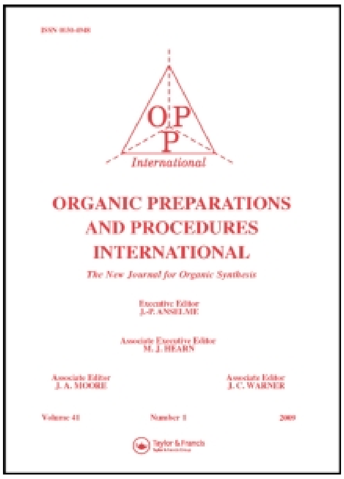

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IMPROVED PREPARATION OF PYRIDO[3',4'(4',3'):4,5]IMIDAZO [1,2-c] [1,2,3]BENZOTRIAZINES

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ducts were recrystallized from methanol to analytical purity to yield: IIa, 63%, mp. 68-69°; IIb, 57%, mp. 67-69° and IIc, 54%, mp. 85-87°, lit.[1] mp. 88-90°.

Anal. Calcd for $C_{13}H_{13}NO_5S$ (IIa): C, 52.88; H, 4.43; N, 4.74.

Found: C, 52.96; H, 4.38; N, 4.50.

Anal. Calcd for $C_{14}H_{15}NO_6S$ (IIb): C, 51.68; H, 4.64; N, 4.30.

Found: C, 51.69; H, 4.66; N, 4.23.

REFERENCES

† Present address: Rohm and Haas Co., Philadelphia, Pa.

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1. P. Rajagopalan and C. N. Talaty, Heterocycles, 3, 563 (1975).
2. T. Bacchetti and A. Alemagna, Rend. ist. lombardo sci. Pt. I, 91, 30 (1975). See Chem. Abstr., 52, 11749e (1958).
3. T. Bacchetti and A. Alemagna, Atti acad. nazl. Lincei Rend., Classe sci. fis. mat. e nat., 24, 161 (1958). See also Chem. Abstr., 52, 18299 (1958).

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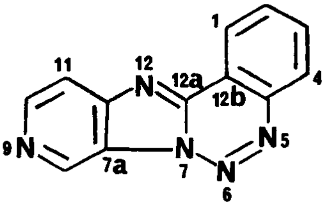
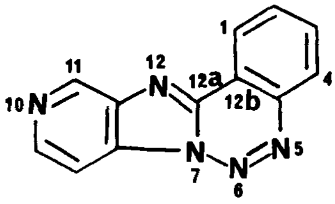
In 1968, we reported a new system, pyrido[3',4',(4',3'):4,5]imidazo[1,2-c][1,2,3]benzotriazine (1) which could theoretically exist in two isomeric forms 1a or 1b[1]. At that time, chromatographic analyses afforded only



1a



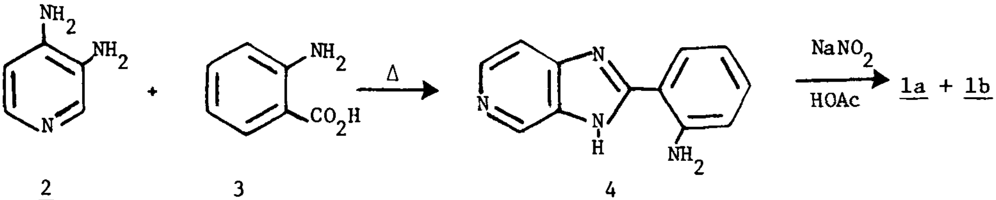
1b

a single product and available chemical and physical methods proved inadequate to establish the identity of our product as 1a, 1b, or a mixture of both. Recently, 1 was reported to exhibit confirmed activity in the leukemia P 388 test system,[2] renewing our interest in this class of compounds as potential anticancer agents. ^{13}C NMR and ^{1}H NMR studies revealed that the product is indeed a mixture of 1a and 1b. If we had been dealing with a single isomer, a total of seven absorptions would have been expected in the ^{13}C spectrum (excluding the quaternary carbons). However, thirteen absorptions were noted. The following chemical shifts were observed:

C^1	128.1 128.5	C^2	131.1 131.5	C^3	132.5	C^4	121.3 121.6
C^{11}	112.9 (1a) 104.5 (1b)	C^{10}	144.4 (1a) 142.2 (1b)	C^8	133.6 (1a) 141.6 (1b)		

In the ^{1}H NMR, each of the isomers exhibited distinct resonances for protons 11, 10, and 8: δ 8.14, 8.62, and 9.66 (1a); 8.19, 8.62, and 9.32 (1b), all appearing as complex multiplets. The isomerism described appears general for all unsymmetrical 1,2,3-benzotriazines that have been synthesized by similar procedures.[3]

We recently prepared the title compound by condensing 3,4-diaminopyridine (2) and anthranilic acid (3) in polyphosphoric acid to afford 2-o-aminophenylimidazo[4,5-c]pyridine (4), which on diazotization undergoes cyclization to 1. This procedure is much superior to that described earlier[1] and is now reported herein.



2-o-Aminophenylimidazo[4,5-c]pyridine (4).- Polyphosphoric acid (175 ml) was heated to 120°, and then added to a mixture of 3,4-diaminopyridine (6.7 g, 0.0616 mol) and anthranilic acid (8.44 g, 0.0616 mol) in a 1000 ml 3-necked round-bottomed flask provided with a mechanical stirrer, calcium chloride drying tube, and nitrogen inlet. The temperature of the reaction mixture was then raised, with constant stirring, to 250° ± 5°. After 3 hrs at 250° and an additional hour at 210°, the mixture was cooled to 70° and poured into a beaker containing 1000 ml of cold water (0°C). The flask was rinsed with an additional 500 ml of water and the total solution was brought up to pH 8 with concentrated ammonium hydroxide. The pale yellow precipitate that formed was washed with water, dried and extracted with 250 ml of boiling methanol. Treatment of the hot extract with decolorizing carbon, filtration, and evaporation of the solvent under reduced pressure afforded the crude product which was further triturated with warm acetonitrile (about 150 ml). The mixture was cooled in an ice bath for 2 hrs, and the product was isolated by filtration and dried; yield: 8.7 g (67.5%), mp. 192-196°. This material was found to be pure enough to be used in the next step. A pure sample can be obtained by fractional recrystallization from ethanol, mp. 202-204°, lit.[4] mp. 242-245°, R_f = 0.10 using a Brinkman silica plate and acetonitrile as the eluting solvent.

Pyrido[3',4'(4',3'):4,5]imidazo[1,2-c][1,2,3]benzotriazine(1).- 2-o-Aminophenylimidazo[4,5-c]pyridine (5 g, 0.024 mol), 17 ml of acetic acid and 25 ml of water were placed in a 100 ml round-bottomed flask. The mixture was heated to 35-40° to effect solution and a solution of sodium nitrite (3.4

g, 0.049 mol) in 6 ml of water was added with stirring. The resulting mixture was heated rapidly to 70°, then cooled to ambient temperature and, after 1 hr, diluted with 300 ml of water. The mixture was made basic with concentrated ammonium hydroxide (pH 8). The solid that was formed was removed by filtration, washed thoroughly with water, and extracted with hot ethanol (100 ml). The extract was treated with decolorizing charcoal and then filtered hot. Crude product crystallized from the filtrate on cooling. It was collected by filtration, washed with ether, and dried *in vacuo* to afford 3.5 g, 66.5% yield (average yield = 66-72%), mp. 194-195°, lit.[1] mp. 192-194°. Tlc on a Brinkman silica gel plate, $R_f = 0.15$ (acetonitrile) revealed only one spot.

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REFERENCES

1. H. Spector and M. M. Joullié, J. Heterocyclic Chem., 5, 301 (1968).
2. Private communication from Dr. Robert B. Ing in the Drug Research and Development Program of the National Cancer Institute (Compound NSC 128734).
3. L. L. Zaika and M. M. Joullié, J. Heterocyclic Chem., 3, 289, 444 (1966).
4. Richard H. Spector, Ph.D. Dissertation, University of Pennsylvania, 1968, p. 36. The literature melting point appears to be a typographical error. The given melting point is correct and was determined by different workers on different samples.