Pyridazino[4,5-*b*]indole derivatives

THOMAS NOGRADY AND LEESON MORRIS
Chemistry Department, Loyola College, Montreal 262, Quebec

Received March 13, 1968

A series of pyridazino[4,5-*b*]indole lactams and their reduction products was prepared in an attempt to uncover monoamine oxidase inhibitory activity. The reduction and nuclear magnetic resonance spectra of these compounds are dealt with. Some are weak analgesics but no other pharmacological activity was found.

Canadian Journal of Chemistry, 47, 1999 (1969)

In our attempts to uncover novel monoamine oxidase inhibitory compounds we synthesized some 2-indolylcarbohydrazide derivatives (1). It seemed interesting to close ring C by insertion of one more carbon atom and this way obtain the pyridazino[4,5-*b*]indole ring system which can be considered as an azacarboline. Since many carboline alkaloids related to harmine are strong reversible MAO inhibitors (2), the combination of the carboline system with hydrazine seemed to be attractive also from a pharmacological point of view.

Only basic information is available on pyridazinoindoles and very few derivatives known. The [3,4-*b*] isomer was described by Kobayashi and Furukava (3). The [4,5-*b*] isomer was first reported by King and Stiller (4) who obtained it by heating 2-carbethoxy-3-formylindole *p*-nitrophenylhydrazone to 300° and obtained the cyclic hydrazide. Other authors (5–7) used basically the same method of ring closure, while some (8, 9) started from 2- or 3-indolylmethylhydrazines and condensed them with aldehydes to obtain the cyclized product.

In our series the 4-oxopyridazino[4,5-*b*]-indoles and their 1,2,3,4-tetrahydro derivatives were prepared according to the scheme shown below.

It is quite remarkable that the sequence of basically identical reactions, i.e. formylation and condensation with hydrazine derivatives, used in preparing the compounds, is responsible for the formation or absence of the Δ^1 double bond. This is due to the unusual formation of the

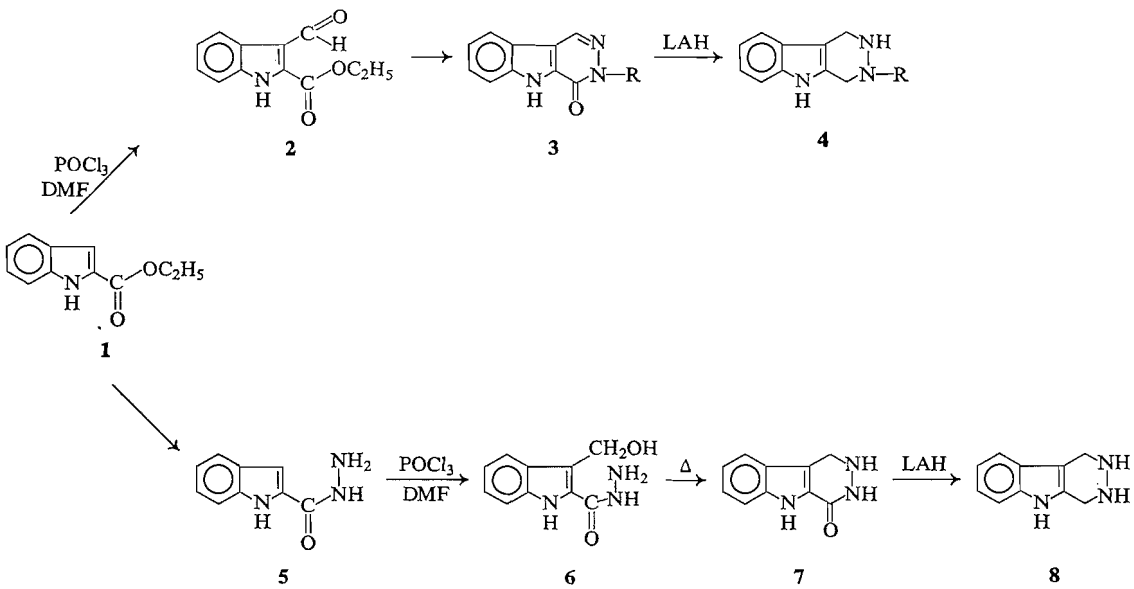
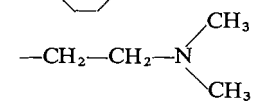
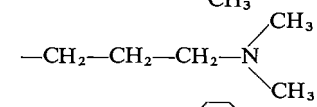
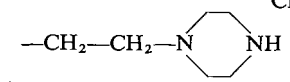


FIG. 1. Synthesis of pyridazoindoles.

TABLE I

3-Substituted 3,4-dihydro-4-oxo-pyridazino[4,5-*b*]indoles

Compound	R	Melting point (°C)	Solvent of crystallization	Nitrogen analysis Found	Nitrogen analysis Calcd.	Yield (%)	Method
9	—H	333–336	Dioxane	22.55	22.70	70	*
10	—CH(CH$_3$)$_2$	219–220	Ethanol	18.64	18.49	61	A
11	—CH$_3$	298–299	Butanol	20.87	21.09	95	A
12		229–230	DMF–water	15.71	16.08	85	B
13		183–184	Ethanol	17.26 (2·HCl)	17.02	76	A
14		164–165	Methanol–water	21.01	20.72	77	C
15		224–225	Ethanol	23.42	23.55	70	C

*Method taken from ref. (7*a*).

3-hydroxymethylindole-2-carbohydrazine (**6**) during the DMF–$POCl_3$ formylation of indole-2-carbohydrazide (**5**) as described by Harradance and Lions (5), who obtained this compound in another way. The presence of the hydroxymethyl group (and the absence of any aldehyde proton) in **6** was proved by spectroscopy. The nuclear magnetic resonance (n.m.r.) spectrum of **6** (in DMSO-d_6) showed a CH_2 singlet at 2.80 p.p.m. (δ) integrating for two protons, an aromatic multiplet centered at 7.4 p.p.m., and two broad NH bands at 10.56 and 11.38 p.p.m., both exchangeable by D_2O. No aldehyde proton could be seen in the 9–10 p.p.m. region of the spectrum. The CH_2 singlet at 2.80 p.p.m. might appear more upfield than usual, since the corresponding resonance in benzyl alcohol is at 4.58. On inspecting the n.m.r. spectrum of 3-indolylmethanol however, one finds the CH_2 singlet at 3.83 p.p.m. (δ), also higher than expected.

In the ultraviolet (u.v.) spectrum, three maxima are visible: 306 (3.87), 251 (3.43), and 220 (3.69) mμ. In an alkaline medium practically no bathochromic shift could be seen, the maxima being at 310, 250, and 220 mμ. By comparison the ester-aldehyde **2** shows maxima at 322 (4.19), 253 (4.10), 245.5 (4.16), and 279.5 (4.22) mμ, which shift in an alkaline medium to 360 (4.79) and 273.5 (4.86), with strong tailing around 220–230 mμ. This bathochromic shift is due to the formation of the indolenine alcohol (cf. ref. 10).

The infrared (i.r.) spectrum (in KBr disk) shows a broad associated band in the OH/NH stretching region at 3.05–3.25 μ, the amide carbonyl at 6.40 μ, a fairly sharp, strong peak at 7.70 μ which could be O—H deformation, C—O stretching at 9.10 μ, and the disubstituted phenyl at 13.5 μ, as the principal peaks.

The condensation of 2-carbethoxy-3-formylindole (**2**) with hydrazine derivatives is more capable of variations in introducing a substituent in N-3, so our efforts were concentrated on preparing a series of 3,4-dihydro-4-oxopyridazines (Table I) rather than the tetrahydro derivatives and reduce them afterwards.

The reduction of the cyclic hydrazide (**3**) proved to be surprisingly facile considering reports on the failure to reduce aliphatic hydrazides (11) and 1-oxocarbolines (12) with $LiAlH_4$. The 4-oxopyridazino[4,5-*b*]indoles were refluxed overnight with a great excess of LAH in dioxane and excellent yields were obtained (Table II). After completion of our experiments the LAH reduction of 1-methyl-3-arylpyridaz-6-

TABLE II

3-Substituted 1,2,3,4-tetrahydro-pyridazino[4,5-*b*]indoles

Compound	R	Melting point (°C)	Solvent of crystallization	Nitrogen analysis Found	Nitrogen analysis Calcd.	Yield (%)
16	—H	235–237	Methanol	19.86	20.04	90
17	$-CH_3$	245–246	Methanol	18.29 (.HCl)	18.02	96
18	$-CH(CH_3)_2$	163–164	Methanol–water	19.65	19.52	95
19	—C$_6$H$_5$	222–223 (decomp.)	Acetone	16.55	16.99	95
20	$-CH_2-CH_2-N(CH_3)_2$	159–160	*i*-Propanol–hexane	22.66	22.93	90
21	$-CH_2-CH_2-CH_2-N(CH_3)_2$	146–147	Acetone	21.59	21.68	95
22	$-CH_2-CH_2-N$(piperazine)$-NH$	183–184	Benzene	24.66	24.54	86

one and related compounds was reported (13) but a 96 h reflux period yielded only 20% of pure reduced product.

In this reaction however the C=N double bond remains intact. In our reductions the C=N double bond is also reduced, as proved by n.m.r. spectra. In a representative example, the 1,2,3,4-tetrahydro-5*H*-pyridazino[4,5-*b*]indole (compound **17**), an N—CH_3 singlet is found at 2.88 p.p.m. (δ), and an aromatic multiplet centered at 7 p.p.m. The fairly well separated singlets at 4.16 and 4.23 p.p.m. (δ) are of equal intensity and integrate for 4 protons. They represent the 1- and 4-CH_2 groups; no olefinic protons are discernible. In the *N*-phenyl analogue, the corresponding protons are at 4.68 and 4.70 p.p.m. respectively.

In attempts to obtain the 4-methylpyridazino-[4,5-*b*]indole, the aza analogue of harmane, we tried the Bischler–Napieralski ring closure with phosphorus pentoxide, polyphosphoric acid, polyphosphate ester, and ethanolic HCl on 3-formylindole acetylhydrazone, without success.

Pharmacological Results

The only pharmacological effect shown by compounds **9**, **12**, **15**, and **16** was a weak analgetic activity (Median effective dose 50–150 mg/kg). No anti-histamine or central nervous system activity was noticed.

Experimental

All melting points were determined on a Gallenkamp block and are corrected; boiling points are uncorrected. The i.r. spectra were taken in KBr disks on a Beckman IR-8 instrument, and n.m.r. spectra were taken on a Varian A-60 spectrometer in trifluoracetic acid if not stated otherwise. Analyses were performed by Dr. C. Daesslé, Montreal.

3-Dimethylaminopropylhydrazine

Dimethylaminopropyl chloride·HCl (14.8 g) was dissolved in 75 ml ethanol, added slowly to 13.5 g refluxing hydrazine (anhydrous), and the solution refluxed for 4 h. After cooling, the precipitated hydrazine salt was filtered off, the solvent removed, and the residue distilled. The yield was 5.8 g (53.0%) b.p.$_{10}$ 75–80°; n_D^{20} 1.4611. The hydrochloride was prepared in ethanol–ether, and melted at 197–198°.

Anal. Calcd. for $C_5H_{15}N_3 \cdot 2HCl$: N, 22.05. Found: N, 21.78.

N-(β-Hydrazinoethyl)piperazine

N-(β-chloroethyl)piperazine (5 g) was dissolved in 10 ml water, 20 ml of anhydrous hydrazine added, and the solution refluxed for 4 h. After cooling, the solution was saturated with solid NaOH and the separated oil extracted with tetrahydrofuran. The organic phase was dried over K_2CO_3 and distilled; yield 3.2 g (95%), b.p.$_{12}$ 140–145°. The HCl salt, prepared in ethanol, melted at 107–109° (decomp.).

Anal. Calcd. for $C_6H_{16}N_4 \cdot 3HCl$: N, 22.09. Found: N, 21.70.

1,2,3,4-Tetrahydro-4-oxo-5H-pyridazino[4,5-b]indole (7) (5)

Indole-2-carbohydrazide **5** (I) (0.5 g) was dissolved in 4 ml dimethyl formamide and added slowly to a solution of 0.5 ml $POCl_3$ in 4 ml dimethyl formamide. After 1 h at room temperature the solution was diluted with water and 0.41 g (77%) yellow crystals isolated by filtration, m.p. 195°. The melt resolidified and melted again at 285–288°. Recrystallized from *n*-butanol or dioxane they melted directly at 294–295°.

Anal. Calcd. for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.19; H, 4.63; N, 22.56.

The low melting compound is supposedly the 3-hydroxymethyl derivative **6** which cyclizes on heating in any way to **7**. Spectra of this compound were discussed in the theoretical part. The cyclized product shows a single carbonyl peak at 6.15 μ and broad indistinct bands in the 3–4 μ region.

Method A. 3,4-Dihydro-3-methyl-4-oxo-5H-pyridazino[4,5-b]indole (11)

A solution of 4.32 g 2-carbethoxy-3-formylindole and 7.5 ml methylhydrazine was refluxed gently in 50 ml glycerol for 15 min. The solution first became yellow, then colorless crystals separated. These were filtered off after cooling and dilution with water; yield 3.79 g (95%), m.p. 298–300°, unchanged after recrystallization from *n*-butanol.

Nuclear magnetic resonance spectrum: 4.30 (—CH_3) (3H), 7.2–8.2 (aromatic and C—H) (5H), 9.1 (N—H) (1H).

Method B. 3,4-Dihydro-3-phenyl-4-oxo-5H-pyridazino[4,5-b]indole (12)

2-Carbethoxy-3-formylindole (1.08 g) was dissolved in 20 ml glacial acetic acid and 2.5 ml freshly distilled phenylhydrazine were added. The solution became warm and yellow crystals of the phenylhydrazone separated, but dissolved upon heating. After refluxing for 1 h the crystals were filtered from the cooled reaction mixture and washed with water; yield 1.1 g (85%) m.p. 329–330° (from DMF–water).

Nuclear magnetic resonance spectrum: 7.6–8.6 (aromatic and C—H) (10H), 9.2 (N—H) (1H).

Method C. 3,4-Dihydro-3-(γ-dimethylaminopropyl)-4-oxo-5H-pyridazino[4,5-b]indole (14)

2-Carbethoxy-3-formylindole (1.08 g), 3.45 g 3-dimethylaminopropyl hydrazine, and 3 drops of glacial acetic acid were heated on the steam bath for 30 min until a gentle gas evolution ceased. The homogeneous mixture was now kept at 135–140° for 2 h more. On cooling, white needles separated which were filtered off, washed with water, and recrystallized from 50% methanol–water, yield 1.05 g (77%), m.p. 164–165°.

Reduction with $LiAlH_4$

The cyclic hydrazides were dissolved in 25–50 volumes of dry dioxane, an equal weight (5–8 moles) of $LiAlH_4$ was added cautiously, and the reaction mixture refluxed for 16 h. After cooling, 3 ml water were added for each gram of $LiAlH_4$ and worked up in the usual way. The pyridazines separated as solids in very good yields (see Table II).

Acknowledgments

This investigation was supported by Bristol Laboratories, Syracuse, New York. Pharmacological screening was performed by Dr. M. H. Pindell and his staff of Bristol Laboratories, to whom thanks are due.

1. T. Nogrady and L. Morris. J. Med. Chem. **9**, 438 (1966).
2. A. Pletscher, K. F. Gey, and P. Zeller. *In* Progress in drug research. Vol. 2. *Edited by* E. Jucker. Interscience Publishers, Inc., New York. 1960. p. 455.
3. G. Kobayashi and S. Furukawa. Chem. Pharm. Bull. **12**, 1129 (1964).
4. H. King and E. T. Stiller. J. Chem. Soc. 468 (1937).
5. R. H. Harradance and F. Lions. J. Proc. Roy. Soc. New South Wales, **72**, 221 (1939); Chem. Abstr. **33**, 6838 (1939).
6. R. S. Staunton and A. Topham. J. Chem. Soc. 1889 (1953).
7. (*a*) N. N. Suvorov, Zh. D. Ovchinnikova, and Yu. N. Sheinker. Zh. Obshch. Kim. **31**, 2333 (1961); Chem. Abstr. **56**, 3478 (1962). (*b*) N. N. Suvorov, Zh. D. Ovchinnikova, E. M. Peresleni, and Yu. N. Sheinker. Khim. Geterocikl. Soed. 926 (1965); Chem. Abstr. **64**, 17588 (1966).
8. J. Thesing and C. H. Willersinn. Chem. Ber. **89**, 1195 (1956).
9. H. Keberle and K. Hoffman. Gazz. Chim. Ital. **93**, 238 (1963).
10. M. F. Bartlett, D. F. Dickel, and W. I. Taylor. J. Am. Chem. Soc. **80**, 126 (1958).
11. R. L. Hinman. J. Am. Chem. Soc. **78**, 2463 (1956).
12. R. A. Abramovitch and D. Shapiro. J. Chem. Soc. 4589 (1956).
13. G. Leclerc and C. G. Wermuth. Bull. Soc. Chim. France, 1307 (1967).