1,4-Bis(2-indol-3-ylethyl)piperidines

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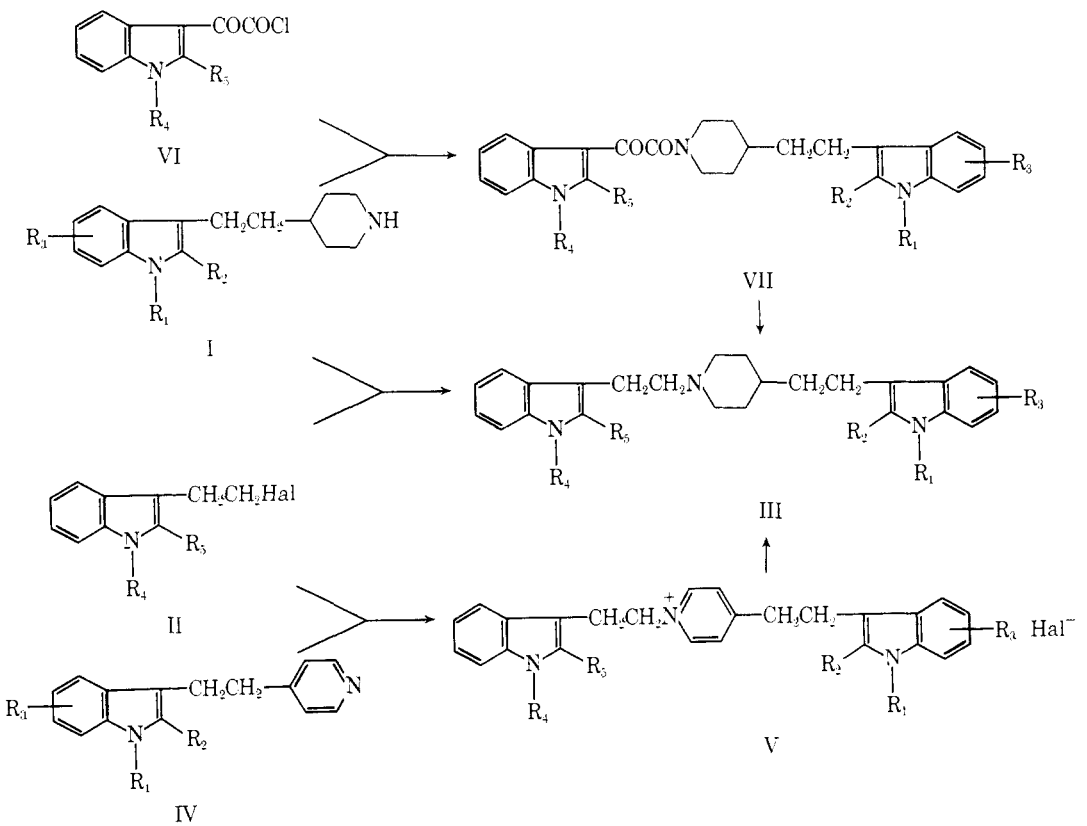
Access to a new class of indole derivatives was gained when Gray and Archer published their work on the pyridylethylation of indoles.[1] The usefulness of this general reaction was enhanced by the finding that catalytic hydrogenation of indolylethylpyridines led to selective saturation of the pyridine ring.[2,3] Alkylation of the resultant indolylethylpiperidines gave products which displayed marked depressant effects on the central nervous system of mice and dogs. Certain examples were also claimed to possess analgetic activity equivalent to morphine when tested in mice and rabbits.

We were interested in studying what effect incorporation of a tryptamine moiety in this type of molecule would have on the profile of activity. Our primary objective was accomplished by alkylation of 4-[2-(indol-3-yl)ethyl]piperidine (I, $R_1 = R_2 = R_3 = H$) with 3-(2-bromoethyl)indole (II, $R_4 = R_5 = H$) to provide 1,4-bis(2-indol-3-ylethyl)piperidine (III, $R_{1-5} = H$) (Scheme I).

SCHEME I



Compound III ($R_{1-5} = H$) showed some CNS activity, the pattern being reminiscent of chlorpromazine, but of greater significance was the discovery of marked hypotensive and antihypertensive activity. Tryptamine derivatives possessing potent hypotensive activity are not unknown. For instance, a series of such compounds (β-hydroxytryptamines) has been reported by Heinzelman and Szmuszkovicz.[4] These compounds were, however, quite toxic and a clinical study of one example failed to detect any drop in blood pressure, possibly due to inability to assess blood pressure effects in the face of severe side effects.

Considering 1,4-bis(2-indol-3-ylethyl)pip ridine as the prototype of a new series, synthesis and pharmacological evaluation of a variety of substituted derivatives was undertaken in order to determine the extent and scope of the antihypertensive activity. In the first place a number of new 4-[2-(indol-3-yl)ethyl]pyridines (IV) were prepared by acid-catalyzed condensation of 4-vinylpyridine with the appropriate indoles essentially according to the procedure of Gray and Archer.[1] Catalytic hydrogenation[2] of these compounds, which are listed in Table I, gave the corresponding 4-[2-(indol-3-yl)ethyl]piperidines (I).

Three main routes were developed for the synthesis of symmetrically and unsymmetrically substituted 1,4-bis(indolylethyl)piperidines. The first has already been mentioned in connection with the preparation of III ($R_{1-5} = H$). It consisted of alkylation of a suitably substituted I with a 3-(2-haloethyl)indole (II) derivative. The second route consisted of quaternization of an indolylethylpyridine (IV) with II, followed by catalytic hydrogenation (with or without isolation of the intermediate quaternary (V) salt). In the third, 1,4-bis(indolylethyl)piperidines were prepared by acyla-

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TABLE I
NOVEL INDOLYLETHYLPYRIDINES (IV)

No.	R_1	R_2	R_3	Yield, %	Mp, °C	Formula	Analyses
1	H	H	5-CH_3O	63	136–137	$C_{16}H_{16}N_2O$	C, H, N
2	H	H	6-CH_3O	50	135–137	$C_{16}H_{16}N_2O$	C, H, N
3	H	H	5-$C_6H_5CH_2O$	74	160–163	$C_{22}H_{20}N_2O$	C, H, N
4	H	H	5-OH	23	180–181	$C_{15}H_{14}N_2O$	C, H, N
5	H	C_6H_5	H	41	199–201	$C_{21}H_{18}N_2$	C, H, N
6	H	CH_3	5-CH_3O	82	150–152	$C_{17}H_{18}N_2O$	C, H, N
7	*p*-ClC_6H_4CO	H	H	13	93–94	$C_{22}H_{17}ClN_2O$	C, H, N, Cl
8	H	C_2H_5	H	89	149–150	$C_{17}H_{18}N_2$	C, H, N
9	H	$(CH_3)_2CH$	H	90	210–211	$C_{18}H_{20}N_2$	C, H, N
10	H	H	5-Br	43	224–225	$C_{15}H_{13}BrN_2$	C, H, N, Br

TABLE II
COMPOUNDS OF TYPES VII, III, AND V

No.	Structure	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula	Analyses	Method
11	VII	H	H	H	H	H	35	109–111	$C_{25}H_{25}N_3O_2$	C, H, N	A
12	VII	H	H	H	H	CH_3	20	202–203	$C_{26}H_{27}N_3O_2$	C, H, N	A
13	VII	H	CH_3	H	H	CH_3	73	128–129	$C_{27}H_{29}N_3O_2$	C, H, N	A
14	V	H	CH_3	H	H	H		155–157	$C_{26}H_{26}BrN_3 \cdot H_2O$	C, H, N, Br	C
15	V	H	$(CH_3)_2CH$	H	H	H	29	244–245	$C_{29}H_{30}BrN_3$	C, H, N, Br	C
16	III	H	H	H	H	H	53	145–147	$C_{25}H_{29}N_3$	C, H, N	B
17	III	H	CH_3	H	H	H	35	242–243	$C_{26}H_{31}N_3 \cdot HBr$	C, H, N, Br	C
18	III	$C_6H_5CH_2$	H	H	H	H	45	199–200	$C_{32}H_{35}N_3 \cdot HCl$	C, H, N, Cl	B
19	III	CH_3	H	H	CH_3	H	37	123–124	$C_{27}H_{33}N_3$	C, H, N	D
20	III	CH_3	H	H	H	H		Indef	$C_{26}H_{31}N_3$	C, H, N	B
21	III	H	H	5-CH_3O	H	H	23	211–212	$C_{26}H_{31}N_3O \cdot HBr$	C, H, N, Br	C
22	III	H	H	H	H	CH_3	49	154–155	$C_{26}H_{31}N_3$	C, H, N	A
23	III	H	CH_3	H	H	CH_3	76	165–167	$C_{27}H_{33}N_3$	C, H, N	A

tion of an indolylethylpiperidine with a suitably substituted indole-3-glyoxyloyl chloride (VI), followed by LAH reduction of the intermediate amide (VII).

Although monosubstitution on the indole nitrogen atoms has to be incorporated in the respective indole components prior to coupling, symmetrical indole N substituents can also be introduced directly into the bis products.

The bis(indolylethyl)piperidines that were prepared are listed in Table II.

Biological Activity.—Renal hypertension was produced in female rats and their systolic pressure was recorded indirectly by methods previously described.[5] Drugs were administered intraperitoneally to groups of four animals and pressures were recorded before and 2 and 4 hr after dosing. Maximal effects usually occurred at 2 hr and are shown in Table III.

TABLE III
ANTIHYPERTENSIVE ACTIVITY

No.	Dose, mg/kg ip	Blood pressure response[a]
16	75	+++
17	40	+++
18	30	+
19	75	++
20	30	++
22	40	+

[a] Control pressures in each group averaged 160–190 mm; + = decrease of 15–30 mm, ++ = decrease of 30–50 mm, +++ = decrease of >50 mm.

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were all within ±0.4% of the theoretical values.

4-[2-(Indol-3-yl)ethyl]pyridines.—Pyridylethylation of the 3-unsubstituted indole starting materials was carried out using a slight modification of the reported procedure.[1] Since considerably increased yields were achieved, a representative example is given.

4-[2-(2-Methylindol-3-yl)ethyl]pyridine.—2-Methylindole (26.2 g), 4-vinylpyridine (21.0 g), and AcOH (80 ml) were mixed under N_2 (exotherm) and refluxed under N_2 for 3 hr. AcOH was then removed on a rotary evaporator at 100° (0.1 mm). The residual oil was crystallized (EtOH–H_2O) to provide 42.6 g (91%) of colorless prisms, mp 157–159° (lit.[1] yield 54%, mp 153–154°).

4-[2-(Indol-3-yl)ethyl]piperidines.—Indolylethylpyridines were reduced catalytically according to procedure B of Gray and Kraus.[2]

1,4-Bis(2-indol-3-ylethyl)piperidines.—Intermediates incorporating two indole rings and final products are listed in Table II. Representative examples of each of the main synthetic pathways are given as follows.

A. 4-[2-(2-Methylindol-3-yl)ethyl]-1-(2-methylindole-3-glyoxyloyl)piperidine.—A solution of 4-[2-(2-methylindol-3-yl)-ethyl]piperidine[2] (19.3 g) in EtOAc (500 ml) and a solution of K_2CO_3 (18.0 g) in H_2O (100 ml) were stirred together vigorously while a solution of 2-methylindole-3-glyoxyloyl chloride[6] (17.7 g) in EtOAc (500 ml) was slowly added dropwise, with cooling if necessary to keep <25°. Stirring was continued for 1 hr, a small amount of insoluble material was filtered off, and the organic layer was separated, washed (H_2O, 500 ml), and dried ($MgSO_4$). Evaporation *in vacuo* gave a foam which was crystallized from EtOAc to provide 24.9 g (73%) of product, mp 128–129°.

1,4-Bis[2-methylindol-3-yl)ethyl]piperidine.—The foregoing amide 15.0 g was added portionwise to a stirred suspension of LAH (7.0 g) in 1,2-dimethoxyethane (300 ml). The mixture was stirred under reflux for 18 hr, cooled, and decomposed by dropwise addition of H_2O (20 ml). The inorganic material was filtered off and washed with fresh solvent. Evaporation of the filtrate *in vacuo* gave an oil which crystallized on standing. Recrystallization from aqueous DMF provided 10.7 g (76%) of III (R_1, R_3, R_4 = H; R_2 = R_5 = CH_3), mp 165–167°.

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B. 1,4-Bis(2-indol-3-ylethyl)piperidine.—A mixture of 4-[2-(indol-3-yl)ethyl]piperidine[2] (15 g) and finely powdered $Na_2CO_3 \cdot H_2O$ (15 g) in *i*-PrOH (100 ml) was stirred and refluxed while 3-(2-bromoethyl)indole (15 g) in *i*-PrOH (100 ml) was added dropwise during 1 hr. Stirring and refluxing were continued for 18 hr, then the mixture was evaporated to dryness *in vacuo*. The residue was triturated under $CHCl_3$ several times and an insoluble white solid was filtered off. Evaporation of the filtrate and recrystallization of the residue from AcMe–H_2O gave 13.5 g (53%) of product, mp 145–147°.

C. 1-(2-Indol-3-ylethyl)-4-[2-(2-methylindol-3-yl)ethyl]piperidine.—A mixture of 4-[2-(2-methylindol-3-yl)ethyl]pyridine (23.6 g) and 3-(2-bromoethyl)indole (22.4 g) in absolute EtOH (500 ml) was kept at room temperature in the dark for 1 week. The resultant solution of quaternary salt was hydrogenated at 50° and 28.12 kg/cm² in the presence of PtO_2 (2.0 g) for 18 hr. The product precipitated and was filtered off along with the catalyst. Separation from catalyst was achieved by stirring with $AcNMe_2$ and filtering. H_2O was added to the filtrate until crystallization commenced to give 15.9 g (55%) of product hydrobromide, mp 242–243°.

D. 1,4-Bis[2-(1-methylindol-3-yl)ethyl]piperidine.—1,4-Bis(2-indol-3-ylethyl)piperidine (2.0 g) was added portionwise to $NaNH_2$ in liquid NH_3 prepared from 248 mg of Na. After stirring for 1 hr, MeI (1.56 g) in Et_2O (10 ml) was added dropwise and stirring was continued for 2 hr. NH_3 was allowed to evaporate and the residue was stirred with Et_2O (100 ml) and H_2O (100 ml). Evaporation of the dried ($MgSO_4$) ether layer and recrystallization of the solid residue from AcMe–H_2O provided colorless needles (1.2 g), mp 123–124°.

Derivatives of 9-Thioxanthenecarbonitrile

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Since the discovery of methadone, the analgetic first synthesized by Bockmühl and Ehrhart,[1] the medicinal chemist has found 3,3-diphenylpropylamines in general to be a fertile source of diverse biological activities.[2] Our brief excursion into this area was directed toward amalgamation of the analgetic properties of the diphenylpropylamines with the antianxiety properties of the thioxanthene-9-alkylamines by attempting to prepare the thioxanthene analog (**9**) of methadone and some of its congeners.

Application of the classic methadone synthetic scheme[1] to the thioxanthene ring system embraced two problems: (1) preparation of 9-thioxanthenecarbonitrile (**3**) in adequate yield for use as an intermediate, and (2) conversion of a crowded nitrile to the corresponding ethyl ketone.

Preparation of **3a** from thioxanthen-9-ol (**1a**), obtained by $NaBH_4$ reduction of thioxanthen-9-one,[3] was accomplished in 61% over-all yield by treating intermediate 9-chlorothioxanthene (**2a**)[4] with CuCN. (Scheme I). Conversion of **1a** to other reactive intermediates, *e.g.*, bromide, tosylate, or mesylate, in each case produced markedly inferior results, even when a variety of CN^- sources was employed. This is not unreasonable in the light of our experience with chloride **2a** which is rapidly converted to **1a** and thioxanthen-9-one in the presence of air. Thus the yield of nitrile depends upon the care exercised in isolation of the intermediate.

Alkylation of the Na derivative of **3a** with 2-chloro-*N*,*N*-dimethylethylamine proceeds smoothly to **4a**, which reacts with EtMgBr at 0°. The ketimine is completely hydrolyzed to the corresponding ketone (**5a**) after 30 min at reflux in dilute aqueous acid. By the same scheme 2-chlorothioxanthen-9-ol (**1b**)[5] is converted to **5b**. In each case temperature control during the Grignard addition is critical, since the Mg derivative of the ketimine is unstable above 25°. In fact, if **4b** and the Grignard reagent are heated to 100° before hydrolysis, no **5b** can be detected. The major product, **6**, apparently arises by fragmentation of the Mg adduct driven by the propensity of the thioxanthene system to delocalize anionic charge at C-9.

Alkylation of the Na derivative of **3a** with 2-(dimethylamino)isopropyl chloride provides the two expected isomers **7** and **8**, which can be separated on alumina. Structural assignments are based upon several bits of data: (1) relative chemical shifts of the N-Me and C-Me protons based on models reported by Casy,[6] (2) isomer **7** runs faster than **8** on both alumina and silica gel, and (3) relative reactivity toward the Grignard reagent. Neither isomer reacts with EtMgBr at room temperature. Isomer **8** is consumed only at temperatures above 100°, but after aqueous acid treatment no ketonic material can be detected by ir analysis of the total product. Isomer **7** reacts at *ca.* 50–60° with similar results. Apparently steric hindrance by the α-Me is sufficient to preclude attack of the reagent at a temperature compatible with adduct stability. Further studies indicate that variation of the solvent and or the halogen has no influence on the temperature requirement. The utility of EtLi has not yet been explored.

The intermediates **4**–**8** were devoid of activity at 10 mg/kg (administered subcutaneously) when subjected to three well-known laboratory methods for evaluating analgetic activity: the hot plate method,[7] the tail flick method,[8] and the phenylbenzoquinone writhing method.[9]

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4%, of the theoretical values. Melting points (Thomas–Hoover capillary melting point apparatus) are uncorrected. The ir spectra were measured with a Perkin-Elmer Model 21 spectrophotometer, uv spectra with a Cary Model 11 recording spectrometer, and nmr spectra with a Varian A-60 spectrometer with Me_4Si as an internal standard.

9-Thioxanthenecarbonitrile (3a).—A suspension of thioxanthen-9-ol[3] (21.4 g, 0.100 mole) in 200 ml of anhydrous Et_2O under N_2 was treated carefully with $SOCl_2$ (8.0 ml) with stirring at 0–5°. The alcohol dissolved before a white solid began to separate. After 1 hr at 25°, the solvent was removed *in vacuo*, 100 ml of anhydrous C_6H_6 added, and the solution again evaporated. All manipulations were performed with rigorous exclusion of air. Anhydrous C_6H_6 (100 ml) and CuCN powder

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