

**6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazines.
A New Heterocyclic Ring System (1,2)**

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Received August 13, 1971

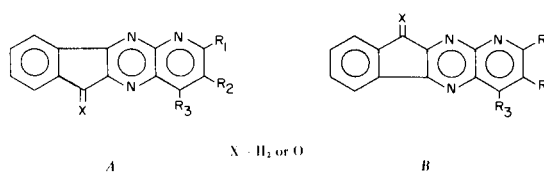
Condensation of 1,2-indanedione and 1,2,3-indanetrione hydrate (ninhydrin) with 2,3-diaminopyridines gave a number of compounds belonging to the hitherto unknown 6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine ring system. The unsymmetrical nature of the reactants can theoretically result in isomeric ring closure products. Assignment of the 6*H*-ring system was based upon the identity of 6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one obtained from 2,3-diaminopyridine and ninhydrin with material prepared by unequivocal synthesis. The direction of cyclization of ninhydrin and 1,2-indanedione with the diamines was shown to be the same by reduction of the indenopyridopyrazinones to the corresponding indenopyridopyrazines. Some physical, chemical, and tumor growth-inhibitory properties of the products are reported.

Surprisingly, the reactions of 1,2-indanedione and 1,2,3-indanetrione (ninhydrin) with 2,3-diaminopyridine and its derivatives have not been previously reported, although the analogous reactions with *o*-phenylenediamine have been known since early in this century (3,4). We should like now to describe the synthesis and characterization of a number of 6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine derivatives, which were made and evaluated for antitumor activity in part because of the structural resemblance of the indenopyridopyrazine ring system with the pyridocarbazole system found in ellipticine, a tumor-inhibitory alkaloid (5).

Indenopyridopyrazinones **1-8** (Table I) were obtained by mixing warm equimolar solutions of the appropriately substituted 2,3-diaminopyridine and ninhydrin in 50% acetic acid. Indenopyridopyrazines **12-15** and **17** (Table II) were similarly prepared by condensation of 1,2-indanedione with the appropriate diamine in aqueous acetic acid. Yields for the ninhydrin reactions ranged between 90 and 97%, but for the 1,2-indanedione reactions between 33 and 77%. The lower range of yield figures for the indanedione reactions reflects the ability of 1,2-indanedione to undergo self-condensation (6) and to, therefore, be unavailable in part for condensation with the diamine.

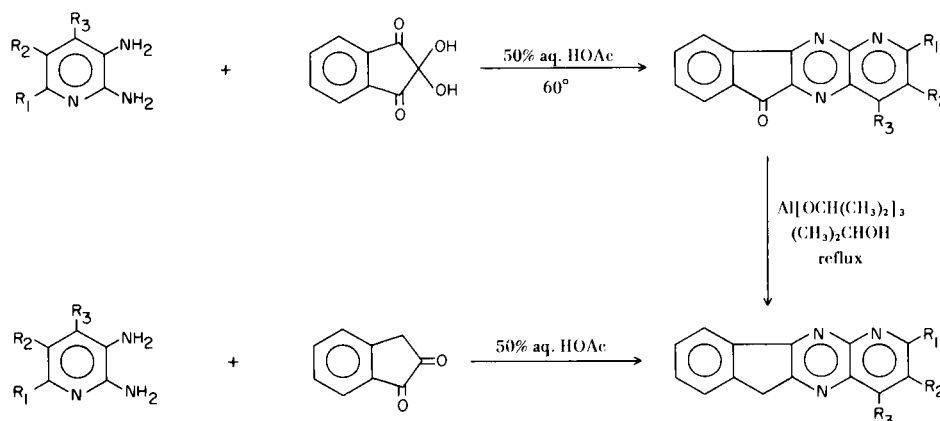
However, because the heterodiamine is unsymmetrical in nature, these condensation reactions can give two theoretically possible ring closure products. Thus, the reactions of 2,3-diaminopyridines with 1,2-indanedione can result in products in which the methylene function is located *anti* (structure *A*) or *syn* (structure *B*) with respect to the pyridine ring nitrogen atom. Similarly with

ninhydrin, the condensation products may have the *anti* or *syn* arrangement with respect to the carbonyl group and the pyridine nitrogen atom. Furthermore, it cannot be assumed that the direction of cyclization of 1,2-indanedione with the diamine is necessarily the same as that of ninhydrin. Based upon the evidence described below, the various condensation products obtained during this investigation have been assigned the 6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine ring system (*A*), rather than the isomeric 10*H*-system. In no instance was there observed the formation of mixtures of isomeric ring closure products.

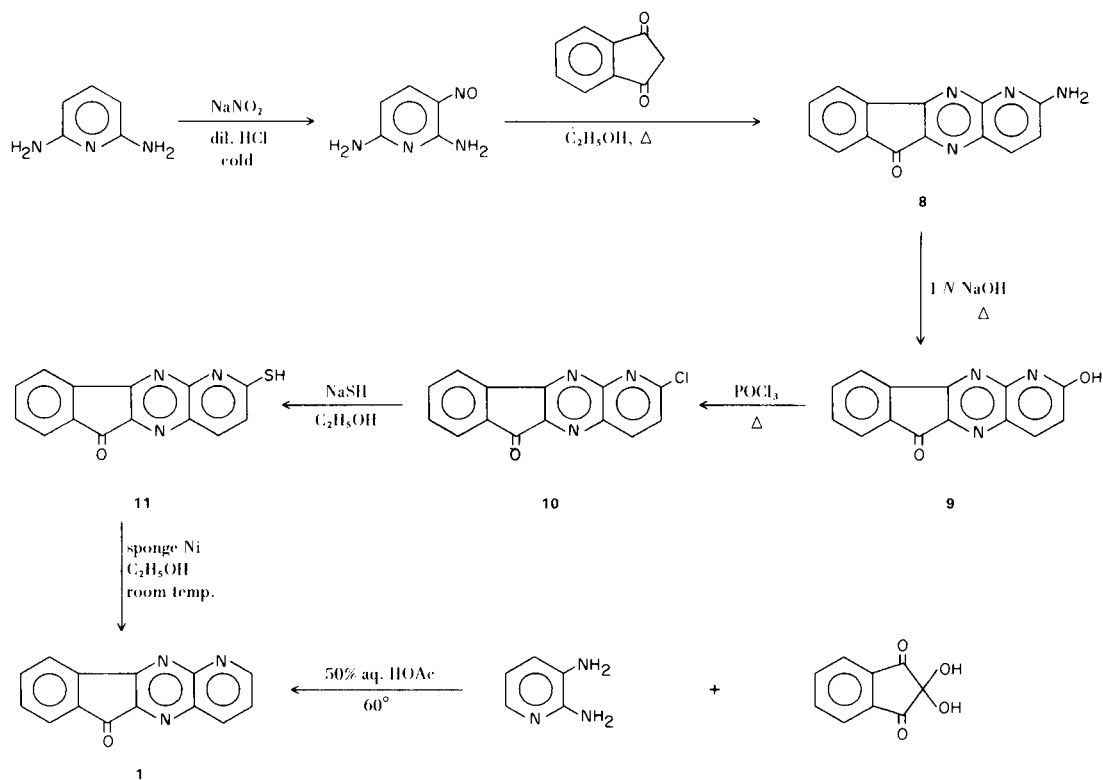


Reduction of the carbonyl function of some selected ninhydrin condensation products to methylene (Scheme I) showed that the direction of cyclization of ninhydrin and 1,2-indanedione with the diaminopyridine was the same. Reduction of **3** ($R_1 = R_3 = \text{H}$, $R_2 = \text{Br}$) and **5** ($R_1 = \text{CH}_3$, $R_2 = \text{Br}$, $R_3 = \text{H}$) with aluminum isopropoxide in refluxing isopropanol afforded **13** and **15**, respectively. These products were indistinguishable from the materials which were obtained by condensation of 1,2-indanedione with 2,3-diamino-5-bromopyridine and 2,3-diamino-5-bromo-6-methylpyridine. The reduction of a carbonyl group to methylene, rather than to a carbinol,

SCHEME I



SCHEME II



under Meerwein-Ponndorf conditions is unusual but not unprecedented: a similar reduction was observed by Pearson, Mitsch, and Cromwell (7) in the closely related formation of 11*H*-indeno[1,2-*b*]quinoxaline from the corresponding 11-one derivative. Since the ninhydrin condensations and the aluminum isopropoxide reductions both go in high yield, this two-step sequence for the preparation of 6*H*-indenopyridopyrazines offers an advantage over the 1,2-indanedione condensation method:

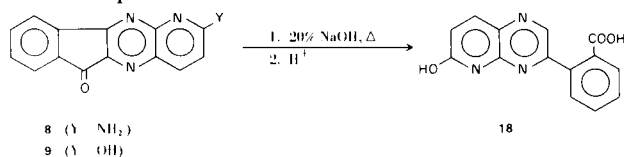
it avoids the necessity of preparing 1,2-indanedione, which, to our knowledge, is not commercially available. In the present study, compound **16**, for example, was made exclusively by the two-step route in 77% overall yield based upon the starting diamine.

The absolute characterization of the 6*H*-ring system (structure *A*) for the products reported herein is based upon the identity of the ninhydrin-2,3-diaminopyridine condensation product with an authentic sample of **1**,

prepared according to the sequence shown in Scheme II. Condensation of 2,6-diamino-3-nitrosopyridine with 1,3-indanedione in boiling ethanol afforded an unambiguous specimen of 2-amino-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (**8**). Although this sample was identical with samples of **8** obtained from the reaction of ninhydrin with 2,3,6-triaminopyridine, we hesitated to rely entirely on this evidence for the characterization of compounds **1-7**; it was conceivable that, because of the additional amino function, the mode of cyclization of the triamine with ninhydrin might be different from that of 2,3-diaminopyridine and its methyl and/or halogen substituted derivatives. We, therefore, related compound **8** to compound **1** by conversion of **8** into the 2-hydroxy derivative, **9**, by the action of warm dilute sodium hydroxide. Treatment of **9** with phosphorus oxychloride gave the 2-chloro compound (**10**). Since this material proved unexpectedly resistant to catalytic dehalogenation, it was treated with sodium hydrosulfide in ethanol to give the mercapto derivative, **11**, which was then dethiated to **1** by means of sponge nickel catalyst.

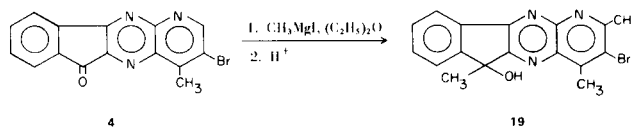
The indenopyridopyrazinones (Table I) are yellow to orange solids, insoluble in water but moderately soluble in a variety of organic solvents. They have high decomposition points and, with the exception of compound **8**, show a characteristic ultraviolet absorption pattern with long wavelength absorption at 375-385 nm [for example, for **1**: λ max (ethanol) (log ϵ) 224 (4.40), 239 (4.24), 267 (4.45), 310 (4.17), 327 shoulder (4.07), 341 shoulder (3.96), and 379 (3.79) nm]. The 2-amino function in **8** somewhat modifies the uv profile and shifts the long wave absorption signal to 421 nm. The infrared spectra show complex aromatic character and strong carbonyl absorption at 5.80-5.81 μ . The indenopyridopyrazines (Table II) are also water insoluble but are more soluble than their keto derivatives in organic solvents. The methylene function can be seen clearly in the nmr spectra as a sharp singlet at δ 4.22-4.25 ppm. The ultraviolet absorption pattern of **12** [λ max (ethanol) (log ϵ) 248 (4.14) and 348 (4.32) nm] is typical of the light absorption properties of the compounds in Table II.

The indenopyridopyrazinone system is stable to acid and to dilute base. Compounds **8** and **9**, but not **1-7**, were degraded, however, by the action of hot 20% sodium hydroxide. These reactions gave the same product, 3-(*o*-carboxyphenyl)-6-hydroxypyrido[2,3-*b*]pyrazine (**18**), the structure of which is supported by infrared, ultraviolet, and mass spectral data.



Compounds **1-7** could not be oxidized to their mono- or di-*N*-oxide derivatives under a variety of conditions attempted. Failure to achieve *N*-oxidation of indenopyridopyrazinones is consistent with earlier failures to prepare mono- and di-*N*-oxides of simple substituted pyridopyrazines (**8**). This is in contrast to the ease with which quinoxalines in general (**9**) and the 1-deaza analog of **1** in particular (**7**) undergo *N*-oxidation.

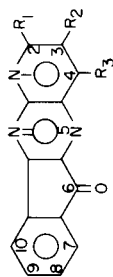
As indicated by some selected reactions, the keto function of the indenopyridopyrazinones behaved in a normal fashion with typical carbonyl reagents. Thus, compounds **1** and **4** gave their corresponding 2,4-dinitrophenylhydrazone derivatives on treatment with 2,4-dinitrophenylhydrazine and compounds **4**, **5**, and **6** afforded their respective oximes on reaction with hydroxylamine. The carbinol **19** was obtained from the reaction of **4** with methylmagnesium iodide in ether. The presence of an extra methyl group, besides that of the methyl carbinol, in the product was confirmed by microchemical analysis and by mass spectral data. The additional methyl group was assigned to the 2-position of the ring on the basis of the well-established addition of organometallic reagents across the azomethine linkage of pyridines (**10**).



Antitumor Activity.

Eight (**1**, **3**, **4**, **5**, **6**, **12**, **13**, and **14**) of the indenopyridopyrazine derivatives reported herein have been examined for *in vivo* antitumor activity against one or more transplantable mouse tumors following the standard assay procedures employed at The Children's Cancer Research Foundation (11). Compounds **4** and **6** exhibited slight to marked, but irregular, tumor inhibition in the P1534 and C1498 systems when administered intraperitoneally as suspensions in 10% polysorbate 80 (**12**) at nontoxic dosages; the drug was found to be poorly absorbed from the peritoneal cavity. Compound **4** was also slightly inhibitory towards the DBRB mammary adenocarcinoma when administered *i.p.* as a suspension in dimethylsulfoxide and water; under these conditions, compound **3** was moderately, but irregularly, tumor inhibitory in the C1498 system. There was no concomitant increase in the survival time of tumor-bearing animals treated with any of these agents. We are indebted to the late Dr. Charlotte L. Maddock and to Miss Barbara Brown for the *in vivo* antitumor data.

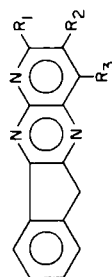
TABLE I
6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-ones



Cmpd. No.	R ₁	R ₂	R ₃	Yield, %	Decomposition Point, °C	Recrystallization Solvent	Molecular Formula	Analysis			
								C	H	N	Other
1	H	H	H	96 (a)	297-298 (b)	2-ethoxyethanol	C ₁₄ H ₇ N ₃ O	72.09 (72.11) (71.99)	3.03 (3.16) (3.16)	18.02 (18.15) (18.15)	
2	H	Cl	H	75 (c)	294-297 (b)	95% ethanol	C ₁₄ H ₆ ClN ₃ O	62.81 (62.80)	2.26 (2.36)	15.71 (15.64)	Cl, 13.24 (13.29)
3	H	Br	H	91 (a)	275 (d)	acetic acid-water	C ₁₄ H ₆ BrN ₃ O	53.87 (53.76)	1.94 (2.09)	13.47 (13.42)	Br, 25.60 (25.62)
4	H	Br	CH ₃	91 (a)	240-242 (b)	95% ethanol	C ₁₅ H ₈ BrN ₃ O	55.21 (55.54)	2.45 (2.61)	12.88 (12.73)	Br, 24.54 (24.70)
5	CH ₃	Br	H	95 (a)	230 (d)	ethyl acetate	C ₁₅ H ₈ BrN ₃ O	55.21 (55.02)	2.45 (2.72)	12.88 (12.56)	Br, 24.54 (24.54)
6	CH ₃	Br	CH ₃	96 (a)	248-251 (b)	95% ethanol	C ₁₆ H ₁₀ BrN ₃ O	56.49 (56.54)	2.96 (3.05)	12.35 (12.53)	Br, 23.49 (23.50)
7	H	CH ₃	H	92 (a)	285 (d)	2-ethoxyethanol	C ₁₅ H ₉ N ₃ O	72.86 (72.72)	3.68 (3.52)	17.00 (16.82)	
8	NH ₂	H	H	91 (a)	310 (d)	acetic acid	C ₁₄ H ₈ N ₄ O	67.73 (67.54) (67.52)	3.25 (3.51) (3.51)	22.57 (22.65) (22.49)	
9	OH	H	H	42	(d)	ethylene glycol	C ₁₄ H ₇ N ₃ O ₂	67.46 (67.00)	2.84 (3.10)	16.86 (16.79)	
10	Cl	H	H	22	(d)	ethyl acetate	C ₁₄ H ₆ ClN ₃ O	62.82 (62.79)	2.26 (2.39)	15.70 (16.14)	
11	SH	H	H	95			C ₁₄ H ₇ N ₃ OS	63.38 (63.35)	2.66 (2.95)	15.84 (15.74)	S, 12.08 (12.50)

(a) Condensation of the appropriately substituted pyridinediamine with ninhydrin. (b) Decomposes to a black tar. (c) Dethiation of **11**. (d) Turns black but does not melt. (e) Condensation of 2,6-diamino-3-nitrosopyridine with 1,3-indanedione.

TABLE II
6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazines



Cmpd. No.	R ₁	R ₂	R ₃	Method of Prepn. (a)	Yield, %	Decomposition Point, °C	Crystallization Solvent	Molecular Formula	Analysis			
									Calcd. (Found), %	C	H	N
12	H	H	H	A	70	209-213 (b)	ethyl acetate	C ₁₄ H ₉ N ₃	76.69 (76.70)	4.15 (4.15)	19.17 (19.27)	
13	H	Br	H	A	67	209-214	95% ethanol	C ₁₄ H ₈ BrN ₃	56.39 (56.09)	2.71 (2.80)	14.10 (14.10)	Br, 26.80 (27.11)
14	H	Br	CH ₃	B	60	212-219	acetone	C ₁₅ H ₁₀ BrN ₃	57.70 (57.49)	3.24 (3.32)	13.46 (13.22)	Br, 25.60 (25.10)
15	CH ₃	Br	H	A	53	228	methanol	C ₁₅ H ₁₀ BrN ₃	57.70 (57.55)	3.24 (3.21)	13.46 (13.51)	Br, 25.60 (25.84)
16	CH ₃	Br	CH ₃	B	80	242	methanol	C ₁₆ H ₁₂ BrN ₃	58.90 (58.65)	3.72 (3.88)	12.88 (12.48)	
17	NH ₂	H	H	A	33	208	methanol	C ₁₄ H ₁₀ N ₄	71.77 (71.84)	4.30 (4.47)	23.92 (23.73)	

(a) Method A: Condensation of the appropriately substituted pyridinediamine with 1,2-indanedione. Method B: Aluminum isopropoxide reduction of the corresponding indeno-pyridopyrazinone. (b) Melts without decomposition.

EXPERIMENTAL (13)

Ultraviolet absorption spectra were measured with Cary Model 11 and Model 15 spectrophotometers in 95% ethanol solution. Infrared spectra were determined with a Perkin-Elmer Model 137B spectrophotometer. Nmr spectra were obtained by means of a Varian Associates A-60 spectrometer, with tetramethylsilane as the internal standard. Melting points were taken by the capillary method in a modified Wagner-Meyer melting point apparatus (14) at a rate of heating of 2°/minute and are corrected for stem exposure.

Starting Materials.

With the exception of 2,3-diaminopyridine (purchased from Aldrich Chemical Company), the pyridinediamines required in this investigation were prepared in the laboratory according to previously described procedures. 2,3-Diamino-5-chloropyridine was made from 2-amino-5-chloropyridine (Aldrich) according to the procedure of Vaughan, Krapcho, and English (15). The following starting materials were obtained from Reilly Tar and Chemical Corporation: 2-aminopyridine, 2-amino-4-methylpyridine, 2-amino-5-methylpyridine, 2-amino-6-methylpyridine, 2-amino-4,6-dimethylpyridine, and 2,6-diaminopyridine. The preparation of 2-amino-5-bromopyridine *via* bromination of 2-aminopyridine has been described by Case (16). The method of Vaughan, Krapcho, and English (15) was used to prepare 2,3-diamino-5-bromopyridine from 2-amino-5-bromopyridine. 2,3-Diamino-5-bromo-4-methylpyridine and 2,3-diamino-5-bromo-6-methylpyridine were obtained according to the procedure of Israel and Day (8). The method of Graboyes and Day (17) was used to obtain 2,3-diamino-5-bromo-4,6-dimethylpyridine. 2,3-Diamino-5-methylpyridine was prepared from 2-amino-5-methylpyridine by nitration in concentrated sulfuric acid at 45-50°, followed by hydrogenation in the presence of 5% palladium on carbon; our results disagree with a recent claim (18) that 2-amino-5-methyl-3-nitropyridine is not effectively reduced by catalytic means. The method of Titov (19) was used to obtain 2,6-diamino-3-nitrosopyridine from 2,6-diaminopyridine. 2,3,5-Triaminopyridine was prepared *in situ* by catalytic hydrogenation of the nitroso compound as described below; the triamine free base is extremely unstable and cannot be isolated, although the product can be obtained as the dihydrochloride (19) or sulfate (17) salt.

The procedure of House, Gannon, Ro, and Wluka (6) was used to prepare 1,2-indanedione from 1-indanone.

Condensation of Pyridinediamines with Ninhydrin: Preparation of 6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-ones (1-7).

Equimolar quantities of the pyridinediamine and ninhydrin (1,2,3-indanetrione hydrate) were dissolved separately in 50% aqueous acetic acid (40 ml./gram). The individual solutions were warmed to 60° and the ninhydrin solution was added to the diamine solution with stirring. The reaction mixture turned yellow to green and a bright yellow powder began to separate. The suspension was stirred for 1 hour at 60° and then permitted to stand at room temperature overnight. The product was collected and purified by crystallization. The crystallization solvent, yield, decomposition temperature, and analytical data for compounds 1-7, prepared by this general procedure, are given in Table I. Purified samples showed single spots on paper chromatography in two solvent systems [1-butanol:acetic acid:water (4:1:1) and 2-propanol:ammonia:water (3:1:5)].

2-Amino-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (8).

A. Condensation of 2,3,6-Triaminopyridine with Ninhydrin.

A solution of 1.0 g. (7.2 mmoles) of 2,6-diamino-3-nitrosopyridine in 25 ml. of absolute ethanol and 20 ml. of glacial acetic acid was shaken under hydrogen in a Parr apparatus in the presence of 200 mg. of 5% palladium on charcoal; reduction of the nitroso function was complete within 30 minutes. The catalyst was separated by filtration and the filtrate (pale blue solution) was permitted to fall directly into a solution of 1.28 g. (7.2 mmoles) of ninhydrin in 100 ml. of 50% aqueous acetic acid. The solution turned dark red almost instantaneously and a dark red precipitate began to form. The suspension was stirred at 60-65° for 2 hours under nitrogen. After overnight refrigeration, the product was collected, washed with cold methanol, and air dried.

B. Condensation of 2,6-Diamino-3-nitrosopyridine with 1,3-Indanedione.

To a suspension of 3.45 g. (0.025 mole) of 2,6-diamino-3-nitrosopyridine in 250 ml. of absolute ethanol was added, with stirring, a solution of 3.65 g. (0.025 mole) of 1,3-indanedione in 75 ml. of absolute ethanol. The mixture was heated at reflux for 3 hours under nitrogen, during which time the nitroso compound gradually dissolved. After overnight refrigeration, a dark red-brown solid was separated by filtration, washed with cold methanol, and dried. The crude product was crystallized several times from glacial acetic acid with the aid of charcoal. The purified material (5.75 g.) crystallized from acetic acid as small yellow needles, which turned orange on drying. Drying at elevated temperature (120°) under vacuum turned the product back to bright yellow.

2-Hydroxy-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (9).

A suspension of 1.24 g. (5 mmoles) of **8** in 100 ml. of 1*N* sodium hydroxide was heated at reflux with stirring for 3 days. The resulting dark red solution was refrigerated overnight and the small quantity of inorganic material which precipitated was removed and discarded. The reaction solution was acidified to pH 1 by the addition of 6 *N* hydrochloric acid. The yellow solid which formed was collected by suction filtration, washed with water, and dried. The crude product was subjected to continuous extraction with pyridine in a Soxhlet apparatus overnight. Upon cooling, the pyridine solution deposited small yellow-orange crystals which were separated, washed with ethanol, and dried. Two crystallizations from ethylene glycol afforded the analytical sample.

2-Chloro-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (10).

A suspension of 800 mg. (2.4 mmoles) of **9** in 15 ml. of freshly distilled phosphorus oxychloride was heated at reflux for 2 hours. Excess phosphorus oxychloride was removed under reduced pressure and the dark green residue was hydrolyzed by the addition of ice and water. The pH of the resulting suspension was adjusted to 7 with dilute ammonia. The aqueous mixture was shaken with chloroform (6 x 40 ml.) and the combined chloroform extracts were treated with charcoal and dried over magnesium sulfate. Evaporation of the chloroform solution left a dark yellow powder, which was crystallized several times from ethyl acetate to give bright yellow microcrystalline solid.

2-Mercapto-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (11).

A sodium hydrosulfide-ethanol solution was prepared by passing hydrogen sulfide for 30 minutes through 100 ml. of absolute ethanol in which 250 mg. of sodium metal had previously been

dissolved. To this solution was added 810 mg. (3 mmoles) of **10** and the orange suspension was heated at reflux for 30 minutes. The resulting red solution was reduced to half volume. Addition of 10 ml. of water and a few drops of concentrated hydrochloric acid resulted in the precipitation of bright orange solid. The product was separated by filtration, washed well with water, and dried. No purification method could be found for this product and it was submitted for microanalysis after verification of the presence of sulfur and absence of chlorine by the sodium fusion method. The material showed a single spot on thin layer chromatography in a benzene:ethanol (4:1) solvent system.

Dethiation of 11: Alternate Preparation of 6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one (1).

A sample of **11** (1.0 g., 3.8 mmoles) was suspended in 25 ml. of absolute ethanol. To this orange suspension was added a suspension of 7 ml. (packed volume) of Davison sponge nickel, apparent bulk density 0.9 (20), in absolute ethanol. The mixture was stirred at room temperature for 5 hours. The catalyst and unchanged starting material were separated by filtration through glass fiber filter paper with the aid of Celite (21). The yellow filtrate was evaporated to dryness and the residue (0.67 g.) was washed several times with hot ethyl acetate. The solid was crystallized several times from 95% ethanol to give yellow microcrystalline material, m.p. 294-297° dec., identical with the product from the reaction of 2,3-diaminopyridine with ninhydrin.

6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (12).

To a solution of 3.27 g. (0.03 mole) of 2,3-diaminopyridine in 50 ml. of 50% aqueous acetic acid was added with stirring a solution of 4.38 g. (0.03 mole) of 1,2-indanedione in 50 ml. of 50% aqueous acetic acid. The reaction mixture was warmed at 80° for 30 minutes. Evaporation of the dark green solution left an oily residue, which was taken up in absolute ethanol. After overnight refrigeration, the small quantity of yellow-green solid which had precipitated was separated and discarded. The filtrate was evaporated to dryness and the oily residue was dissolved in isopropyl alcohol. The solution was treated with charcoal and evaporated to dryness. This process of dissolution in isopropyl alcohol with charcoal, followed by evaporation, was repeated until the residue appeared as a solid. The pale green solid was crystallized twice from ethyl acetate, once with the aid of charcoal; pale yellow needles, 4.6 g.

3-Bromo-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (13).

A. Condensation of 2,3-diamino-5-bromopyridine with 1,2-Indanedione.

To a solution of 0.94 g. (5 mmoles) of 2,3-diamino-5-bromopyridine in 30 ml. of 50% aqueous acetic acid was added with stirring a solution of 0.73 g. (5 mmoles) of 1,2-indanedione in 125 ml. of 50% aqueous acetic acid. The bright orange colored reaction solution was stirred for 2.5 hours at room temperature. Water was added to precipitate the product, which was collected and dried; pale yellow needles, 1.0 g.

B. Meerwein-Ponndorf Reduction of 3.

A mixture of 0.94 g. (3 mmoles) of **3** and 3.37 g. (5.5 times excess) of aluminum isopropoxide in 70 ml. of isopropyl alcohol was heated at reflux for 19 hours. The apparatus was set for distillation and 55 ml. of isopropyl alcohol-acetone azeotrope were collected. To the dark green residue was added 210 ml. of 0.3 *N* hydrochloric acid and the mixture was refrigerated overnight. The pale green solid was separated by filtration and resus-

pended in 100 ml. of 5% sodium bicarbonate. The product was again collected, washed with water, and dried. Repeated crystallization of the crude material from acetone with the aid of charcoal gave 0.53 g. of pale yellow needles, identical with the material prepared by method A.

3-Bromo-4-methyl-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (14).

2,3-Diamino-5-bromo-4-methylpyridine (3.03 g., 0.015 mole) in 125 ml. of 50% aqueous acetic acid was treated with 1,2-indanedione (2.19 g., 0.015 mole) in 50 ml. of 50% aqueous acetic acid at 60° for 10 minutes. The mixture was refrigerated for a few hours and the product was collected, washed with water, and dried; pale yellow needles, 3.61 g.

3-Bromo-2-methyl-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (15).

A. Condensation of 2,3-Diamino-5-bromo-6-methylpyridine with 1,2-Indanedione.

2,3-Diamino-5-bromo-6-methylpyridine (1.01 g., 5 mmoles) in 30 ml. of 50% aqueous acetic acid was treated with 1,2-indanedione (0.73 g., 5 mmoles) in 80 ml. of 50% aqueous acetic acid at 80° for 2 hours. The solution was cooled and refrigerated overnight. A small quantity of dark solid was separated and discarded, then water was added to the reaction solution to precipitate the product as a pale-green powder. The solid was collected and crystallized several times from methanol until it showed as a single spot on thin layer chromatography (1-butanol:acetic acid:water 4:1:1); pale yellow needles, 0.83 g.

B. Meerwein-Ponndorf Reduction of 5.

The reduction procedure was the same as that described for the preparation of **13** by method B. A 0.98 g. sample of **5** gave 0.75 g. of product after crystallization from absolute ethanol. The pale yellow solid obtained from aluminum isopropoxide reduction of **5** was indistinguishable from material prepared by method A.

3-Bromo-2,4-dimethyl-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (16).

To a suspension of 0.68 g. (2 mmoles) of **6** in 250 ml. of hot isopropyl alcohol was added dropwise over a period of 1 hour a solution of 2.24 g. of aluminum isopropoxide (5.5 times excess) in 125 ml. of isopropyl alcohol. During the addition, solvent was continuously removed by distillation at a rate which maintained constant volume in the reaction flask. After complete addition, the reaction mixture was heated for 6 hours with slow distillation to ensure immediate removal of acetone formed in the reaction. The solvent was then reduced to 15 ml. by distillation. To the dark green solution was added 200 ml. of 1 *N* hydrochloric acid and the mixture was refrigerated for several hours. A green solid was collected, then resuspended in 100 ml. of 5% sodium bicarbonate solution. The solid was again collected, washed with water, and dried. The reaction gave 0.52 g. of pale yellow needles after crystallization.

2-Amino-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (17).

A 0.59 g. sample of 2,6-diamino-3-nitrosopyridine (4.3 mmoles) dissolved in 40 ml. of absolute ethanol-glacial acetic acid (5:3 v:v) was hydrogenated on a Parr apparatus in the presence of 200 mg. of 5% palladium on charcoal. The catalyst was separated by suction filtration and the pale blue filtrate was allowed to pass directly into a solution of 0.63 g. (4.3 mmoles) of 1,3-indanedione in 20 ml. of 50% aqueous ethanol. The reaction mixture was immediately flushed with nitrogen and was warmed at 50-55° for 1 hour. The mixture was stirred at room temperature overnight.

The yellow-orange solid was collected, washed with water, and dried. Crystallization of the product from methanol gave 0.33 g. of orange needles.

3-(*o*-Carboxyphenyl)-6-hydroxypyrido[2,3-*b*]pyrazine (**18**).

A mixture of 1.24 g. (5 mmoles) of **8** in 80 ml. of 20% sodium hydroxide was heated at reflux for 24 hours. When cool, the reaction mixture was filtered through glass fiber filter paper to remove a small quantity of dark green solid and the yellow filtrate was acidified, with cooling, to pH 1 by the addition of 6 *N* hydrochloric acid. The yellow powder which separated was collected, washed well with water, and dried under vacuum. The crude product was crystallized twice from 95% ethanol, then repeatedly from glacial acetic acid until it showed a single spot on thin layer chromatography (*n*-butanol:acetic acid:water, 4:1:1). The purified material (0.80 g., 60%) melted with decomposition at 295°; mass spectrum (70 ev): *m/e* 267 (M^+), 250 (*M*-OH), and 223 (*M*-CO₂); *ir*: λ max 3.24, 3.42, 3.58, 5.85 (sh), 5.99, 6.15 (sh), 6.25, 6.39, 6.58, 6.76, 7.20, 7.62, and 7.85 μ .

Anal. Calcd. for C₁₄H₉N₃O₃: C, 62.91; H, 3.40; N, 15.73. Found: C, 62.17; H, 3.75; N, 15.63.

Compound **18** was also obtained when **9** was treated with 20% sodium hydroxide under the same conditions.

3-Bromo-6-hydroxy-2,4,6-trimethyl-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine (**19**).

A solution of methylmagnesium iodide in ether was prepared in the usual manner from 290 mg. (12 mg.-atoms) of magnesium and 1.70 g. (0.75 ml., 12 mmoles) of methyl iodide. A suspension of 980 mg. (3 mmoles) of **4** in ether was added in small portions with vigorous stirring to the Grignard preparation. After complete addition, the reaction mixture was allowed to stir for 1 hour at room temperature. After addition of cold dilute sulfuric acid the yellow-green solid was collected, washed with water, and air-dried. Crystallization of the crude product several times from 50% aqueous ethanol gave small yellow crystals, m.p. 223° darkening, 246-249° tarry melt (600 mg., 58%); mass spectrum (70 ev): *m/e* 357 (M^+), 342 (*M*-15), 327 (*M*-30), and 312 (*M*-45).

Anal. Calcd. for C₁₇H₁₄BrN₃O: C, 57.31; H, 3.96; Br, 22.43; N, 11.79. Found: C, 57.31; H, 4.65; Br, 21.95; N, 11.43.

6*H*-Indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one 2,4-Dinitrophenylhydrazone Hemihydrate.

Bright yellow needles (91%), m.p. 286° dec., from glacial acetic acid.

Anal. Calcd. for C₂₀H₁₁N₇O₄·½H₂O: C, 56.87; H, 2.86; N, 23.22. Found: C, 56.74; H, 2.78; N, 23.16.

3-Bromo-4-methyl-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one 2,4-Dinitrophenylhydrazone.

Bright yellow needles (81%), m.p. 289° dec., from 1,4-dioxane and water; mass spectrum (70 ev); *m/e* (relative intensity) 507 (94) (M^+), 506 (25) (M^+) and 505 (100) (*M*-1).

Anal. Calcd. for C₂₁H₁₂BrN₇O₄: C, 49.81; H, 2.39. Found: C, 49.39; H, 3.13.

3-Bromo-4-methyl-6-oximino-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine.

Pale yellow solid (56%), m.p. 262-263° dec., from 95% ethanol.

Anal. Calcd. for C₁₅H₉BrN₄O: C, 52.80; H, 2.66; Br, 23.42; N, 16.43. Found: C, 52.62; H, 2.72; Br, 23.16; N, 16.12.

3-Bromo-2-methyl-6-oximino-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine.

Pale yellow solid (49%), m.p. 249° dec., from acetic acid and water; mass spectrum (70 ev): *m/e* (relative intensity) 342

(95) (M^+), 341 (20) (M^+), and 340 (100) (*M*-1).

Anal. Calcd. for C₁₅H₉BrN₄O: C, 52.80; H, 2.66. Found: C, 52.75; H, 2.98.

3-Bromo-2,4-dimethyl-6-oximino-6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazine.

Pale yellow solid (42%), m.p. 221° dec., from 2-ethoxyethanol and water; mass spectrum (70 ev): *m/e* (relative intensity) 356 (100) (M^+), 355 (20) (M^+), and 354 (100) (*M*-1).

Anal. Calcd. for C₁₆H₁₁BrN₄O: C, 54.08; H, 3.13. Found: C, 54.40; H, 3.64.

Acknowledgment.

We are grateful to Mr. Chester H. Rosansky for obtaining the quantitative ultraviolet spectral data reported herein.

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