Synthesis of Potential Antineoplastic Agents. XXI. Compounds Related to Ellipticine (1)

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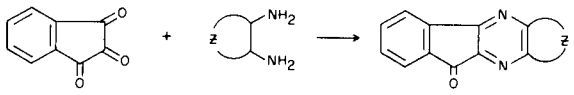
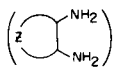
The reaction of pyridinediamines with isatin and with ninhydrin would appear to provide an attractive approach for the synthesis of compounds with a structural resemblance to the tumor-inhibitory (2) alkaloid ellipticine (1).

Reaction of 2,3- and 3,4-diaminopyridine with ninhydrin in ethanol, acetic acid, or 50% acetic acid gave indenopyridopyrazinones. Related compounds were also prepared from 4,5-dimethyl-*o*-phenylenediamine and from

TABLE I

Condensation of Ninhydrin with *o*-Diamines

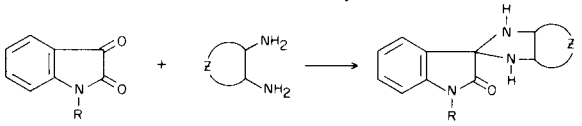


Diamine 	M.p.	Yield %	Reaction Solvent (a)	Formula	Analysis	Calcd. Found	
o-Phenylenediamine	219-220 (b)	90	A	$C_{15}H_8N_2O$ (c)			
		78	B				
		87	C				
2,3-Diaminonaphthalene	298-300 (d)	91	A	$C_{19}H_{10}N_2O$	80.84	3.57	9.93
					80.49	3.78	9.81
4,5-Dimethyl-*o*-phenylenediamine	248-249	97	A	$C_{17}H_{12}N_2O$ (e)	78.44	4.65	10.77
					78.21	4.73	10.73
Diaminomaleonitrile	262-263	89	A	$C_{13}H_4N_4O$ (f)	67.24	1.74	24.13
					67.12	1.84	24.25
2,3-Diaminopyridine	294-296 (g)	73	A	$C_{14}H_7N_3O$ (h)	72.10	3.03	18.02
		51	B		71.98	2.97	18.17
		39	C				
4,5-Diaminopyrimidine	>300	95	A	$C_{13}H_6N_4O \cdot 2H_2O$ (i)	57.77	3.73	20.78
					57.57	3.92	20.48
3,4-Diaminopyridine	267-268	95	A	$C_{14}H_7N_3O$ (j)	72.10	3.03	18.02
		89	C		72.15	3.06	18.05

(a) A = absolute ethanol, B = glacial acetic acid, C = 50% aq. acetic acid. (b) Reported (3) m.p. 218-219°. (c) Mass Spectrum: 232 (100), 205 (12), 204 (65), 203 (14), 178 (5), 177 (14), 176 (5), 116 (5), 102 (7), 77 (5), 76 (34), 75 (11). (d) Recrystallized from ethanol-ethyl acetate. (e) Mass Spectrum: 260 (100), 259 (5), 245 (8), 233 (4), 232 (19), 231 (10), 217 (8), 130 (6), 104 (9), 103 (14), 102 (5), 78 (7), 77 (7). (f) Mass Spectrum: 232 (100), 205 (7), 204 (43), 131 (7), 130 (66), 129 (6), 128 (51), 104 (9), 102 (17), 101 (11), 100 (5), 76 (18), 75 (12), 74 (12). (g) Reported (4) m.p. 297-298°. (h) Mass Spectrum: 233 (100), 206 (10), 205 (67), 204 (23), 179 (6), 178 (12), 151 (4), 130 (3), 128 (6), 103 (8), 102 (9), 78 (4), 77 (28), 76 (30), (i) Mass Spectrum: 234 (100), 207 (6), 206 (27), 180 (7), 179 (27), 152 (7), 132 (4), 130 (8), 129 (21), 128 (22), 127 (5), 126 (4), 110 (14), 104 (13), 103 (7), 102 (7), 101 (4), 82 (5), 78 (15), 77 (9), 76 (19). (j) Mass Spectrum: 232 (100), 206 (10), 205 (58), 204 (14), 179 (5), 178 (14), 177 (4), 151 (6), 129 (4), 128 (13), 127 (5), 103 (10), 102 (9), 78 (4), 77 (16), 76 (24).

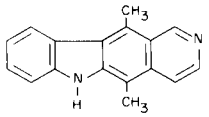
TABLE II

Condensation of Isatin and *N*-Acetylisatin with *o*-Diamines



Diamine	R	M.p.	Yield %	Reaction Solvent (a)	Formula	Analysis		Calcd. Found
2,3-Diaminopyridine (b)	CH_3CO	294-295	65	A	$C_{15}H_{12}N_4O_2$	64.28	4.32	19.99
			11	B		64.27	4.40	20.05
4,5-Diaminopyrimidine (c)	CH_3CO	265-267	31	A	$C_{14}H_{11}N_5O_2$	59.78	3.94	24.90
						59.89	3.95	24.84
3,4-Diaminopyridine (d)	CH_3CO	270-272	17	A	$C_{15}H_{12}N_4O_2 \cdot H_2O$	60.39	4.73	18.78
						59.79	4.86	18.52
2,3-Diaminopyridine (e)	H	254-256	40 (f)	A	$C_{13}H_{10}N_4O$	65.54	4.23	23.52
						65.21	4.27	23.86
4,5-Diaminopyrimidine	H	242-244 (g)	46	A	$C_{12}H_9N_5O$	60.24	3.79	29.28
						59.66	3.88	28.38

(a) A = absolute ethanol, B = glacial acetic acid. (b) This product was inactive against L1210 with T/C = 103 at 400 mg./kg. (see ref. (5). Mass Spectrum (h): 280 (62), 265 (6), 239 (17), 238 (80), 237 (26), 222 (14), 221 (87), 220 (87), 211 (14), 210 (100), 209 (19), 183 (15), 182 (5), 119 (7), 118 (7), 93 (18), 92 (13), 91 (8), 76 (5), 66 (11), 65 (9), 64 (6). (c) Mass Spectrum (h): 281 (37), 240 (10), 239 (100), 238 (8), 233 (4), 222 (20), 221 (30), 208 (6), 207 (38), 206 (6), 184 (6), 167 (4), 121 (5), 119 (5), 118 (11), 102 (4), 94 (7), 93 (4), 92 (4), 91 (4), 76 (4), 67 (6), 66 (5), 65 (5). (d) Mass Spectrum (h): 280 (60), 265 (9), 239 (12), 238 (62), 237 (32), 222 (9), 221 (42), 220 (83), 211 (16), 210 (100), 209 (22), 183 (17), 182 (9), 119 (7), 118 (9), 93 (6), 92 (11), 91 (10), 76 (9), 66 (12), 65 (12), 64 (19). (e) Mass Spectrum (h): 238 (100), 237 (8), 222 (5), 221 (21), 220 (25), 211 (8), 210 (50), 209 (17), 194 (4), 183 (12), 182 (4), 121 (4), 120 (11), 119 (12), 118 (8), 93 (9), 92 (12), 91 (8), 87 (4), 84 (6), 83 (5), 81 (10), 77 (7), 73 (6), 71 (8), 68 (9), 65 (11), 64 (8). (f) A small amount of material which was believed to be the linear product was obtained but was not investigated further. The linear product has been reported by N. P. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. France*, 1920 (1960). (g) This material could not be adequately recrystallized. (h) Mass spectral data for similar compounds has been reported by J. A. Ballantine, R. G. Fenwick, and F. D. Popp, *Org. Mass Spect.*, **5**, 1003 (1971).



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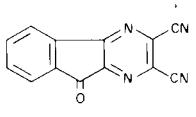

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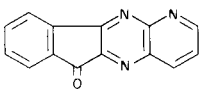

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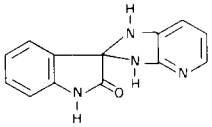

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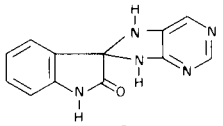

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2,3-diaminonaphthalene. The analogous reaction with *o*-phenylenediamine is well known (3). 4,5-Diaminopyrimidine also appears to react in an analogous manner. The reaction of diaminomaleonitrile with ninhydrin gave the analogue **2**. While this work was in progress the synthesis of **3** from ninhydrin and 2,4-diaminopyridine was reported (4). In view of that report and because of the lack of activity of **3** as reported (4) and as found in our work (5) we have discontinued further work on this synthetic approach to compounds related to ellipticine. The compounds prepared are shown in Table I together with mass spectral data which indicates the expected favorable loss of HCN and CO from these compounds.

The reaction of isatin with some aromatic *o*-diamines has already been reported (6) to give spiro as well as linear products. The reaction of isatin with 3,4-diaminopyridine in ethanol proceeded to give the linear product; however, 2,3-diaminopyridine and 4,5-diaminopyrimidine gave the spiro compounds **4** and **5**. With *N*-acetylisatin all three diamines gave spiro compounds. The spiro compounds are described in Table II.

EXPERIMENTAL (7)

Condensation of Ninhydrin with Diamines.

Equimolar quantities of ninhydrin and the diamine in absolute ethanol, glacial acetic acid, or 50% acetic acid were heated on the

steam bath for 30 to 60 minutes. After cooling the product was filtered (in some cases water was added to induce precipitation) and recrystallized from ethanol to give the compounds listed in Table I.

Condensation of Isatin with Diamines.

In a typical experiment equimolar quantities of isatin and 3,4-diaminopyridine were heated in absolute ethanol on the steam bath for 1 hour. After cooling addition of a small quantity of water gave a solid which was recrystallized from ethanol to give a 17% yield of linear product (6), m.p. 298-300°; Mass Spectrum: m/e (%): 220 (100), 219 (14), 194 (6), 193 (9), 192 (3), 169 (3), 168 (3), 167 (8), 166 (3), 165 (2), 115 (6), 114 (6), 102 (6), 92 (3), 90 (3), 88 (3), 76 (5), 75 (3).

Anal. Calcd. for $C_{13}H_8N_4$: C, 70.89; H, 3.66; N, 25.44. Found: C, 70.75; H, 3.72; N, 25.65.

Other reactions of isatin and *N*-acetylisatin with diamines were carried out in a similar manner to give the spiro products listed in Table II.

REFERENCES

(1) Part XX. F. D. Popp, *J. Med. Chem.*, **12**, 182 (1969).

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(2) L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Aust. J. Chem.*, **20**, 2715 (1967).

(3) S. Ruhemann, *J. Chem. Soc.*, 1449 (1910).

(4) M. Israel, L. C. Jones, and E. J. Modest, *J. Heterocyclic Chem.*, **9**, 255 (1972).

(5) Compound **3** had a T/C of 98 at 400 mg./kg. against L1210 lymphoid leukemia as reported to us by Drug Research and Development, Chemotherapy, National Cancer Institute. The compound from 3,4-diaminopyridine and ninhydrin was also inactive against L1210 (T/C 97 at 200 mg./kg.) as was the compound from 2,3-diaminonaphthalene and ninhydrin (T/C 97 at 400 mg./kg.). Compound **2** had a T/C of 112 at 25 mg./kg. against L1210 and an ED50 of <1.0 micrograms/ml. against KB cell culture.

(6) F. D. Popp, *J. Heterocyclic Chem.*, **6**, 125 (1969).

(7) Analyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan. All melting points are taken in capillaries and are corrected. We are indebted to Dennis Chesney for obtaining the mass spectral data and to the National Science Foundation for funds used in the purchase of the mass spectrometer.