Table III. Formulas and Physical Data of the Compounds Prepared

no.	mp, °C	anal.	formula
1	142-144	C, H	$C_{30}H_{30}O_{13}$
2	125-126	C, H	$C_{29}H_{28}O_{13}$
3	106-110	C, H	$C_{30}H_{30}O_{13}\cdot 0.5H_2O$
4	144-147	C, H	$C_{32}H_{32}O_{14}\cdot 0.5H_2O$
5	122-124	C, H	$C_{31}H_{32}O_{14}\cdot 0.5H_2O$
6	228-232	C, H	$C_{26}H_{25}O_{11}\cdot 0.5H_2O$
7	214-228	C, H	$C_{25}H_{24}O_{11}\cdot 0.5H_2O$
8	188-190	C, H	$C_{26}H_{26}O_{11}\cdot 0.5H_2O$
9	230-233	C, H	$C_{28}H_{30}O_{12}\cdot 0.5H_2O$
10	217-220	C, H	$C_{27}H_{28}O_{12}\cdot 0.5H_2O$

group at the 5′ position, so that the sugar can flip into a form that cannot bind with a receptor site. As for the rubidazone analogue, it might be too lipophilic to be active in vivo, due to solubility problems.

Experimental Section

Melting points were determined with a Kofler block and are uncorrected. Nuclear magnetic resonance spectra were run on Varian HA-100 or 360-A spectrometers. Microanalyses were run in the Department of Chemistry and Chemical Engineering microanalysis laboratory by Mrs. S. Brotherton on a Perkin-Elmer 240 elemental analyzer. Preparative chromatography columns were packed with Sargent-Welch SC14608 silica gel (60–200 mesh).

Synthesis of Blocked Glycosides. A suspension of the desired anthracyclinone (100 mg, 0.26 mmol), ground 3A molecular sieves (500 mg), mercuric bromide (110 mg, 128 mmol), and mercuric cyanide (10 mg, 0.40 mmol) in tetrahydrofuran (15 mL) was stirred at room temperature. The appropriate glycosyl halide (120 mg, 0.41 mmol) was added, and the mixture was refluxed for 0.5 h, after which another portion of the glycosyl halide (120 mg) was added, and the mixture was refluxed for another hour. The mixture was allowed to cool and was then filtered to remove the molecular sieves. The residue was washed well with chloroform, and the combined filtrates were evaporated to a syrup under reduced pressure. The syrup was dissolved in chloroform (500 mL) and washed with 2 M potassium iodide solution (4 × 50 mL). The chloroform solution was dried over sodium sulfate and evaporated to dryness under reduced pressure. The resulting product was dissolved in absolute ether (25 mL) and applied to a silica gel column (2 × 20 cm), which was washed with absolute ether (100 mL). The desired blocked glycoside was eluted with 2% methanol in chloroform crystallized from 95% ethanol. (See Table III).

Synthesis of Deblocked Glycosides. The blocked glycoside (50 mg) was dissolved in methanol (15 mL) containing an excess of freshly prepared sodium methoxide and stirred at room temperature for 20 min. The purple solution was then poured into a separately funnel containing a sodium hydrogen sulfate solution (0.5 M, 100 mL). The combined chloroform extracts were dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was dissolved in hot 95% ethanol (30 mL), filtered, reduced in volume to 10 mL, and allowed to evaporate slowly in an open beaker. The crystals were filtered and washed with ether. (See Table III.)

Synthesis of Rubidazone Analogue (11). 2′-Deoxy-L-fucopyranosylcarminomycinone (6; 10 mg, 19 μmol) and benzoyl hydrazine (2.7 mg, 20 μmol) were refluxed in absolute ethanol (5 mL) overnight. After the solvent was removed, the benzoylhydrazone (11) was crystallized from 95% ethanol, filtered, and washed with isopropyl ether, yield 8 mg (64%). Anal. ($C_{27}H_{22}N_2O_8$) C, H, N.

Acknowledgment. The authors express their gratitude to Bristol Laboratories, a division of Bristol-Myers Co., for financial support and for samples of carminomycin and ϵ-pyrromycinone and to the National Cancer Institute for a sample of daunomycinone.

2-(Aminomethyl)phenols, a New Class of Saluretic Agents. 2. Synthesis and Pharmacological Properties of the 5-Aza Isostere of 2-(Aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol

G. E. Stokker,* R. L. Smith, E. J. Cragoe, Jr.,

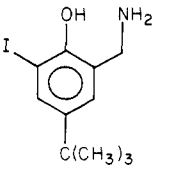
Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486

C. T. Ludden, H. F. Russo, C. S. Sweet, and L. S. Watson[1]

Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486. *Received June 30, 1980*

The synthesis and biological evaluation of 4-(aminomethyl)-6-(1,1-dimethylethyl)-2-iodo-3-pyridinol dihydrochloride (**7b**) are described. Compound **7b** proved to be highly active as a saluretic diuretic in both rats and dogs.

Recently, we reported[2] on a series of 2-(aminomethyl)-phenols which were shown to possess a high order of diuretic activity in rats and dogs. It was shown that the molecular features essential for activity are (1) a hydrogen, methyl, or methoxyl group in the 3 position; (2) a halo or C_3–C_4 α-branched alkyl substituent in the 4 position; (3) a hydrogen, lower alkyl, or lower alkoxy moiety in the 5 position; and (4) a chloro, bromo, or iodo group in the 6 position. The highest level of activity was achieved with 2-(aminomethyl)-4-(1,1-dimethylethyl)-6-iodophenol (1), which not only was an excellent diuretic but also displayed good antihypertensive activity in the spontaneously hypertensive rat.



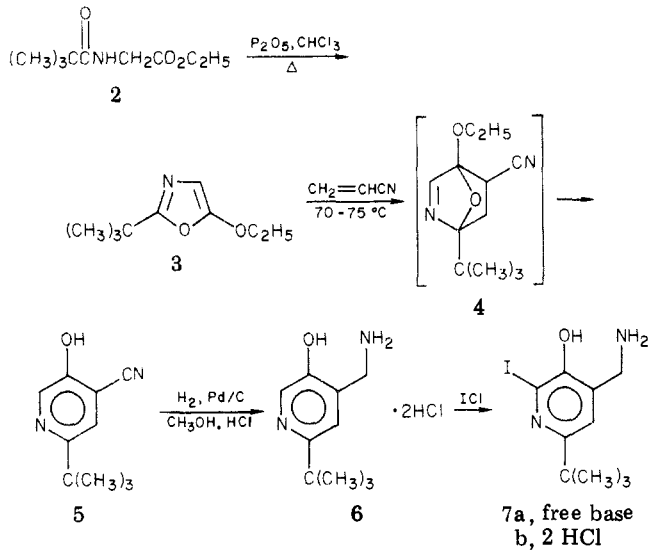
1

In this paper, we describe the synthesis and biological activity of 4-(aminomethyl)-6-(1,1-dimethylethyl)-2-iodo-3-pyridinol dihydrochloride (**7b**), the 5-aza isotere of **1**, as

(1) Deceased, May 31, 1977.
(2) For Part 1, see Stokker, G. E.; Deana, A. A.; deSolms, S. J.; Schultz, E. M.; Smith, R. L.; Cragoe, E. J., Jr.; Baer, J. E.; Ludden, C. T.; Russo, H. F.; Scriabine, A.; Sweet, C. S.; Watson, L. S. *J. Med. Chem.*, **1980**, *23*, 1414.

0022-2623/81/1824-0115$01.00/0

Scheme I



part of an effort to attenuate potassium excretion in the 2-(aminomethyl)phenol series via enhancement of molecular basicity.

Chemistry. The synthetic sequence shown in Scheme I was utilized for the preparation of target **7**. The key step in the synthesis was the Diels–Alder condensation[3] of acrylonitrile and **3** to provide the desired regioisomer **4**. Interestingly, a perturbed molecular orbital analysis based on CNDO calculations offered little preference for the formation of either regioisomer; only if one invoked possible secondary orbital interactions between the ethoxy and cyano groups could such a regiochemical preference, albeit slight, be predicted by these calculations. Intermediate **4** spontaneously eliminated ethanol to afford **5** as the only detectable product in low yield (the yield was 58–69% based on unrecovered starting oxazole). Addition of various Lewis acid catalysts (e.g., $AlCl_3$ or $BF_3{\cdot}Et_2O$) or heating at a higher temperature (e.g., 120 °C) in an autoclave proved to be either ineffectual or deleterious to the reaction. Subsequent catalytic hydrogenation of **5**, followed by iodination of the resulting product **6**, provided **7** in good yield.

Pharmacology. The diuretic and saluretic effects of **6** and **7b** are compared with those of **1**, hydrochlorothiazide, and furosemide in both rats and dogs in Table I. The deiodopyridinol **6** displayed only slight diuretic and saluretic effects as did its carbocyclic counterpart described in our first publication.[2] Iodopyridinol **7b** exhibited diuretic and saluretic effects comparable to those of **1** in rats which were superior to those of hydrochlorothiazide an furosemide. However, its diuretic and saluretic effects in dogs were less than those displayed by either **1** or furosemide. The desired reduction of kaluresis to that of control levels was not observed for **7b** in either rats and dogs.

When evaluated in spontaneously hypertensive (SH) rats, **7b** proved to be markedly less potent than **1** when administered orally. Hence, as judged by the above data

Table I. Comparative Oral Diuretic Effects on Rats and Dogs and Effect on Arterial Pressure of Spontaneously Hypertensive Rats[a]

	diuretic effects									effects in SH rat		
		oral rat assay[b]				intravenous dog assay, 5 mg/kg stat						
		mequiv × 100/cage				mequiv/min						
compd	dose, mg/kg	Na^+	K^+	Cl^-	no. of expt av	Na^+	K^+	Cl^-	dose mg/kg, po	no. of rats	max fall, mmHg ± SE, in MAP	duration of effect, h
6	3	14	14	14	2	279	20	303	20[c]	1	12	
	9	8	7	11								
	27	22	15	37								
	81	63	23	98								
7b	3	178	51	279	2	611	48	729	20	4	13 ± 6	
	9	224	63	351					20[c]	2	61 ± 9	>24
	27	276	83	444								
	81	330	108	528								
1	3	146	51	211	2[d]	716	66	822	0.312	24	26 ± 2.1	12–18
	9	270	77	364					1.25	24	38 ± 1.6	>24
	27	319	88	435								
	81	351	99	489								
hydrochlorothiazide	3	123	34	154	3	166	33	156	20	9	25 ± 2.9	<8
	27	131	34	156					40	10	26 ± 3.9	12
	81	128	37	143								
furosemide	9	7	14	22	2[d]	960	141	1081	30	5	12 ± 3.3	
	27	125	55	213								
	81	244	77	370								
placebo		28	16	25	15	21	10	4		10	13 ± 1.4	

[a] For testing protocols, see ref 2. [b] For oral rat assay, three animals per cage, three cages per dose for 0–5 h. [c] ip administration. [d] 1 mg/kg.

(3) For other examples of condensations of oxazoles with dienophiles to yield 3-pyridinols, see Harris, E. E.; Firestone, R. A.; Pfister, K., III; Boettcher, R. R.; Cross, F. J.; Currie, R. B.; Monaco, M.; Peterson, E. R.; Reuter, W. *J. Org. Chem.* **1962**, *27*, 2705. Firestone, R. A.; Harris, E. E.; Reuter, W. *Tetrahedron* **1967**, *23*, 943. Doktorova, N. D.; Ionova, L. V.; Karpeisky, M. Ya.; Padyukova, N. SH.; Turchin, K. F.; Florentiev, V. L. *Tetrahedron* **1969**, *25*, 3527.

for **7b**, enhancement of basicity in this instance resulted in a slight diminution of diuretic activity while substantially diminishing antihypertensive activity.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM390 NMR spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined using a Perkin-Elmer Model 240 elemental analyzer and are within ±0.4% of theory unless noted otherwise.

2-(1,1-Dimethylethyl)-5-ethoxyoxazole (3). To a vigorously stirred slurry of P_2O_5 (163.8 g, 1.15 mol) in $CHCl_3$ (600 mL) maintained under an N_2 atmosphere was added slowly a solution of ethyl *N*-(2,2-dimethyl-1-oxopropyl)glycinate[4] (107.8 g, 0.576 mol) in $CHCl_3$ (350 mL). After the addition was completed, the reaction mixture was stirred and heated at reflux under N_2 for 14 h. The cooled reaction mixture was treated with 20% NaOH (800 mL), vigorously stirred for 0.5 h, and allowed to separate into two phases. After the aqueous phase was discarded, the organic phase was washed with H_2O and saturated brine, dried ($MgSO_4$), and filtered. Distillation of the filtrate provided **3** as a pale yellow oil (64 g, 66%): bp 58–64 °C (0.7 mmHg); NMR ($CDCl_3$) 1.30 (9 H, s, *t*-C_4H_9), 1.40 (3 H, t, CH_2CH_3), 4.07 (2 H, q, OCH_2), 5.90 ppm (H-4, s). Anal. ($C_9H_{15}NO_2$) H, N; C: calcd, 63.88; found, 64.49.

4-Cyano-6-(1,1-dimethylethyl)-3-pyridinol (5). A neat mixture of **3** (17 g, 0.1 mol) and acrylonitrile (6.1 g, 0.11 mol) was stirred with heating at 70–75 °C for 16 h. The resulting dark mixture was cooled to 20 °C and chromatographed on silica gel (600 g). Elution with 1% MeOH in $CHCl_3$ (4.35 L) yielded recovered **3** (10.7 g, 63% recovery). Continued elution with the same eluant (300 mL) afforded a mixture of **3** and **5** (3.2 g). Further elution (2.5 L) gave the desired product as a solid (6.5 g, 37%), mp 185–195 °C. Two crystallizations of the latter from MeOH–H_2O (1:1; v/v) provided an analytical sample of **5** as colorless crystals (4.5 g, 26%): mp 201–202 °C; NMR (Me_2SO-d_6) 1.23 (9 H, s, *t*-C_4H_9), 7.63 (H-5, s), 8.45 ppm (H-2, s). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

(4) Voinescu, V.; Balog, A. *Rev. Roum. Chim.* **1961**, *14*, 951.

Alternatively, unreacted **3** could be recovered by distillation, e.g., by heating the reaction mixture at 80 °C (0.5 mmHg). In this way (11.1 g, 65.6 mmol) of **3** was recovered. The residue was triturated with hexane (30 mL) to give cyanopyridinol **5** (3.5 g, 19.9%), mp 192–197 °C.

4-(Aminomethyl)-6-(1,1-dimethylethyl)-3-pyridinol Dihydrochloride (6). A solution of **5** (5.7 g, 32 mmol) in MeOH–12 N HCl (30:1, v/v, 310 mL) was hydrogenated over 10% Pd/C (1 g) at 25 °C and 40–45 psi pressure. The reaction mixture was then filtered, and the collected catalyst was washed with EtOH. Evaporation (in vacuo) of the combined filtrate and washings yielded **6** (7.9 g, 98%), mp 304–306 °C dec. Crystallization from EtOH–Et_2O–H_2O (100:100:4, v/v) afforded an analytical sample of **6** as colorless crystals: mp 304–306 °C dec; NMR (Me_2SO-d_6) 1.47 (9 H, s, *t*-C_4H_9), 4.23 (2 H, CH_2N, br s), 8.17 (H-5, s), 8.45 ppm (H-2, s). Anal. ($C_{10}H_{16}N_2O$·2HCl) C, H, N.

4-(Aminomethyl)-6-(1,1-dimethylethyl)-2-iodo-3-pyridinol (7a). A solution of ICl (2.68 g, 20 mmol) in 4 N HCl (15 mL) was added to a solution of **6** (5.06 g, 20 mmol) in H_2O (30 mL). The resulting solution was kept at 20–25 °C for 18 h, diluted with H_2O to a volume of 100 mL, and then treated with 15 N NH_4OH (12 mL). The resulting precipitate was collected, washed with H_2O, and air-dried to give crude **7a** (4.8 g, 78%), mp 162–165 °C. Crystallization from 50% EtOH provided an analytical sample of **7a** as pale tan crystals: mp 170–171 °C; NMR (Me_2SO-d_6) 1.19 (9 H, s, *t*-C_4H_9), 3.90 (2 H, CH_2N, s), 6.92 ppm (H-5, s). Anal. ($C_{10}H_{15}IN_2O$) C, H, N.

4-(Aminomethyl)-6-(1,1-dimethylethyl)-2-iodo-3-pyridinol Dihydrochloride (7b). To a solution of **7a** (4.8 g, 16 mmol) in EtOH (50 mL) was added 12 N HCl (3 mL). The resulting solution was diluted slowly with Et_2O (150 mL) and then cooled to 0 °C. The precipitate was collected, washed with Et_2O, and air-dried to afford **7b**·2HCl (5.4 g, 91%), mp 177–179 °C dec. Crystallization from Et_2O–EtOH–H_2O (125:50:2; v/v) provided an analytical sample as colorless needles: mp 178–179 °C dec. Anal. ($C_{10}H_{15}IN_2O$·2HCl) C, H, N.

Acknowledgment. The authors thank Drs. C. A. Stone and R. Hirschmann for their encouragement throughout the course of this investigation, K. B. Streeter and associates for microanalysis, Dr. B. Schlegel for interpretation of the CNDO data, and Mrs. J. Murphy for determining the ^{1}H NMR spectra.

Synthesis and Study of the Potential Antiallergic Activity of Some Pyrazole Derivatives

María T. Di Parsia, Cecilia Suárez, María J. Vítolo, Víctor E. Márquez,*[1]

Departamento de Investigación, Laboratorio de Química, Laboratorios Cosmos, S.A., Caracas, Venezuela

Bernardo Beyer,

Instituto de Investigación y Desarrollo Industrial y Departamento de Química, Universidad Simón Bolívar, Caracas 106, Venezuela

Cecilia Urbina, and Inés Hurtado

Laboratorio de Alergia Experimental, Centro de Microbiología y Biología Celular, Instituto Venezolano de Investigaciones Científicas, Caracas 101, Venezuela. *Received July 14, 1980*

The synthesis and study of the oral antiallergic activity of a series of monopyrazole derivatives (**2**–**14**) considered as analogues of active bispyrazole **1** are described. None of the compounds showed significant inhibition of the rat passive cutaneous anaphylaxis (PCA), with the exception of the already known 5-aminoindazole (**2**). The activity of this compound is, however, lower than that of compound **1**.

The discovery of the significant and prolonged antiallergic activity of bispyrazole **1** prompted us to investigate some related compounds in order to ascertain the relative importance of the pyrazole rings in relation to the an-

0022-2623/81/1824-0117$01.00/0