Synthesis and Evaluation of 3-Substituted 1-[4-(2-Indol-3-ylethyl)piperazinyl]ureas as Potential Antihypertensive Agents

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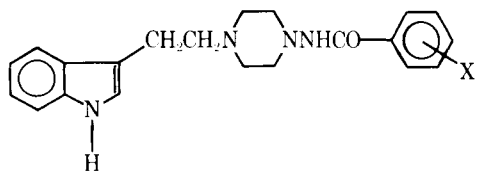
Received February 6, 1978, from the *Chemical Research Department and the ‡Department of Pharmacology, Hoechst-Roussel Pharmaceuticals, Inc., Somerville, NJ 08876. Accepted for publication May 2, 1978.

Abstract □ A series of 3-substituted 1-[4-(2-indol-3-ylethyl)piperazinyl]ureas was synthesized and screened for antihypertensive activity in spontaneously hypertensive rats. Two compounds with aryl urea substituents were very potent and lowered blood pressure 55 mm or more at oral doses of 100 mg/kg. However, both compounds failed to produce a cardiovascular response in the normotensive dog.

Keyphrases □ (Indolylethyl)piperazinylureas, substituted—synthesized, evaluated for antihypertensive activity in rats and dogs □ Antihypertensive activity—substituted (indolylethyl)piperazinylureas evaluated in rats and dogs □ Structure–activity relationships—substituted (indolylethyl)piperazinylureas evaluated for antihypertensive activity in rats and dogs

Previously (1), the synthesis and antihypertensive activity of 3-(4-acylaminopiperazinylalkyl)indoles of type I were described. These compounds are structurally related to indoramin (II), a drug clinically useful in lowering blood pressure (2, 3). The substituted indoles were derived by replacing the central portion of the indoramin molecule with the pharmacologically interesting *N*-aminopiperazine moiety.

It was of interest to modify the indoramin structure further by changing the connection between the phenyl and the piperazine rings from the amide to a urea linkage. Such a modification provided 3-substituted 1-[4-(2-indol-3-ylethyl)piperazinyl]ureas III*a*–III*h* (Table I), whose synthesis and antihypertensive effects are the subject of this report.



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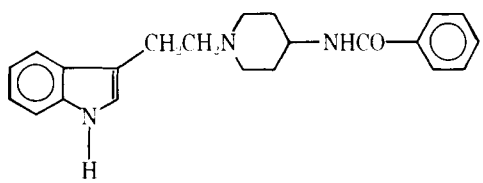


II

EXPERIMENTAL

Chemistry[1]—This class of compounds was synthesized by reacting the amino group of IV*a* and IV*b* (Scheme I) with a variety of aryl and alkyl isocyanates in dichloromethane as the solvent. The physical properties and analytical data for the resulting ureas (III*a*–III*h*) are recorded in Table I. The preparation of the precursors (IV*a* and IV*b*) was reported previously (1).

General Procedure for III*a*–III*h*.—The common method used to prepare the ureas of Table I is illustrated for 1-[4-(2-indol-3-ylethyl)-piperazinyl]-3-phenylurea (III*a*). To a stirred solution of 6.13 g (0.025 mole) of 3-[2-(4-aminopiperazinyl)ethyl]indole (IV*a*) in 100 ml of dry dichloromethane was added dropwise 3.53 g (0.035 mole) of phenyl isocyanate[2] while the reaction temperature was kept below 35°. After 3 hr at room temperature, 100 ml of ether was added to promote precipitation. The solid was filtered, washed well with ether, and dried. After two recrystallizations from ethanol–water (1:1), 5.5 g (61% yield) of pure urea, mp 168–171°, was obtained.

Pharmacology—Compounds III*a*–III*h* were tested for antihypertensive activity using genetically spontaneous hypertensive rats by an indirect tail cuff method (1, 4). In a standard 3-day test, systolic blood pressure readings were made at 0 hr (control) on Days 1 and 3 and at 2 hr after administration of the compound on Days 1 and 3. The dose administered was 100 mg/kg po at 0 hr on Days 1, 2, and 3 to groups of six rats per test.

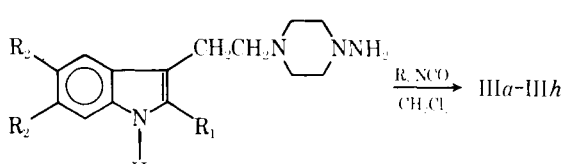
An equal number of nondosed rats were used in each test as a control. Blood pressure for the latter group generally varied from −2 to −10 mm during the test, with readings mostly near the lower value. Activity was determined by comparison of the treatment blood pressure values with the zero-time (control) blood pressure readings. Comparisons were made using the paired *t* test method for evaluation of statistical significance (5). A value of −15 mm or more is considered significant.

RESULTS AND DISCUSSION

The pharmacological data in Table II show that compounds with either aryl or alkyl groups at R_3 were active in lowering blood pressure. Various substituents at the *para*-position in the phenyl ring (III*b*–III*e*) reduced potency relative to the parent molecule (III*a*), a nitro group being particularly deleterious. Cyclohexyl (III*g*) was better than a small alkyl group (III*f*). An analog with 2-methyl and 5,6-dimethoxy substituents (III*h*) in the indole portion of the molecule was less active than III*a* where these groups are absent.

Compound III*a*, which more closely resembles indoramin in structure than the others, was the most potent member of this series. At 100 mg/kg po, III*a* was about as active by Day 3 in lowering blood pressure as 50 mg of indoramin/kg. Compounds III*a* and III*e* were selected for further evaluation in the unanesthetized normotensive dog. Over a 3-day test period, dosing orally each day with 50 mg/kg, no significant decrease in blood pressure was observed for either compound.

The latter result is in sharp contrast to the related and previously described (1) series of formula I, which was very active in both rats and dogs,



IV*a*: $R_1 = R_2 = H$
IV*b*: $R_1 = CH_3$, $R_2 = CH_3O$

Scheme I

[1] Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by MicroTech Laboratories, Skokie, Ill. The structures of all novel compounds were confirmed by their IR (Perkin-Elmer 457) and NMR (Jeolco $C_{60}HL$) spectra.

[2] The various isocyanates required to prepare the target ureas were obtained from Aldrich Chemical Co., Milwaukee, Wis.

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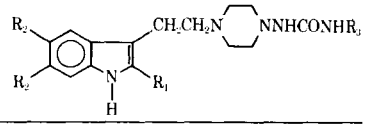
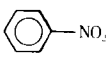
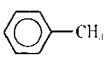


Table I—3-Substituted 1-[4-(2-Indol-3-ylethyl)piperazinyl]ureas

Compound	R_1	R_2	R_3	Yield[a], %	Melting Point	Recrystallization Solvent[b]	Formula	Analysis, %	Calc.	Found
III*a*	H	H		61	168–171°	A	$C_{21}H_{25}N_5O$	C	69.40	69.00
								H	6.92	6.97
								N	19.27	19.45
III*b*	H	H		64	203–205°	B	$C_{21}H_{24}FN_5O$	C	66.13	65.96
								H	6.34	6.30
								N	18.36	18.22
III*c*	H	H		55	212–214°	C	$C_{21}H_{24}ClN_5O$	C	63.38	63.25
								H	6.07	5.98
								N	17.60	17.50
III*d*	H	H		60	206–208°	B	$C_{21}H_{24}N_6O_3$	C	61.75	61.75
								H	5.92	5.88
								N	20.57	20.23
III*e*	H	H		58	201–203°	B	$C_{22}H_{27}N_5O$	C	70.00	69.64
								H	7.21	7.31
								N	18.55	18.58
III*f*	H	H	CH_2CH_3	63	196–199°	C	$C_{17}H_{25}N_5O$	C	64.74	64.60
								H	7.99	7.93
								N	22.20	21.88
III*g*	H	H		63	178–180°	B	$C_{21}H_{31}N_5O$	C	68.26	68.55
								H	8.46	8.55
								N	18.95	18.72
III*h*	CH_3	CH_3O		45	170–173°	C	$C_{24}H_{31}N_5O_3$	C	66.79	66.60
								H	6.95	7.11
								N	15.57	15.92

[a] Yield of analytically pure product; no effort was made to optimize yields. [b] A = dimethylformamide–water, B = ethanol–water, and C = ethyl acetate.

Table II—Hypotensive Response in Spontaneously Hypertensive Rats

Compound[a]	Change in Blood Pressure, mm Hg Day 1	Day 3
III*a*	−47	−77
III*b*	−13	−35
III*c*	−12	−54
III*d*	±[b]	±
III*e*	±	−55
III*f*	−14	−20
III*g*	−46	−44
III*h*	−36	−38
Indoramin hydrochloride	−63	−79[c]

[a] At an oral dose of 100 mg/kg. [b] The ± indicates marginal or transient activity. [c] At an oral dose of 50 mg/kg.

in the latter by a mechanism primarily of α-blockade. Evidently, a subtle change in the linkage between the phenyl and the piperazine rings from amide to urea in structures of this type leads to marked differences in hypotensive activity in the dog.

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ACKNOWLEDGMENTS

The authors thank Lee O'Donnell and Romana Fedasiuk for the IR and NMR spectra, Jeffrey Wilker and his group for performing the pharmacological assays, and Irene Field for assistance in the preparation of this manuscript.