Table II. Methylenemorphinans 3 and 4

compd	X	R	R_1	% yield free base[a]	mp, °C	recrystn solvent[b]	formula[c]
3Pb	c-C_3H_5	CH_3	CH_3	80	91-93	E	$C_{23}H_{31}NO$
3Ba	c-C_4H_7	H	CH_3	26	89-91[d]	E	$C_{23}H_{31}NO \cdot C_4H_6O_6 \cdot 0.5EtOH$
3Bb	c-C_4H_7	CH_3	CH_3	37	221-224[e]	EE-T	$C_{24}H_{33}NO \cdot HCl$
4Pa	c-C_3H_5	H	H	58	220-223	E	$C_{21}H_{27}NO$
4Pb	c-C_3H_5	CH_3	H	21[f]	231-233	E	$C_{22}H_{29}NO$
4Pc	c-C_3H_5	CH_2CH_3	H	62	197-200	E	$C_{23}H_{31}NO$
4Ba	c-C_4H_7	H	H	87	155[g]	A	$C_{22}H_{29}NO \cdot HCl \cdot C_3H_6O$[h]
4Bb	c-C_4H_7	CH_3	H	82	165-169	EE-H	$C_{23}H_{31}NO$
4Bc	c-C_4H_7	CH_2CH_3	H	84	166-168	C	$C_{24}H_{33}NO$

[a] Yield of purified free base after chromatography. [b] A = acetone; C = chloroform; E = ethanol; EE = ethyl ether; H = hexane; T = toluene. [c] All compounds had C, H, and N analysis within ±0.4% of the calculated value. [d] *d*-Tartrate salt, hemiethanol solvate. [e] Hydrochloride salt. [f] Selective extraction prior to workup. [g] Foams, hydrochloride salt, acetone solvate. [h] Acetone.

algesic drug which does not substitute for morphine in rats or monkeys. *N*-(Cyclobutylmethyl)-8β-methyl-6-methylenemorphinan-3-ol (**4Bb**) is currently undergoing further evaluation.[14,15]

Experimental Section[16]

Preparation of *N*-(Cycloalkylmethyl)-3-methoxy- or -hydroxy-6-methylenemorphinans (3 or 4). A solution of $Ph_3P{=}CH_2$[7] was prepared from NaH (14.4 mmol) and Ph_3PCH_3Br (5.14 g, 14.4 mmol) in Me_2SO (30 mL) under an argon atmosphere. To this was added a solution of **1** (6 mmol) or **2** (4 mmol) in Me_2SO (20 mL), and the reaction mixture was stirred at 80 °C in a preheated oil bath for 1 h. The cooled solution was diluted with ice–water–NH_4OH and extracted with 3 portions of toluene. The combined organic extracts were washed 4 times with H_2O, dried, and evaporated to a crude residue, which was chromatographed. Pure fractions were combined on the basis of TLC and evaporated to dryness, and the residue was crystallized directly or converted to the salt as indicated in Table II.

Acknowledgment. The authors thank Drs. R. N. Schut, J. E. Villarreal, and R. K. Razdan for their continued interest and encouragement.

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(16) Methods have been reported. See ref 1 or 2. The presence and the amount of solvent in **3Ba** and **4Ba** were confirmed by NMR in an appropriate solvent. For pharmacological testing, compounds which were prepared as salts were administered in distilled H_2O; free bases were dissolved by the dropwise addition of 1 N HCl and then further diluted. For both agonist and antagonist assays, at least five animals per dose and at least three doses of each drug were utilized in determination of the ED_{50} or AD_{50} values.
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Substituted Imidazo[1,2-*a*]pyridine-2-carbamate Anthelmintics

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Anthelmintic efficacies of a series of 6-substituted methyl imidazo[1,2-*a*]pyridine-2-carbamates were compared to similarly substituted benzimidazole-2-carbamates. With only one exception, methyl 6-benzoylimidazo[1,2-*a*]-pyridine-2-carbamate, both classes of compounds exhibited similar activity vs. *Nematospiroides dubius* in mice. Preliminary screening indicated methyl 6-(1,2,2-trichloroethenyl)imidazo[1,2-*a*]pyridine-2-carbamate to be the most potent derivative in the series. However, evaluation in sheep indicated that its anthelmintic spectrum was inferior to methyl 6-(phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate.

A similarity of structure–activity relationships with benzimidazole anthelmintics has been described for imidazo[1,2-*a*]pyridines.[1] This research has been extended to phenyl thioether derivatives, resulting in the discovery of methyl 6-(phenylsulfinyl)imidazo[1,2-*a*]pyridine-2-carbamate (**1a**) as a potent, broad-spectrum anthelmintic.[2] This report compares anthelmintic structure–activity relationships between benzimidazoles and imidazo[1,2-*a*]-pyridines.

Structures **2a–e** include most of the commercially useful benzimidazole-2-carbamate anthelmintic agents.[3-7] The

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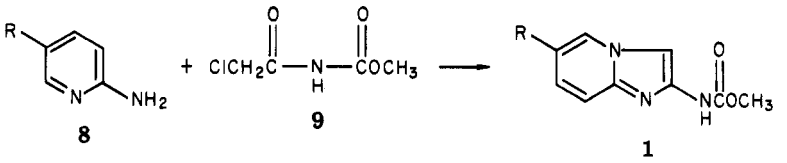
0022-2623/81/1824-1518$01.25/0

Table I. Syntheses of 6-Substituted Imidazo[1,2-*a*]pyridines

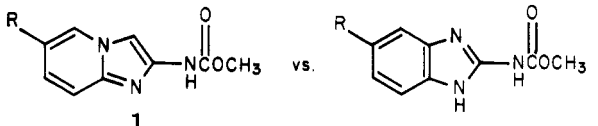


8 9 1

no.	R	mmol of 8	mmol of 9	product no.	% yield[a]	mp (recrystn solvent), °C	anal.
8a	C_3H_7O	6.5	11.1	1c	11	210-212.5 (EtOH)	C, H, N
8b	C_3H_7S	10	11	1d	17	202-204 (DMF-EtOH, 50:50)	C, H, N, S
8c	C_6H_5O	5.05	10	1e	47	241-242 dec (DMF-EtOH)	C, H, N
8d	CCl_2=CCl	2	2.2	1f	12	225-226 (EtOH)	C, H, N, Cl

[a] Isolated but not maximized yields.

Table II. Percent Reduction[a] of *Nematospiroides dubius* in Mice at Necropsy[b]

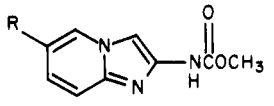


1 vs. 2

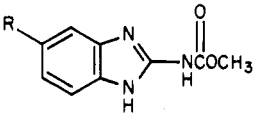
		% reduction				
compd	R	ppm in diet: 1000	500	250	125	62.5
1a	$C_6H_5S(\rightarrow O)$				100	35
1b	C_6H_5S-		100	98	38	0
2b[c]	C_6H_5S-			96	5	0
1c	C_3H_7O-			74	44	0
2c[d]	C_3H_7O-			58	28	0
1d	C_3H_7S-			100	74	0
2d[e]	C_3H_7S-			100	92	0
1e	C_6H_5CO-	0	0	0		
2e[f]	C_6H_5CO-		100	100	88	
1f	CCl_2=CCl-				94	94
2f[g]	CCl_2=CCl-			99	69	57
1g	H	54	0			
thiabendazole[h]		100	86	26	0	
cambendazole[i]			100	73	0	0

[a] <20% reduction recorded as 0. [b] Data were obtained by the method of Baker.[12] There were three mice per treated group. Results are the average of the number of worms per mouse. [c] "Fenbendazole" for synthesis, see ref 13. [d] "Oxybendazole", prepared as in ref 5. [e] "Albendazole", prepared by method reported in ref 14. [f] "Mebendazole" used commercial formulation "TELMIN" by Pittman Moore, which contains 16% **2e** by weight. [g] See ref 8. [h] 2-(4-Thiazolyl)-benzimidazole (Merck & Co.). [i] Isopropyl 2-(4-thiazolyl)-5-benzimidazolecarbamate (Merck & Co.).

trichloroethenyl derivative, **2f**, was a recent discovery in these laboratories.[8]



1a, R = $C_6H_5S(\rightarrow O)$
b, R = C_6H_5S
c, R = C_3H_7O
d, R = C_3H_7S
e, R = C_6H_5CO
f, R = Cl_2C=CCl
g, R = H



2a, R = $C_6H_5S(\rightarrow O)$
b, R = C_6H_5S
c, R = C_3H_7O
d, R = C_3H_7S
e, R = C_6H_5CO
f, R = CCl_2=CCl

Since introduction of the phenylthio group into **1g** effected a dramatic improvement in the in vivo potency of this class of compounds,[2] it was of interest to synthesize the imidazo[1,2-*a*]pyridine analogues **1c-f** to compare anthelmintic activity with their benzimidazole counterparts.

Chemistry. Substituted imidazopyridine-2-carbamates were prepared by reacting the appropriately substituted 2-aminopyridine with methyl *N*-(chloroacetyl)carbamate (Table I).[2] Because of the nature of the substituents, different pathways were necessary to prepare the desired 2-aminopyridines, **8a,b** (Scheme I). Displacement of the halogen from **4** using sodium thiophenylate or 1-propanethiolate yielded **8e** or **8b**, respectively. Similar treatment of **4** with the less nucleophilic propoxide ion yielded **8a** in only 3% yield. However, **8a** was obtained in better yield via the reductive hydrolysis of the azo linkage in **3b**. A modification of the method of Moore and Marascia,[9] utilizing a crown ether assisted alkylation of **3a**, gave **3b** in modest yield.

The reaction of the acid chloride **5b** with $AlCl_3$ and C_6H_6 gave **5c**. The amine **8c** was obtained by subsequent ammonolysis of **5c**. The addition of 2 mol of Cl_2 to 5-ethynyl-2-picoline (**6a**) yielded **6b**, isolated as the HCl salt. In larger experiments, it was preferable to carry out the

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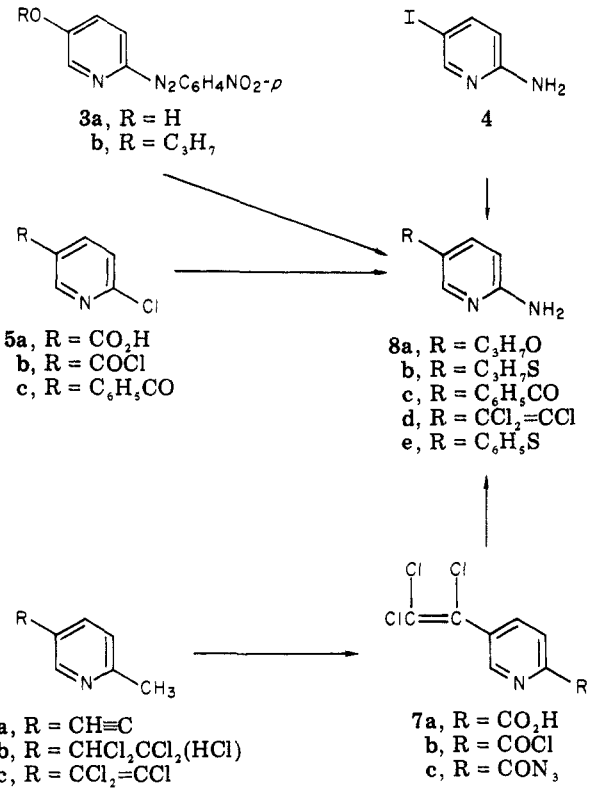
Scheme I. Syntheses of 2-Amino-5-substituted-pyridines



dehydrohalogenation of **6b** without isolation, since analysis of the crude reaction mixture indicated some **6c** was formed during workup. The picoline, **6c**, was oxidized using SeO_2 to yield **7a**, and application of the Curtius reaction yielded **8d**. The reference benzimidazole carbamates were either prepared from published procedures or obtained as commercial samples as indicated in Table II.

Biological Data. Compounds were administered in the diet for 5 days to groups of three mice experimentally infected with *Nematospiroides dubius*. At necropsy, the total worm burdens were compared with those of infected, nontreated controls. Table II lists comparative efficacies of benzimidazole and imidazo[1,2-*a*]pyridines as percent reduction of worm burdens. With the exception of the benzoyl analogue, **1e**, introduction of a 6-substituent into **1g** conferred a dramatic enhancement of anthelmintic potency to imidazo[1,2-*a*]pyridinecarbamates. More interesting is the apparent anthelmintic bioequivalence of both these classes of compounds. It has yet to be determined whether the difference between the biological properties of **1e** and **2e** is due to a unique mode of action of **2e** or simply the physical properties of **1e**.

Based on preliminary screening, the more potent analogues **1a** and **1f** were selected to be evaluated in sheep. Each compound was administered as a single oral dose at 5 mg/kg of body weight to sheep experimentally infected with nematode parasites of the taxa *Ostertagia circumcincta*, *Trichostrongylus axei*, *Cooperia*, and *Oesophagostomum columbianum* and an isolate of *Haemonchus contortus*,[10] known to be resistant to benzimidazole anthelmintics. While both compounds effected significant reduction against most of the parasites, **1a** demonstrated >95% reduction against the resistant *H. contortus*, whereas **1f** showed no discernible effect.

(10) *H. contortus* isolated from naturally infected *Ovis aries* in the region of Ogdensburg, NY, in 1965 and subsequently maintained by serial passage in our laboratories.

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Nujol mull with a Perkin-Elmer 137 IR spectrometer. ^{1}H NMR spectra were obtained on a Varian T-60 NMR spectrometer. An LKB Model 9000 mass spectrometer and Varian Aerograph Series 1200 vapor-phase chromatograph with column packed with 3 to 5% SE-30 in 100/120 Varaport were used to obtain the mass spectral data. Elemental analyses were performed by the staff of the microanalytical laboratory of Merck and are within 0.4% of calculated values.

5-Benzoyl-2-chloropyridine (5c). A suspension of **5a** (55 g, 34.9 mmol) in 250 mL of $SOCl_2$ was heated at reflux for 90 min. The solvent was evaporated in vacuo, and the residual $SOCl_2$ was removed by flushing three times with C_6H_6. The residue was dissolved in 300 mL of C_6H_6 and treated portionwise with powdered $AlCl_3$ (174 g, 1.3 mmol) at 10–20 °C. After the exothermic reaction had subsided (1 h), the mixture was heated at reflux for 6 h, cooled, poured onto ice–H_2O containing 100 mL of HCl, and extracted with $CHCl_3$. The organic layer was washed successively with 2 portions of 1 N NaOH and H_2O (500 mL each), dried, and evaporated to dryness in vacuo to yield 68.3 g (90%) of **5c**, mp 38–39 °C (hexane). Anal. ($C_{12}H_8ClNO$) C, H, N, Cl.

2-Amino-5-benzoylpyridine (8c). Anhydrous liquid NH_3 (35 mL) and **5c** (6.0 g, 27.5 mmol) were heated at 90 °C in a glass-lined autoclave for 90 min. The NH_3 was allowed to evaporate and the residue was stirred with 30 mL of 2.5 N HCl for 1 h. The mixture was extracted with ether. The dried ether extracts were concentrated to dryness in vacuo to yield 3.0 g (50%) of starting **5c**. The aqueous layer was adjusted to NH_4OH to pH 9 and extracted with CH_2Cl_2 to yield 2.57 g (49%) of **8c**, mp 128–133 °C. The material was purified by chromatography over 100 g of silica gel and elution with EtOAc, mp 132–134 °C. Anal. ($C_{12}H_{10}N_2O$) C, H, N.

5-*n*-Propoxy-2-[(*p*-nitrophenyl)azo]pyridine (3b). The K salt of **3a**[9] was prepared by dissolving **3a** (13.52 g, 55.3 mmol) in MeOH (1700 mL) containing 85% KOH (3.64 g, 55.3 mmol). The solvent was removed in vacuo to yield 14.58 g of the crude salt. The K salt was suspended in *p*-dioxane (150 mL) and dicyclohexyl-18-crown-6 (6.63 g, 17.7 mmol) in *p*-dioxane (15 mL) was added. The resultant solution was treated with 1-bromopropane (6.48 g, 52.6 mmol) for 1 h at room temperature. The solution was then heated at reflux for 2 h. After the solvent was removed in vacuo, the residue was chromatographed over 3000 g of silica gel. Elution with CH_2Cl_2 yielded 4.35 g (27.5%) of **3b**, mp 155–157 °C. Anal. ($C_{14}H_{14}N_4O_3$) C, H, N.

2-Amino-5-*n*-propoxypyridine (8a). From 3b. The reduction of **3b** using 10% Pd on C in HOAc according to the method of Moore and Marascia,[9] yielded **8a** in 74% yield, mp 52–54 °C (hexane). Anal. ($C_8H_{12}N_2O$) C, H, N.

From 4. A suspension of **4** (11.0 g, 50 mmol), Cu (1.0 g), $NaOCH_3$ (3.8 g, 70 mmol), and *n*-C_3H_7OH (100 mL) was heated at 150 °C for 12 h. The cooled reaction mixture was filtered and concentrated to dryness in vacuo. The residue was suspended in CH_2Cl_2 and washed two times with H_2O, and the organic layer was separated, dried, and evaporated in vacuo. The residue was chromatographed over 900 g of silica gel and eluted with EtOAc–CH_2Cl_2 (1:4) to yield 200 mg (2.6%) of **8a**.

5-Ethynyl-2-methylpyridine (6a). 2-Methyl-5-vinylpyridine was converted into **6a** in 46% yield, mp 52–53 °C (lit.[11] mp 51–52 °C).

2-Methyl-5-(1,1,2,2-tetrachloroethyl)pyridine Hydrochloride (6b). A. 6a (2.5 g, 21.3 mmol) dissolved in CCl_4 (50 mL) was treated with gaseous Cl_2 for 2 h. The excess Cl_2 was displaced by N_2, and the precipitate was collected by filtration. After washing with CCl_4, the solids were recrystallized from EtOH to yield 1.33 g (21%) of **6b**: mp 195 °C dec; NMR (Me_2SO-d_6)

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δ 2.7 (s, 2-CH_3), 7.7 (s, CCl_2H), 7.8 (d, J = 8 Hz, 3-H), 8.4 (dd, J = 16 Hz, 2 Hz, 4-H), 9.2 (d, J = 2 Hz, 6-H). Anal. ($C_8H_8Cl_5N$) C, H, N, Cl.

B. Free Base of 6b. A solution of **6a** (17.55 g, 0.15 mmol) in CCl_4 (225 mL) was treated with Cl_2 (26 g, 37 mmol) at 0 °C. After 3 h at room temperature, additional Cl_2 (6.5 g, 93 mmol) was introduced and the mixture was stirred at room temperature for an additional 1 h. After the mixture was diluted with H_2O (175 mL), the organic layer was separated and the aqueous layer was extracted several times with $CHCl_3$. The combined $CHCl_3$ extracts were concentrated to dryness in vacuo, yielding 45.6 g of a yellow oil. VPC–MS analysis indicated the composition was the following 5-substituted 2-methylpyridines: 7% 5-(1-chloroethenyl), 21% 5-(1,2-dichloroethenyl), 39% 5-(1,2,2-trichloroethenyl), and 32.6% 5-(1,1,2,2-tetrachloroethyl).

2-Methyl-5-(1,2,2-trichloroethenyl)pyridine (6c). The crude oil isolated from reaction B above was added to EtOH (400 mL) containing 85% KOH (16.5 g, 25 mmol) at 0 °C and then stirred at room temperature for 45 min. Most of the EtOH was removed in vacuo below 30 °C, and the residue was diluted with H_2O (ca. 1 L), and extracted with ether. The combined extracts were dried and evaporated in vacuo to yield 29 g (86.8% from **6a**) of an oil, which slowly crystallized. Recrystallization from *n*-hexane yielded purified **6c**, mp 37–39 °C. Anal. ($C_6H_6Cl_3N$) C, H, N, Cl.

5-(1,2,2-Trichloroethenyl)pyridine-2-carboxylic Acid (7a). A solution of **6c** (27.9 g, 0.126 mol) and SeO_2 (20.9 g, 0.188 mol) in *p*-dioxane (125 mL) was heated at reflux for 8 h. The reaction mixture was filtered and concentrated to dryness in vacuo to yield 13.4 g (42%) of **7a**, mp 156–158 °C. Recrystallization from EtOAc yielded purified **7a**, mp 158–159 °C. Anal. ($C_6H_4Cl_3NO_2$) C, H, N, Cl.

5-(1,2,2-Trichloroethenyl)pyridine-2-carbonyl Azide (7c). A suspension of **7a** (12.3 g, 48.7 mmol) in $SOCl_2$ (145 mL) was heated at reflux for 90 min. The reaction mixture was concentrated to dryness in vacuo to yield 12.5 g (96%) of crude acid chloride **7b**, mp 89–90 °C. A solution of **7b** (3.0 g, 12.0 mmol) in Me_2CO (30 mL) was added to a cooled solution of NaN_3 (0.858 g, 13.2 mmol) in H_2O (2.5 mL). The mixture was stirred at room temperature for 30 min and diluted with H_2O (70 mL). The product was collected by filtration and dried to yield 2.86 g (86.6%) of **7c**, mp 85–86 °C dec. Anal. ($C_8H_3Cl_4N_4O$) C, H, N, Cl.

2-Amino-5-(1,2,2-trichloroethenyl)pyridine (8d). A solution of **7c** (18 g, 66.4 mmol) in 130 mL of 50% aqueous HOAc was heated at 100 °C for 35 min. As the evolution of N_2 subsided, a black gum was deposited. Upon cooling, the reaction mixture was decanted from the tarry precipitate and was basified with 50% NaOH. The resultant precipitate was collected by filtration, dried, and chromatographed over 400 g of silica gel. Elution with successive portions of $CHCl_3$, MeOH–$CHCl_3$ (1:99), and finally MeOH–$CHCl_3$ (5:95) yielded 8.5 g (57%) of **8d**, mp 126–127 °C. Anal. ($C_7H_5Cl_3N_2$) C, H, N, Cl.

2-Amino-5-(propylthio)pyridine (8b). The reaction of **4** (11.0 g, 50 mmol), 1-propanethiol (6.08 g, 80 mmol), $NaOCH_3$ (4.2 g, 77.7 mmol), and Cu (1.0 g) in MeOH (200 mL) according to the method previously reported,[2] yielded 6.1 g (41%) of **8b**, mp 57–58 °C (hexane). Anal. ($C_8H_{12}N_2S$) C, H, N, S.

6-Substituted Imidazo[1,2-*a*]pyridine-2-carbamates (1c–f). The 5-substituted 2-aminopyridines were treated with methyl *N*-(chloroacetyl)carbamate in hexamethylphosphoramide as previously reported.[2] The yields and physical characteristics are recorded in Table I. Syntheses of compounds **1a,b,g** have been reported.[2]

Acknowledgment. The authors thank S. Cifelli, C. Eary, D. Suhayda, and R. Lang of the Merck Institute for Therapeutic Research for assisting in the large animal trials.

Chemistry and Hypoglycemic Activity of Benzimidoylpyrazoles[1]

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A series of benzimidoylpyrazoles was synthesized and evaluated as hypoglycemic agents. Methyl 1-(*N*-cyclohexylbenzimidoyl)-5-methyl-3-pyrazolecarboxylate (**13**) and methyl 1-[*N*-(4-methoxyphenyl)benzimidoyl]-5-methyl-3-pyrazolecarboxylate (**33**) are two of the more interesting compounds. A comparison of these benzimidoylpyrazoles with classical standards (tolazamide, phenformin, and buformin) in several experimental models show that these compounds seem to combine in one molecule some of the biological activities of the β-cytotrophic sulfonylureas and some of the activities of the biguanides. A synthetic scheme for the preparation of the benzimidoylpyrazoles and a preliminary structure–activity relationship are presented.

The hydrazides of benzenecarboximidic acid have yielded compounds with potent hypoglycemic activity.[4] Incorporation of the hydrazide portion of these compounds into a pyrazole ring has now led to a new class of compounds, benzimidoylpyrazoles. We report here the synthesis of some benzimidoylpyrazoles and discuss the hypoglycemic activity demonstrated in this series.

Chemistry. The benzimidoylpyrazoles were prepared by allowing a substituted benzimidoyl chloride to react with a pyrazole in the presence of NaH, $NaNH_2$, or $(C_2H_5)_3N$. The resulting benzimidoylpyrazole was not converted to the desired addition salt but was instead utilized as the free base. The synthetic methods are shown in Scheme I.

The intermediate benzimidoyl chlorides were prepared from the corresponding N-substituted benzamides by treatment with $SOCl_2$ or PCl_5, according to published procedures.[5] When possible, the benzimidoyl chlorides were purified by distillation under vacuum, but some were utilized in the crude state, since distillation caused elimination of HCl with the resultant formation of the nitrile.[6] The pyrazoles were readily prepared by the action of hydrazine on 1,3-diketones.[7] The reaction proceeds via ring closure of the initially formed hydrazone. Interaction of acetylacetone with hydrazine hydrate in ethanol[8] or hy-

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