showed it to possess structure **3a**.

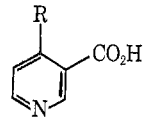


**3a**, R = $CO_2Me$; Y = $Cl_2$
**b**, R = $CO_2Me$; Y = O
**c**, R = H; Y = $Cl_2$
**d**, R = H; Y = O

(1) R. Lukeš and J. Kuthan, *Collect. Czech. Chem. Commun.*, **25**, 2173 (1960).

(2) *Cf.* N. Ikekawa, *Chem. Pharm. Bull. Jap.*, **6**, 269 (1958), for examples of related condensations of **1d**.

In view of these anomalous results, a study of the behavior of 4-methylnicotinic acid (**1d**) toward thionyl chloride was indicated. While Webb and Corwin[3] had reported the isolation of a product containing sulfur and chlorine without suggesting its constitution, Preobrazhenskii and Beer[4] claimed the isolation of 4-trichloromethylnicotinic acid (**4a**) as evidenced by its transformation to cinchomeronic acid (**4b**) on hydrolysis. Repetition of the thionyl chloride reaction now yielded a crystalline $C_7H_3ONSCl_2$ substance whose melting characteristics were identical with those of the products of the aforementioned research groups. Mild hydrolysis of the compound led to the thioanhydride **3d**, which could be prepared also by the successive treatments of acid **4b** with thionyl chloride

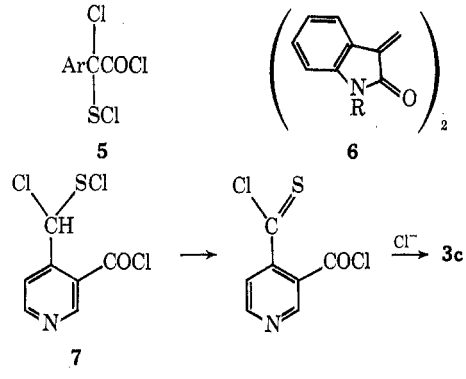


**4a**, R = $CCl_3$
**b**, R = $CO_2H$

and hydrogen sulfide. Thus the dichlorothio compound appeared to possess structure **3c**, consonant with its spectral properties.

The proton magnetic resonance spectra of the abnormal products of thionyl chloride treatment and their hydrolysis products (**3a–d**) revealed the absence of the 4-methyl hydrogens. The infrared spectra of **3a** and **3c** exhibited carbonyl bands attributable to the thiolactone moiety at 5.74–5.79 $\mu$, while the spectra of the thioanhydrides **3b** and **3d** showed peaks at 5.70 and 5.81 $\mu$, respectively.[5] The mass spectra of the sulfur compounds were of greatest diagnostic value. The spectrum of the dichloride **3a** showed a molecular ion peak [$C_9H_5O_3NS^{35}Cl_2$, *m/e* 276.9379 (calcd 276.9367)], a fragment from loss of chlorine [$C_9H_5O_3NS^{35}Cl_2$, *m/e* 241.9687 (calcd 241.9679)], and a subsequent one from loss of methyl chloride [$C_8H_2O_3NS$, *m/e* 191.9761 (calcd 191.9755)]. The latter fragmentation was supported by a metastable ion peak at 152.3. Since this unusual cleavage had to involve the methyl ester unit, an alternate fragmentation pattern was expected for **3c**. The spectrum of this structurally simpler dichloride revealed a molecular ion peak [$C_7H_3ONS^{35}Cl_2$, *m/e* 218.9312 (calcd 218.9312)], a fragment from loss of chlorine, and a subsequent loss of carbon monoxide [$C_6H_3NS^{35}Cl_2$, *m/e* 155.9674 (calcd 155.9675)], as supported by a metastable ion peak at 132.3.

The formation of sulfur compounds in the treatment of 4-methylnicotinic acids with thionyl chloride underlines the ease with which this reagent undergoes base-induced condensation with active methylene compounds of structure **5**[6] and the transformation of oxindoles into isoindigos (**6**).[7] On the assumption of the intermediacy of a chloroalkyl cholorosulfide, in analogy with **5**, the transmutation of **1d** into **3c** can be assumed to follow path **7** → **3c**.



**5** **6**

**7**

## Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Proton magnetic resonance spectra on solutions containing tetramethylsilane as internal standard were recorded on a Varian A-60 spectrometer. Mass spectra were recorded on a A.E.I. MS-9 spectrometer.[8]

**Dimethyl 4-methylpyridine-3,5-dicarboxylate** (**1b**) was prepared by the procedure recorded for the synthesis of the diethyl ester.[1] Crystallization from hexane yielded **1b**: mp 99–100°; ir ($CCl_4$) C=O 5.78 $\mu$ (s); pmr ($CDCl_3$) $\delta$ 2.78 (s, 3, C-Me), 3.95 (s, 6, methoxyls), and 8.92 ppm (s, 2, pyridyl Hs).

*Anal.* Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30. Found: C, 57.59; H, 5.53.

**4-Methyl-5-carbomethoxynicotinic Acid** (**1c**).—A solution of 1.00 g of ester **1b** and 0.33 g of potassium hydroxide in 0.5 ml of water and 15 ml of methanol was left standing for 8 hr. Dry ether, 300 ml, was added and the resultant precipitate filtered and dried. The solid was dissolved in a minute amount of water and the solution brought to pH 4 with hydrochloric acid. The resultant precipitate (0.70 g) was filtered and dried. Its sublimation under vacuum gave the acid **1c**: mp 190–192°; ir (Nujol) C=O 5.78–5.92 $\mu$ (s).

*Anal.* Calcd for $C_9H_9O_4N$: C, 55.38; H, 4.65. Found: C, 55.25; H, 4.53.

**Lactonic Diester 2.**—A solution of 0.2 ml of freshly distilled oxalyl chloride in 3 ml of chloroform was added over a 0.5-hr perid to an ice-cold mixture of 186 mg of **1c** and 0.3 ml of triethylamine in 15 ml of dry chloroform and the orange mixture kept at room temperature for 1 hr. Methanol (1 ml) and chloroform (25 ml) were added and the solution was washed with a solution of an excess of sodium bicarbonate. Evaporation of the solvent and crystallization of the residue yielded 140 mg of lactone **2**: mp 196–197°; ir (Nujol) C=O 5.74 (s), 5.82 (s), C=C 6.10 $\mu$ (s); pmr ($CDCl_3$) $\delta$ 3.99, 4.04 (s, 3, methoxyls), and 8.59, 9.55, 9.70 ppm (s, 1, ring Hs).

*Anal.* Calcd for $C_{12}H_9O_6N$: C, 54.76; H, 3.45. Found: C, 54.82; H, 3.57.

The mother liquor from crystallization of **2** contained a trace of **1b**.

**Dichlorothiolactone 3a and Its Hydrolysis Product 3b.**—A mixture of 250 mg of the acid **1c** and 2.5 ml of thionyl chloride was refluxed for 3 hr. The solution was evaporated under vacuum and the dark residue extracted with hot, dry hexane. Concentration of the extract yielded 170 mg of a solid mixture of **3a** and **3b**. Attempts to isolate pure **3a** invariably failed. Gradient sublimation of the mixture followed by crystallization from hexane produced the thioanhydride **3b**: mp 72–74°; ir ($CCl_4$) C=O 5.70 (s), 5.81 $\mu$ (s); pmr ($CCl_4$) $\delta$ 3.98 (s, 3, OMe), and 9.09, 9.32 ppm (s, 1, pyridyl Hs); (mass) $C_9H_5O_4NS$, *m/e* 222.9944 (calcd 222.9939).

*Anal.* Calcd for $C_9H_5O_4NS$: C, 48.43; H, 2.26. Found: C, 48.08; H, 2.20.

**Dichlorothiolactone 3c.**—4-Methylnicotinonitrile was prepared by the method of Bobitt and Scola[9] and hydrolyzed by the acid scheme used by Webb and Corwin.[3] A mixture of 200 mg of acid **1d** and 2 ml of thionyl chloride was refluxed for 2 hr. The

(3) J. L. Webb and A. H. Corwin, *J. Amer. Chem. Soc.*, **66**, 1456 (1944).
(4) N. A. Preobrazhenskii and A. A. Beer, *Zh. Obshch. Khim.*, **15**, 667 (1945); *Chem. Abstr.*, **40**, 5724 (1946).
(5) *Cf.* a review of infrared spectra of thio acids and derivatives by R. A. Nyquist and W. J. Potts, *Spectrochim. Acta*, **7**, 514 (1959).
(6) M. S. Simon, J. B. Rogers, W. Saenger, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **89**, 5838 (1967).
(7) T. L. Reid, Ph.D. Dissertation, Iowa State College, 1954; F. De Martiis, *Ann. Chim.* (Rome), **47**, 1238 (1957); A. Katner, private communication.
(8) The spectrometer was acquired under Grant GP-5234 of the National Science Foundation.
(9) J. M. Bobitt and D. A. Scola, *J. Org. Chem.*, **25**, 560 (1960).

solution was evaporated under vacuum, benzene was added to the residue and the solution taken to dryness once again. Sublimation of the residue gave 225 mg of crystalline **3c**: mp 162–163° (lit.[3] mp 163–164°,[3] 161–162° [4]); ir ($CCl_4$) C=O 5.79 $\mu$ (s).

*Anal.* Calcd for $C_7H_3ONSCl_2$: C, 38.20; H, 1.37; Cl, 32.11. Found: C, 38.02; H, 1.47; Cl, 32.06.

**Thioanhydride 3d.**—Exposure of the benzene solution of **3c** to atmospheric moisture some time prior to the above work-up gave **3d**: mp 92–93°; ir ($CCl_4$) C=O 5.81 $\mu$ (s); pmr ($CDCl_3$) $\delta$ 7.84, 9.09 (d, 1, $J$ = 8.0 cps, pyridyl Hs), and 9.25 [s, 1, $C_2$–H]; (mass) mol wt, 165.

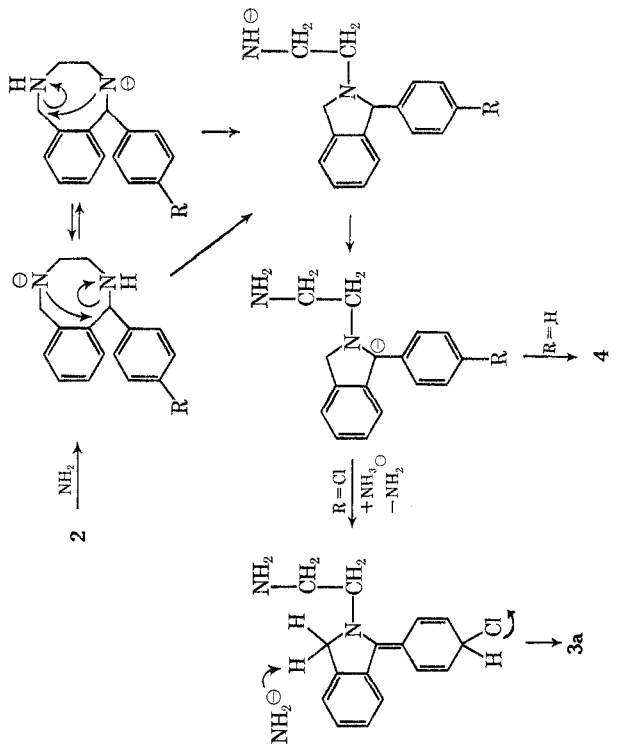
*Anal.* Calcd for $C_7H_3O_2NS$: C, 50.90; H, 1.83. Found: C, 50.84; H, 2.00.

A mixture of 3 g of cinchomeronic acid (**4b**) and 5 ml of thionyl chloride in 25 ml of benzene was refluxed for 1 hr. The solution was evaporated to dryness and the dark residue taken up in 15 ml of pyridine under cooling in an ice bath. A slow stream of hydrogen sulfide was passed through the solution over a period of 2 hr. The solvent was evaporated under vacuum and the residue shaken with a mixture of benzene and sodium bicarbonate solutions. The organic extract was evaporated and the residue crystallized from cyclohexane. Sublimation of the product, 1 g, yielded **3d**: mp, mmp 92–93°; spectra identical with those above.

**Registry No.**—**1c**, 18181-21-0; **2**, 18181-22-1; **3b**, 18181-23-2; **3d**, 18181-24-3.

**Acknowledgment.**—Support of this work by the U. S. Department of Health, Education and Welfare (Grant GM-11571) is acknowledged gratefully.

SCHEME II



## Rearrangements of Benzodiazocines to Isoindoles and Isoindolines

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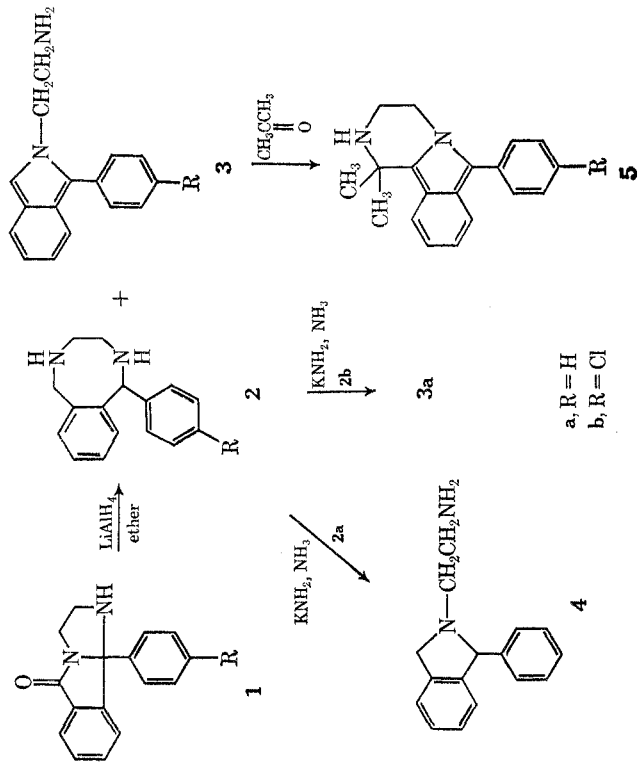
*Received July 12, 1968*

The syntheses of 2,5-benzodiazocines **2a** and **2b** have recently been reported.[1] In the course of studying the alkylation of **2a** in liquid ammonia containing potassium amide, we have discovered a novel ring contraction in which **2a** is converted into the known isoindoline **4**.[2] Surprisingly, when the chlorophenyl analog **2b** was treated with potassium amide in liquid ammonia, the chloro analog of **4** was not obtained, but dehydrochlorination occurred giving the isoindole **3a** in good yield (Scheme I). This is unusual in that the leaving group is on an aromatic ring.

It was also found that the isoindoles **3a** and **b** are byproducts in the synthesis of the 2,5-benzodiazocines themselves. These isoindoles could not be crystallized but underwent a novel reaction with acetone leading to the pyrazino[2,1-*a*]isoindoles **5a** and **b**, which were crystalline. They presumably arise through an attack of the electron-rich $\alpha$ position on the imine formed from acetone and the primary amine. The isoindole ring is so reactive that no catalyst was necessary. Merely dissolving **3** in excess acetone yields **5**.

The structure of **3a** was evident from its nmr spectrum and positive Ehrlich test[3] which indicates a

SCHEME I



(1) J. S. Sulkowski, M. A. Wille, A. Mascitti, and J. L. Diebold, *J. Org. Chem.*, **32**, 2180 (1967).

(2) W. Metlesics, T. Anton, and L. H. Sternbach, *ibid.*, **32**, 2185 (1967).

(3) D. F. Veber and W. Lwowski, *J. Amer. Chem. Soc.*, **86**, 4152 (1964).