

in water, basified with 10% NaOH, and extracted with CHCl_3 . The organics were dried (MgSO_4) and evaporated. Crystallization from a small amount of hexane yielded 0.6 g (24%) of 36, mp 90–117 °C.

Pharmacological Evaluation. The test animal is the unanesthetized decerebrated cat¹⁶ (midpontine) in which the L-5 to S-2 spinal segments have been exposed, and the spinal cord was cut at L-1. The dorsal and ventral roots of a L-6, L-7, or S-1 segment are attached to two pairs of silver J-type electrodes, and the drugs are administered intravenously over 1–2 min into the right cephalic vein as solutions in physiological saline. The compounds are tested for effects on the ventral reflex response resulting from electrical stimulation of the dorsal root with a monophasic pulse (0.5-ms duration) delivered at a rate of 30/min. The monosynaptic and polysynaptic responses are amplified and displayed on a cathode ray oscilloscope and photographed with a Polaroid camera for subsequent analysis. Administration of the saline vehicle did not affect either response.

The analgetic effect was observed in the incisor tooth pulp preparation¹⁷ using dogs and cats. In both species activity was observed at 5 mg/kg iv.

Acknowledgment. The authors thank Dr. R. Babington of the Squibb Institute Pharmacology Department for obtaining the biological data.

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Synthesis of 3-(4-Acylaminopiperazin-1-ylalkyl)indoles as Potential Antihypertensive Agents

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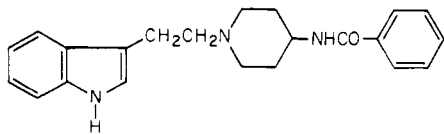
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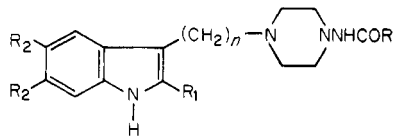
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A series of 3-(4-acylaminopiperazin-1-ylalkyl)indoles was synthesized and tested for antihypertensive activity. Compounds with no substituents in the indole portion of the molecule were generally most effective in lowering blood pressure in the spontaneous hypertensive rat model. Of these, several analogues were very potent and lowered blood pressure more than 55 mmHg at oral doses of 100 mg/kg.

Appropriately substituted piperazines often exhibit potent antihypertensive activity.¹ However, derivatives of *N*-aminopiperazine have been much less investigated for their pharmacological effects. In view of the clinically useful antihypertensive properties of indoramin (I),² we thought it would be of interest to replace the central portion of this molecule by *N*-aminopiperazine (formula II) and assess the effect of this moiety on blood pressure lowering ability. The hydrazine linkage present in this novel series also exists in other hypotensive agents, most notably hydralazine.



I

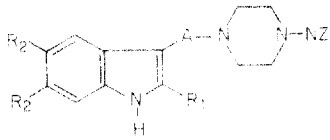


II

Chemistry. The key intermediates, the 3-(4-amino-piperazin-1-ylethyl)indoles (V), were prepared by the method of Speeter and Anthony³ as shown in Scheme I. This synthetic approach involved acylation of an appropriately substituted indole with oxalyl chloride, reaction of the resulting 3-indoleglyoxylyl chloride (III) with *N*-nitrosopiperazine to give the glyoxamide (IV), and lithium aluminum hydride (LiAlH_4) reduction to the corresponding intermediates of type V. Acylation of the *N*-amino group then afforded the target compounds.

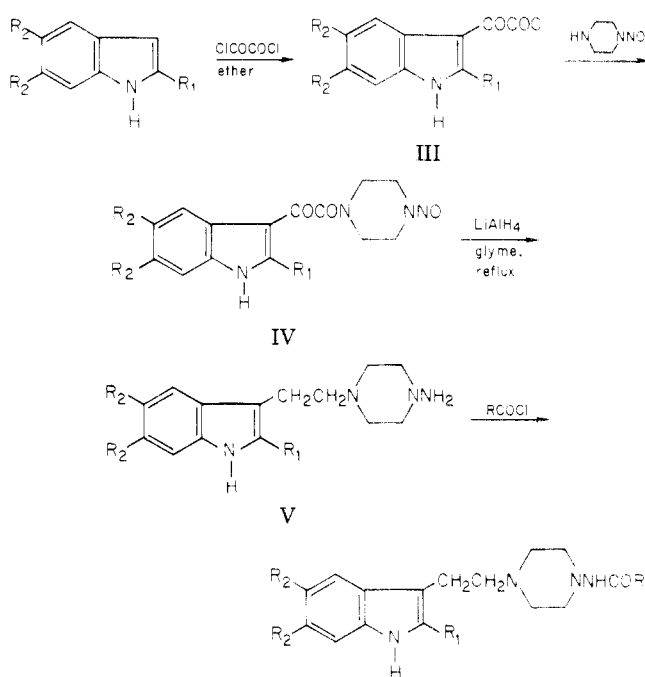
Some aspects of this chemistry deserve further comment. The reaction of indole and 2-methylindole proceeded smoothly with oxalyl chloride in ether to precipitate the brightly yellow 3-indoleglyoxylyl chlorides in better than 90% yield. These could be filtered and stored in the cold virtually unchanged for long periods of time. However, in our hands, the glyoxylyl chloride from 5,6-dimethoxy-2-methylindole (III, $\text{R}_1 = \text{CH}_3$; $\text{R}_2 = \text{OCH}_3$) was unstable, the reaction mixture rapidly turning purple and yielding no isolable solid. To circumvent this problem, the reaction was carried out at 0 °C in a two-phase chloroform-water system containing potassium carbonate as base. After a brief reaction time, *N*-nitrosopiperazine was added to trap the unstable glyoxyl intermediate. Addition

Table I. Intermediates. 3-(4-Nitroso- and aminopiperazin-1-ylalkyl)indoles

Compd	R ₁	R ₂			Yield, ^a %	Mp, °C	Recrystn solvent ^b	Formula ^c
			A	Z				
1	H	H	COCO	=O	100	223-225	A	C ₁₄ H ₁₄ N ₃ O ₃
2	CH ₃	H	COCO	=O	97	231-232	A	C ₁₅ H ₁₅ N ₃ O ₃
3	CH ₃	OCH ₃	COCO	=O	75 ^d	223-225	A	C ₁₇ H ₂₀ N ₃ O ₅
4	H	H	CH ₂	=O	90	116-118	B	C ₁₃ H ₁₆ N ₄ O
5	H	H	CH ₂ CH ₂	H ₂	94	115-117	C	C ₁₄ H ₂₀ N ₄
6	H	H	CHOHCH ₂	H ₂	20 ^e	174-177	D	C ₁₄ H ₂₀ N ₄ O
7	H	H	CH ₂	H ₁	83	147-149	E	C ₁₃ H ₁₈ N ₄
8	CH ₃	H	CH ₂ CH ₂	H ₂	95	118-120	C	C ₁₅ H ₂₂ N ₄
9	CH ₃	OCH ₃	CH ₂ CH ₂	H ₂	86			C ₁₇ H ₂₆ N ₃ O ₂ ^f

^a Isolated yield of crude solid of sufficient purity to use as is in the next step. ^b A = DMF + H₂O, B = toluene, C = benzene, D = EtOH, E = EtOH + H₂O. ^c All compounds analyzed for C, H, and N within $\pm 0.4\%$ of the calculated values. ^d Overall yield from 5,6-dimethoxy-2-methylindole. ^e Yield of analytically pure product. ^f This intermediate could not be worked to an analytically pure state either as the base or a salt.

Scheme I



of ether then precipitated the desired product IV where R₁ = CH₃ and R₂ = OCH₃ in 75% overall yield.

The reduction of the glyoxamides IV with LiAlH₄ was interesting in that in refluxing 1,2-dimethoxyethane (glyme, bp 83 °C) both carbonyl groups and the nitroso moiety were all fully reduced in situ to the desired 3-(4-aminopiperazin-1-ylethyl)indoles of type V. This result may be due to the relatively high boiling point coupled with a specific solvent effect. In lower boiling solvents, ether or tetrahydrofuran (THF), even after prolonged heating periods and excess LiAlH₄, the reduction remained incomplete. Using a shorter reflux period (e.g., 2 h) in THF, a 20% yield of the 1-hydroxyethylindole 6 could be isolated after separation from the fully reduced product 5 by fractional crystallization (Table I). Previously, such β -hydroxytryptamines had been encountered by similar reduction of 3-indolylglyoxamides only when there was an alkyl substituent on the indole nitrogen.⁴ In agreement with these earlier findings, the hydroxyl group in 6 was relatively unreactive toward acylation, and it was possible

to prepare the *N*-benzoyl compound 31 free from contamination (TLC and IR analysis) by any *O*-benzoyl ester.

The method of synthesis for compounds with a single carbon bridge between indole and the piperazine ring starting from gramine is outlined in Scheme II.

Pharmacological Results and SAR. Compounds were screened for antihypertensive activity in the spontaneous hypertensive rat (SHR). The details of the test procedure are given in the Experimental Section. From Table II it can be seen that many 3-(4-acylamino-piperazin-1-ylethyl)indoles with a wide range of acyl groups are active in lowering blood pressure in the SHR screen. Of these, compounds with a substituted phenyl appear to be the most potent. Among the halogen substituents, F confers greater activity than Cl. A CH₃ at any position in the ring reduces activity, as well as electron-withdrawing groups CF₃ and NO₂. A single CH₃O substituent, ortho, meta, or para, leads to weakly active compounds. However, multiple CH₃O substitution (compounds 23 and 24) provides the most potent antihypertensives of this series. Analogues in which R is a heterocycle, e.g., 29 and 30, are also active. On the other hand, when R is an aliphatic moiety, the compounds are generally less active than their aryl counterparts, particularly when R is of large steric bulk (27 and 28).

Modifications in the ethyl bridge connecting the indole

Scheme II

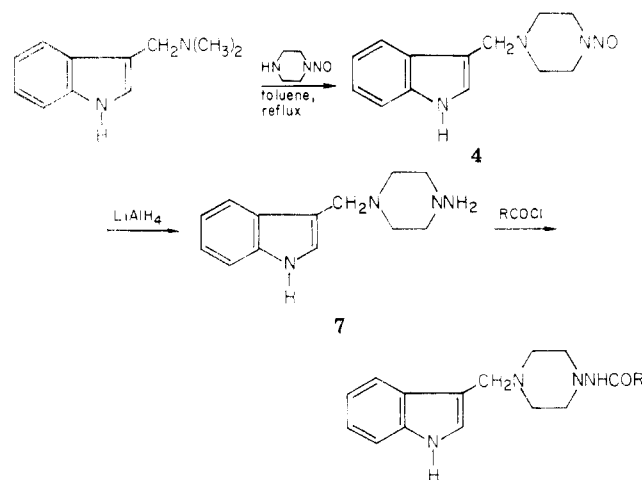
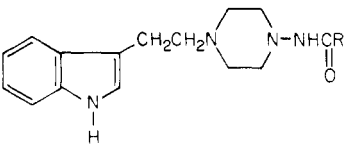


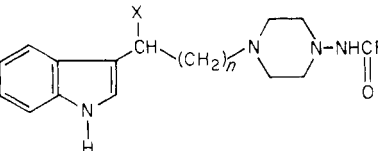
Table II. 3-(4-Acylaminopiperazin-1-ylethyl)indoles



Compd	R	Yield, ^a %	Mp, °C	Recrystn solvent ^b	Formula ^c	Antihypertensive act. (Δ, mm) ^d	
						Day 1	Day 3
10	C ₆ H ₅	80	227-229	A	C ₂₁ H ₂₄ N ₄ O·H ₂ O	-24	-56
11	2-FC ₆ H ₄	50	185-187	A	C ₂₁ H ₂₃ FN ₄ O	-47	-56
12	4-FC ₆ H ₄	57	256-259	A	C ₂₁ H ₂₃ FN ₄ O	-56	-57
13	4-ClC ₆ H ₄	56	258-260	A	C ₂₁ H ₂₃ ClN ₄ O	-17	-22
14	2-CH ₃ C ₆ H ₄	85	211-213	B	C ₂₂ H ₂₆ N ₄ O	-19	-19
15	3-CH ₃ C ₆ H ₄	88	201-203	B	C ₂₂ H ₂₆ N ₄ O	-17	-26
16	4-CH ₃ C ₆ H ₄	50	231-234	C	C ₂₂ H ₂₆ N ₄ O	-18	-43
17	3-CF ₃ C ₆ H ₄	75	194-196	A	C ₂₂ H ₂₃ F ₃ N ₄ O	-49	-19
18	4-CF ₃ C ₆ H ₄	85	216-219	C	C ₂₂ H ₂₃ F ₃ N ₄ O	-9	-36
19	4-NO ₂ C ₆ H ₄	55	205-208	C	C ₂₁ H ₂₃ N ₄ O ₃	-17	-16
20	2-CH ₃ OC ₆ H ₄	64	230-232	B	C ₂₂ H ₂₆ N ₄ O ₂	-7	-23
21	3-CH ₃ OC ₆ H ₄	35	220-222	A	C ₂₂ H ₂₆ N ₄ O ₂	-21	-2
22	4-CH ₃ OC ₆ H ₄	67	210-215	A	C ₂₂ H ₂₆ N ₄ O ₂	-25	-19
23	3,5-(CH ₃ O) ₂ C ₆ H ₃	55	195-197	D	C ₂₃ H ₂₈ N ₄ O ₃	-46	-111
24	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	52	161-163	C	C ₂₄ H ₃₀ N ₄ O ₄	-63	-70
25	CH ₃	42	183-186	C	C ₁₆ H ₂₂ N ₄ O	-32	-40
26	C ₆ H ₁₁	81	205-208	C	C ₂₁ H ₂₉ N ₄ O	-37	-35
27	2-Norbornyl	42	178-181	C	C ₂₂ H ₃₀ N ₄ O	-20	-11
28	CH(C ₆ H ₅) ₂	60	162-163	C	C ₂₈ H ₃₀ N ₄ O	-3	-10
29	4-C ₆ H ₄ N	62	227-229	C	C ₂₀ H ₂₄ N ₄ O	-23	-24
30	2-Furyl	45	201-203	C	C ₁₉ H ₂₂ N ₄ O ₂	-58	-64
Indoramin hydrochloride						-63	-79 ^e

^a Yield of analytically pure product; no effort was made to optimize yields. ^b A = DMF + H₂O, B = CH₃OH, C = EtOH + H₂O, D = EtOAc. ^c All compounds analyzed for C, H, and N within ±0.4% of the calculated values. ^d Dosing was orally at 100 mg/kg; the test procedure is described in the Experimental Section. ^e At an oral dose of 50 mg/kg.

Table III. Modification of the Alkyl Bridge



Compd	X	n	R	Yield, ^a %	Mp, °C	Recrystn solvent ^b	Formula ^c	Antihypertensive act. (Δ, mm) ^{d,e}	
								Day 1	Day 3
31 ^f	OH	1	C ₆ H ₅	42	211-213	A	C ₂₁ H ₂₄ N ₄ O ₂	-30	-33
32	H	0	C ₆ H ₅	57	176-179	B	C ₂₀ H ₂₂ N ₄ O	±	±
33	H	0	4-FC ₆ H ₄	63	210-212	B	C ₂₀ H ₂₁ FN ₄ O	±	±
34	H	0	3,4,5-(CH ₃ O) ₃ C ₆ H ₂	54	206-208	B	C ₂₃ H ₂₈ N ₄ O ₄	-20	-36

^{a-d} See corresponding footnotes in Table II. ^e ± indicates marginal or transient activity. ^f This compound is a racemate, and the antihypertensive activity is that of the racemic mixture.

and the piperazine rings diminish activity (Table III). The presence of an OH in the ethyl bridge (31) reduces activity (day 3) by almost 50% vs. 10. Shortening the link between rings from two to one carbon (compounds 32, 33, and 34) results in an even greater diminution of blood pressure lowering ability.

The effect of substituents in the indole portion of the molecule on hypotensive activity is shown in Table IV. A CH₃ at the 2 position (R₁ in the formula) results in compounds of lesser activity. Analogues with combined 2-methyl and 5,6-dimethoxy substituents (38-41) are even more weakly active in the SHR model.

In summary, several of the compounds of this series, 12, 23, 24, and 30, were very effective in lowering blood pressure in spontaneous hypertensive rats. Compound 23,

in particular, was in the potency range of indoramin. These have therefore been selected as candidates for further study in the dog, and these results will be published in a separate communication.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The structures of all compounds were confirmed by their IR (Perkin-Elmer 457) and NMR (Jeolco C₆₀HL) spectra.

Indole, 2-methylindole, and gramine were purchased from Aldrich Chemical Co., Milwaukee, Wis.; 5,6-dimethoxy-2-methylindole was prepared according to a literature procedure.⁵

1-(Indol-3-ylglyoxyloyl)-4-nitrosopiperazine (1). To a solution of 13.6 g (0.096 mol) of K₂CO₃ in 60 mL of H₂O was added

Table IV. Nuclear Substituted 3-(4-Acylaminopiperazin-1-ylethyl)indoles

Compd	R ₁	R ₂	R	Yield, ^a %	Mp, °C	Recrystn solvent ^b	Formula ^c	Antihypertensive act. (Δ, mm) ^d	
								Day 1	Day 3
35	CH ₃	H	C ₆ H ₅	79	130-133	A	C ₂₂ H ₂₄ N ₄ O	-39	-37
36	CH ₃	H	4-FC ₆ H ₄	93	222-224	A	C ₂₂ H ₂₃ FN ₄ O	-29	-25
37	CH ₃	H	4-NO ₂ C ₆ H ₄	75	136-139	B	C ₂₂ H ₂₃ N ₅ O ₃	-25	-20
38	CH ₃	CH ₃ O	C ₆ H ₅	65	128-131	B	C ₂₄ H ₃₀ N ₄ O ₃	-9	-12
39	CH ₃	CH ₃ O	4-FC ₆ H ₄	77	116-119	B	C ₂₄ H ₂₉ FN ₄ O ₃	-9	-23
40	CH ₃	CH ₃ O	2-CH ₃ OC ₆ H ₄	45	122-123	C	C ₂₅ H ₃₂ N ₄ O ₄ ·HCl	-4	-15
41	CH ₃	CH ₃ O	4-CF ₃ C ₆ H ₄	20	172-175	C	C ₂₅ H ₂₉ F ₃ N ₄ O ₃ ·HCl	-2	-5

^a Yield of analytically pure product; no effort was made to optimize yields. ^b A = DMF + H₂O, B = EtOH + H₂O, C = *i*-PrOH. ^c All compounds analyzed for C, H, and N within ±0.4% of the calculated values. ^d The test procedure is described in the Experimental Section.

a solution of 8.06 g (0.070 mol) of *N*-nitrosopiperazine⁶ in 60 mL of CHCl₃. The two phases were stirred vigorously while 12.4 g (0.060 mol) of 3-indoleglyoxylyl chloride³ was added in portions over a 15-min period while maintaining the reaction temperature at 20-25 °C. The gummy mixture was then stirred for 0.5 h when 60 mL of ether was added in portions to induce crystallization. After 15 min of additional stirring, the product was filtered, washed with H₂O and then with EtOH (2 × 25 mL), and dried to afford 17.2 g (100%). Recrystallization from 1:1 DMF-H₂O gave 12.4 g of pure 1.

1-(2-Methylindol-3-ylglyoxyloyl)-4-nitrosopiperazine (2). This intermediate was prepared and purified by the procedure described for 1.

1-(5,6-Dimethoxy-2-methylindol-3-ylglyoxyloyl)-4-nitrosopiperazine (3). To a stirred mixture of 3.82 g (0.02 mol) of 5,6-dimethoxy-2-methylindole and 5.8 g (0.044 mol) of K₂CO₃ in 50 mL of CHCl₃ and 15 mL of H₂O at 0 °C was slowly added 3.2 g (0.024 mol) of oxalyl chloride. The resulting yellow mixture was stirred for 10 min, and then 3.5 g (0.03 mol) of *N*-nitrosopiperazine was added in portions. The reaction mixture turned purple-red and was stirred at ambient temperature for 1 h. To the solution was slowly added 250 mL of ether, causing a tan precipitate to appear. The product was filtered, washed well with H₂O, and dried to afford 5.5 g (75%). Recrystallization from DMF + H₂O afforded 4.2 g of pure 3.

3-(4-Nitrosopiperazin-1-yl)methylindole (4). A stirred mixture of 34.8 g (0.22 mol) of gramine and 23.0 g (0.22 mol) of *N*-nitrosopiperazine in 700 mL of toluene was refluxed under N₂ for 48 h. The resulting solution was concentrated until a precipitate appeared at which time the mixture was cooled to 0 °C. The product was filtered, washed with cold toluene, and dried to give 44 g (90%).

3-[2-(4-Aminopiperazin-1-yl)ethyl]indole (5). To a stirred mixture of 9.0 g of LiAlH₄ in 400 mL of 1,2-dimethoxyethane under N₂ was added 10.5 g (0.035 mol) of 1 in portions and at such a rate as to keep the reaction temperature below 35 °C. When the addition was completed, the mixture was refluxed for 16 h. It was then cooled to -5 °C and a solution of 50 mL of H₂O and 50 mL of 1,2-dimethoxyethane was added slowly keeping the temperature below 15 °C, followed by an additional 50 mL of H₂O to ensure quench. The precipitated salts were removed by filtration, and the filtrate was concentrated in vacuo to a solid (8.0 g, 94%). Recrystallization from benzene furnished 7.5 g of pure amine.

By following a similar procedure, there were prepared 3-(4-aminopiperazin-1-yl)methylindole (8) and 5,6-dimethoxy-2-methyl-3-[2-(4-aminopiperazin-1-yl)ethyl]indole (9).

3-[1-Hydroxy-2-(4-aminopiperazin-1-yl)ethyl]indole (6). Following the above procedure for 5 but using 45 g of LiAlH₄ and 51.6 g (0.182 mol) of 1 in 2 L of THF and refluxing for 2 h, there was obtained 35.2 g of waxy solid. Repetitive (three times) recrystallization from EtOH afforded 10.6 g (20%) of pure 6.

General Acylation Procedure. The common method used to prepare the target amides of Tables II-IV is described in the following example.

3-[2-(4-Benzamidopiperazin-1-yl)ethyl]indole (10). A stirred solution of 6.13 g (0.025 mol) of 5 and 3.65 g (0.035 mol) of triethylamine in 75 mL of CHCl₃ was cooled to 0 °C under N₂. Then a solution of 4.20 g (0.03 mol) of benzoyl chloride in 5 mL of CHCl₃ was added dropwise over 0.5 h while maintaining the temperature below 5 °C. The reaction was stirred at ambient temperature overnight at which time 75 mL of 10% NaOH (this dissolved the salt) and 100 mL of ether (this completed precipitation of the product) were added. After 0.5 h, the amide was filtered, washed with H₂O and then ether, and dried to afford 7.1 g.

In those cases where the amide was very soluble in CHCl₃ (e.g., 20), the organic phase was separated, washed with H₂O, dried over Na₂SO₄, and concentrated to a solid which was recrystallized from the solvent indicated in the tables.

SHR Test for Antihypertensive Activity. Compounds were screened for antihypertensive activity using genetically spontaneous hypertensive rats (SHR) by a standard indirect tail cuff method.⁷ Two rats were placed into a wire basket in an incubator set to 40 °C. Each cage of rats was left to condition in the incubator for 20 min; then the rats were removed and placed in individual trigonal or trapezoidal cages made of Lucite. A tubular inflatable cuff was placed around the base of the tail. A microphone (Narco Bio-Systems or Biodynamics) was placed under the ventral surface of the tail and the tail was strapped down. When the microphone was properly located, the pulse could be detected and was amplified by a universal type amplifier. Each microphone was connected to an individual channel on a recorder and the pulse was recorded. The cuff was inflated to approximately 300 mmHg. The pulse was thereby obliterated. The pressure in the cuff was slowly released and, as the pressure fell below the systolic pressure, the pulse could again be detected by the microphone. The blood pressure of each rat was determined three to five times from which a mean value was derived. Before any animal was included in the screening program, a 2-week training period was employed to acclimate the animal to the test environment. Also, this procedure permitted the establishment of baseline blood pressures for each animal. Any animal whose blood pressure was less than 150 mmHg was withdrawn from the test group.

In a standard 3-day test, systolic blood pressure readings were made at 0 time (control) on days 1 and 3, and at 2 h after administration of the compound on days 1 and 3. Dosing was orally at 100 mg/kg at 0 h on days 1, 2, and 3 on groups of six animals per test. An equal number of nondosed animals were used in each test as a control. Blood pressure for this 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 0 time (control) blood

pressure readings. Comparisons were made using the paired *t* test method for evaluation of statistical significance.⁸ A value of -15 mm or more is considered significant.

Acknowledgment. The authors wish to express their gratitude to Lee J. O'Donnell, Irene W. Tsina, Romana H. Fedasiuk, and Michael Ruberto for the IR and NMR spectral data, to Jeffrey Wilker, Mrs. K. Lubsen, Ronald Matys, Kenneth Malone, Thomas Hynds, Craig Dobson, and Barbara Kirby for performing the pharmacological assays, and to Linda Cuiskelly for assistance in preparation of this manuscript.

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Structure of Warfarin in Solution¹

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Received August 4, 1976

Warfarin in solution is shown to consist of three interconverting tautomeric structures, two of which are cyclic diastereomeric hemiketals, while the third and minor component is the open-chain intermediate form. The configurations of all the tautomers as well as the major conformations of the cyclic tautomers are assigned. The assignments are supported by comparison with the chemical shift and coupling constant parameters of structurally fixed model compounds.

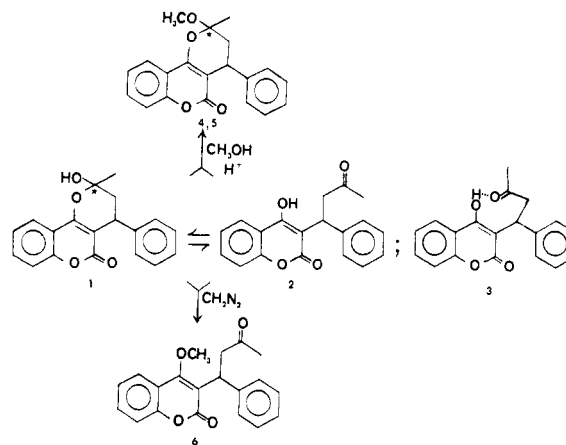
Warfarin [3-(1-phenyl-3-oxobutyl)-4-hydroxycoumarin, **2** (Scheme I)] is usually depicted in textbooks and review articles as the open tautomer, although Chmielewska and Cieslak postulated^{2a} that its antivitamin K activity was due to the hemiketal tautomer, **1**. Hutchinson and Tomlinson, on the basis of NMR and IR data, suggested^{2b} that the active form of the drug was the hydrogen bonded eight-membered ring structure, **3**. They further suggested that steric differences between the *R* and *S* forms of **3** may further account for the differences in potency between them (sic). Although Wawzonek and McIntyre³ did not speculate on the biologically active form of the molecule, they suggested from polarographic data obtained in acetonitrile or 50% aqueous ethanol that warfarin exists in the open form, **2**, and is not in equilibrium with the cyclic form, **1**.

The molecular form in the crystalline state, both of the (*S*)-(-) isomer⁴ and the racemate,⁵ is the cyclic tautomer. Determination of its structure in solution has been hampered by its low solubility in common spectral solvents. Recently, the cyclic structure has been assigned⁶ to warfarin on the basis of its ¹³C NMR spectrum and those for certain model compounds. Our data provide configurational assignments and evidence that warfarin in solution exists in a dynamic equilibrium between the open and diastereomeric cyclic forms.

Results and Discussion

In order to probe the possible tautomeric equilibrium displayed by warfarin, it was necessary to synthesize pure model compounds that would mimic the various tautomeric structures and obtain the spectroscopic parameters which are characteristic of these forms. Warfarin can be converted to three isomeric methyl ethers (Scheme I) depending on the method of methylation. The isomeric

Scheme I



cyclocoumarols [(2*S*,4*S*)-, (2*R*,4*R*)-, (2*R*,4*S*)-, and (2*S*,4*R*)-2,3*H*-2-methyl-2-methoxy-4-phenyl-5-oxobenzopyrano[3,4-*e*]dihydropyran; (2*S*,4*S*)- and (2*R*,4*R*)-4; and (2*S*,4*R*)- and (2*R*,4*S*)-5], prepared by treatment of **1** with methanol and acid, can be separated by fractional crystallization and studied individually. Warfarin 4-methyl ether [3-(1-phenyl-3-oxobutyl)-4-methoxycoumarin, **6**] is the sole product of methylation of **1** with diazomethane in ether.⁷

The structure of **5**, the minor cyclic ketal, in the crystalline state has the *R,S* and *S,R* configurations at C-11 and C-13 (Figure 1). The preferred conformation in the solid state is the half-chair in which the phenyl and methoxyl groups are pseudoaxially and axially disposed, respectively.⁸ There is, therefore, a close nonbonded contact between C-16 and O-3 of 2.924 (4) Å. The relative stability of this unusual arrangement reflects the dipole