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]

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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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(3) Medical Research Division, American Cyanamid Co., Pearl River, NY 10965.
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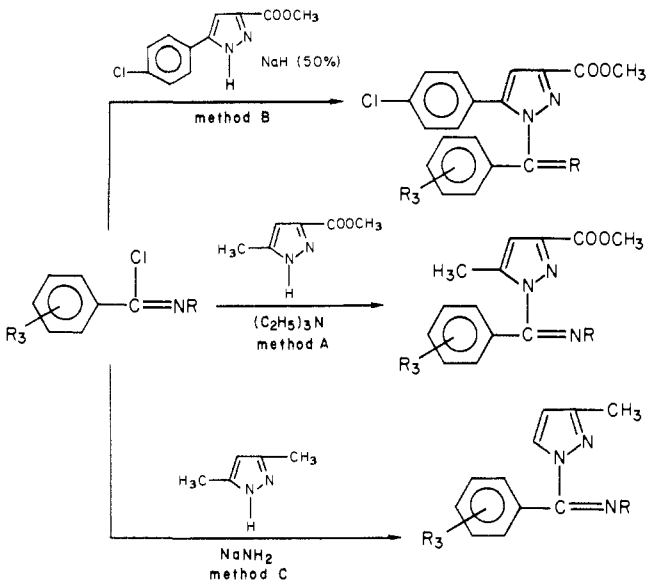
Scheme I



drazine sulfate in aqueous alkali[9-11] led to 3,5-dimethylpyrazole, one of the intermediates in the synthesis of benzimidoylpyrazoles. 3-Carbomethoxy-5-(4-chlorophenyl)pyrazole and methyl 5-methylpyrazole-3-carboxylate were similarly prepared according to published procedures.[12]

Structure–Activity Relationships. The hypoglycemic activities of the benzimidoylpyrazoles are listed in Table I. The activity of compounds in this series was very sensitive to small changes in structure. Of all the substituents introduced at R, 8 (ethyl), 13 (cyclohexyl), and 18 (phenyl) produced the best hypoglycemic activity; 2 (isobutyl) was only slightly less active than 8, 13, or 18. Introduction of a substituent on the phenyl group at R_3 lowered activity (cf. 2 with 3 and 4, 13 with 14, and 18 with 19–22). Introduction of a 4-OCH_3 group on the iminophenyl group enhanced hypoglycemic activity (cf. 18 with 33), whereas 3,4-$(OCH_3)_2$ (38) and 3-CF_3 (32) did not differ in activity from the unsubstituted phenyl (18). Moving the OCH_3 group from the para position (33) to the ortho (34) or meta position (35) caused a decrease in glucose-lowering activity. Substituting a methyl for the carbethoxy group at R_2 caused a decrease in hypoglycemic activity (cf. 13 with 15, 33 with 36, and 8 with 9). Similarly, substitution of 4-Cl-C_6H_4 for the CH_3 group at R_1 had a deleterious effect on hypoglycemic activity (cf. 13 with 16, and 33 with 37).

Hypoglycemic Activity. At the present time there are two clinically useful classes of oral hypoglycemic compounds, viz., the sulfonylureas and the biguanides.[13] The sulfonylureas produce hypoglycemia by stimulating the release of insulin from the pancreas, as well as by potentiating the action of insulin.[13] The sulfonylureas do not stimulate the adrenals to produce hypoglycemia. Therefore, the sulfonylureas lower blood glucose in all of the models described below except in the alloxanized diabetic rat, since alloxan produces diabetes by destroying the insulin-producing β cells of the pancreas. In contrast, the biguanides do not stimulate the release of insulin from the pancreas, although small quantities of insulin do enhance their hypoglycemic action.[13] The biguanides potentiate the action of insulin and do not stimulate the adrenals to produce hypoglycemia. Thus, the biguanides produce hypoglycemia in all of the models described below except in the glucose-primed rat.

The primary screen employed to test these compounds was the method described by Dulin[14] using glucose-primed, fasted rats. Blood glucose concentrations were determined by the Autoanalyzer modification[15] of the method described by Hoffman.[16] Results in Table I are expressed as mean percent change in blood glucose concentration from the control group. Of the 38 compounds screened in the glucose-primed rat (Table I) at a dose level of 100 mg/kg, 7 compounds (8, 13, 18, 32–34, and 38) showed a reduction of 30% or more in blood glucose levels 2 h after drug administration. Based on the percent change in the blood glucose concentration in the initial screen, two compounds, 13 and 33, were selected for further hypoglycemic evaluation. These compounds were tested orally in the normal, fasted guinea pig, the alloxanized rat, the adrenalectomized rat, and the non-glucose-primed rat. The hypoglycemic activities of 13 and 33 were compared to phenformin (1-phenethylbiguanide), buformin (1-butylbiguanide), and tolazamide [1-(hexahydro-1*H*-azepin-1-yl)-3-(*p*-tolylsulfonyl)urea] in the above models, and the results are summarized in Table II. The data show that in the primary hypoglycemic screen (glucose-primed, fasted rat) the order of potency was tolazamide > 33 > 13. Phenformin and buformin were inactive in the primary screen at doses up to 100 mg/kg. In the normal, fasted guinea pig model, 33 was the more active of the two benzimidoylpyrazoles. However, it was less potent than phenformin, buformin, or tolazamide. The order of potency in the alloxanized rat was as follows: phenformin ≥ 13 > 33 > buformin. Tolazamide was inactive at 100 mg/kg. In the glucose-primed, adrenalectomized rat the order of potency was tolazamide > 33 > 13 ≫ buformin, while in the non-glucose-primed rat the order of activity was tolazamide > phenformin ≥ 33 > buformin ≥ 13. Compounds 13 and 33 exhibited hypoglycemic activity in all models studied and, thus, seem to combine in one molecule some of the biological activities of the sulfonylureas and some of the activities of the biguanides (see Pharmacological Methods).

Experimental Section

The compounds were prepared by three general methods. These methods are described by giving the preparation of specific compounds. The general method of synthesis is then designated in Table I. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. IR data were recorded on a Perkin-Elmer Model 621 spectrophotometer. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, IN, and are within ±0.4% of the theoretical values. No attempt was made to maximize yields.

1-(*N*-Ethylbenzimidoyl)-3-carbomethoxy-5-methylpyrazole (8). Method A. To a mixture of 7.0 g (0.05 mol) of

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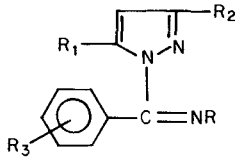
Table I. Benzimidoylpyrazoles



no.	R	R_1	R_2	R_3	mp or bp (mm), °C	yield,[a] %	recrystn solvent	formula[b]	method	mg % blood glucose: control ± SE	mg % blood glucose: treated ± SE	% change[c]	p
1	$CH_2CH(CH_3)_2$	CH_3	CH_3	H	102 (0.02)	43.0		$C_{16}H_{21}N_3$	C	70.3 ± 3.5	62.8 ± 3.1	10.6↓	NS
2	$CH_2CH(CH_3)_2$	CH_3	$COOCH_3$	H	134 (0.4)	27.5		$C_{17}H_{21}N_3O_2$	B	80.2 ± 3.4	59.7 ± 3.0	25.5↓	<0.001
3	$CH_2CH(CH_3)_2$	CH_3	$COOCH_3$	$4\text{-}CH_3$	160 (0.25)	20.5		$C_{18}H_{23}N_3O_2$	A	80.6 ± 2.7	65.2 ± 3.2	19.0↓	<0.001
4	$CH_2CH(CH_3)_2$	CH_3	$COOCH_3$	4-F	140 (0.04)	25.3		$C_{17}H_{20}FN_3O_2$	A	69.8 ± 0.8	68.9 ± 0.8	1.3↓	NS
5	$CH_2CH(CH_3)_2$	CH_3	$COOCH_3$	$3\text{-}CF_3$	120 (0.1)	76.4		$C_{18}H_{20}F_3N_3O_2$	A	83.2 ± 2.5	62.2 ± 3.4	25.2↓	<0.001
6	$CH_2CH_2CH(CH_3)_2$	CH_3	$COOCH_3$	H	120 (0.08)	7.0		$C_{18}H_{23}N_3O_2$	A	92.5 ± 1.1	91.3 ± 2.5	1.3↓	NS
7	$n\text{-}C_4H_9$	CH_3	$COOCH_3$	H	142 (0.2)	24.8		$C_{17}H_{21}N_3O_2$	A	83.9 ± 5.2	66.1 ± 5.2	21.2↓	<0.05
8	C_2H_5	CH_3	$COOCH_3$	H	130 (1)	37.0		$C_{15}H_{17}N_3O_2$	A	83.2 ± 2.5	54.9 ± 1.1	34.0↓	<0.001
9	C_2H_5	CH_3	CH_3	H	82 (0.03)	24.2		$C_{14}H_{17}N_3$	C	77.8 ± 3.9	58.6 ± 4.8	24.7↓	<0.01
10	$n\text{-}C_3H_7$	CH_3	$COOCH_3$	H	104 (0.1)	7.8		$C_{16}H_{19}N_3O_2$	C	75.8 ± 2.9	80.5 ± 3.2	6.2↑	NS
11	$CH_2CH{=}CH_2$	CH_3	$COOCH_3$	H	117 (0.3)	18.8		$C_{16}H_{17}N_3O_2$	B	74.9 ± 3.4	69.6 ± 3.0	7.0↓	NS
12	CH_3	CH_3	$COOCH_3$	H	138 (0.4)	7.0		$C_{14}H_{15}N_3O_2$	A			*d*	
13	C_6H_{11}	CH_3	$COOCH_3$	H	89-90	31.1	heptane	$C_{19}H_{23}N_3O_2$	A	76.7 ± 2.5	52.1 ± 5.9	34.5↓	<0.01
14	C_6H_{11}	CH_3	$COOCH_3$	$2\text{-}OCH_3$	122-123	22.1	*i*-PrOH	$C_{20}H_{25}N_3O_3$	A	86.1 ± 2.5	68.4 ± 4.1	20.5↓	<0.01
15	C_6H_{11}	CH_3	CH_3	H	118 (0.05)	7.8		$C_{18}H_{23}N_3$	C	80.8 ± 3.1	69.8 ± 3.0	13.6↓	NS
16	C_6H_{11}	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	H	139-141		*i*-PrOH	$C_{24}H_{24}ClN_3O_2$	A	79.4 ± 4.3	84.9 ± 4.6	4.4↑	NS
17	C_6H_{11}	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	$2\text{-}OCH_3$	138-140	6.1	MeCN	$C_{25}H_{26}ClN_3O_3$	A	79.4 ± 4.3	69.2 ± 3.0	12.9↓	NS
18	C_6H_5	CH_3	$COOCH_3$	H	90-95	56.9	heptane	$C_{19}H_{17}N_3O_2$	B	88.3 ± 3.3	58.0 ± 2.5	34.3↓	<0.001
19	C_6H_5	CH_3	$COOCH_3$	$2\text{-}OCH_3$	134-135	10.0	*i*-PrOH	$C_{20}H_{19}N_3O_3$	B	78.5 ± 2.6	58.3 ± 7.3	25.7↓	<0.02
20	C_6H_5	CH_3	$COOCH_3$	2-Cl	118-120	40.0	heptane	$C_{19}H_{16}ClN_3O_2$	A	76.8 ± 3.6	70.0 ± 3.0	8.9↓	NS
21	C_6H_5	CH_3	$COOCH_3$	$3,4\text{-}Cl_2$	105-106	40.0	heptane	$C_{19}H_{15}Cl_2N_3O_2$	A	81.8 ± 5.8	101.5 ± 6.2	24.3↑	<0.02
22	C_6H_5	CH_3	$COOCH_3$	$2\text{-}CH_3$	104-107	15.0	MeCN	$C_{20}H_{19}N_3O_2$	A	73.4 ± 1.9	57.7 ± 4.0	21.4↓	<0.001
23	C_6H_5	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	H	187-188	14.0	acet	$C_{24}H_{18}ClN_3O_2$	B	76.8 ± 2.5	81.1 ± 2.7	5.6↑	NS
24	C_6H_5	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	$2\text{-}CH_3$	138-140	17.1	heptane	$C_{25}H_{20}ClN_3O_2$	B	75.9 ± 2.9	71.1 ± 2.3	6.3↓	NS
25	C_6H_5	CH_3	CH_3	H	130 (0.05)	30.0		$C_{18}H_{17}N_3$	B	88.3 ± 3.3	72.1 ± 2.2	18.3↓	<0.001
26	$4\text{-}CH_3\text{-}C_6H_4$	CH_3	$COOCH_3$	H	96-99	24.4	MeOH	$C_{20}H_{19}N_3O_2$	A	88.7 ± 3.2	71.9 ± 2.2	18.9↓	<0.01
27	$4\text{-}CH_3\text{-}C_6H_4$	CH_3	$COOCH_3$	$4\text{-}CH_3$	116-118	32.2	*i*-PrOH	$C_{21}H_{21}N_3O_2$	A	81.0 ± 3.3	60.4 ± 3.3	25.4↓	<0.001
28	$2,3\text{-}(CH_3)_2\text{-}C_6H_3$	CH_3	$COOCH_3$	H	128-130	39.3	*i*-PrOH	$C_{21}H_{21}N_3O_2$	A	82.6 ± 4.0	75.6 ± 3.8	8.3↓	NS
29	$4\text{-}CH_3\text{-}C_6H_4$	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	$4\text{-}CH_3$	147-150	20.7	MeCN	$C_{26}H_{22}ClN_3O_2$	A	76.7 ± 1.8	69.8 ± 3.4	9.0↓	NS
30	$4\text{-}Cl\text{-}C_6H_4$	CH_3	$COOCH_3$	H	88-90	18.6	MeCN	$C_{19}H_{16}ClN_3O_2$	A	74.6 ± 3.1	78.7 ± 2.9	5.5↑	NS
31	$4\text{-}Cl\text{-}C_6H_4$	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	H	152-154	72.2	heptane	$C_{24}H_{17}ClN_2O_2$	A	76.9 ± 3.6	77.7 ± 3.4	1.2↑	NS
32	$3\text{-}CF_3\text{-}C_6H_4$	CH_3	$COOCH_3$	H	73-76	9.6	heptane	$C_{20}H_{15}F_3N_3O_2$	A	87.0 ± 3.7	57.9 ± 4.0	33.5↓	<0.001
33	$4\text{-}OCH_3\text{-}C_6H_4$	CH_3	$COOCH_3$	H	138-140	7.7	heptane	$C_{20}H_{19}N_3O_3$	A	103.8 ± 4.9	62.2 ± 5.1	40.0↓	<0.001
34	$2\text{-}OCH_3\text{-}C_6H_4$	CH_3	$COOCH_3$	H	127-128	23.2	*i*-PrOH	$C_{20}H_{19}N_3O_3$	A	148.0 ± 6.0	96.0 ± 7.3	35.1↓	<0.001
35	$3\text{-}OCH_3\text{-}C_6H_4$	CH_3	$COOCH_3$	H	114-117	17.5	MeCN	$C_{20}H_{19}N_3O_3$	A	80.8 ± 3.1	63.0 ± 3.5	22.0↓	<0.01
36	$4\text{-}OCH_3\text{-}C_6H_4$	CH_3	CH_3	H	160 (13)	46.6		$C_{19}H_{19}N_3O$	A	83.2 ± 1.6	60.6 ± 3.3	27.2↓	<0.001
37	$4\text{-}OCH_3\text{-}C_6H_4$	$4\text{-}Cl\text{-}C_6H_4$	$COOCH_3$	H	140-142	10.5	*i*-PrOH	$C_{15}H_{20}ClN_3O_3$	A	81.6 ± 2.4	78.4 ± 2.7	3.9↓	NS
38	$3,4\text{-}(OCH_3)_2\text{-}C_6H_3$	CH_3	$COOCH_3$	H	114-115	44.7	*i*-PrOH	$C_{21}H_{21}N_3O_4$	A	88.1 ± 3.2	58.0 ± 5.0	34.1↓	<0.001

[a] No attempt was made to maximize yields. [b] Analyzed for C, H, N; analytical results were within ±0.4% of theoretical values. [c] Blood glucose change in the glucose-primed rat at a dose of 100 mg/kg (all doses expressed as base). [d] Percent change in blood glucose not determined. Arrow indicates direction of glycemic change.

Table II. Comparison of Benzimidoylpyrazoles in Standard Hypoglycemic Assays

compd	glucose-primed rat		normal fasted guinea pig		alloxanized rat		adrenalectomized rat		non-glucose-primed rat		mouse LD_{50},[c] mg/kg	
	po dose, mg/kg	% redn of blood glucose[a,d]	po dose, mg/kg	% redn of blood glucose[a]	po dose, mg/kg	% redn of blood glucose[b]	po dose, mg/kg	% redn of blood glucose[a,d]	po dose, mg/kg	% redn of blood glucose	ip	po
13	25	27.0	100	0	50	29.2	25	32.0	100	7.6	1000	1000
	50	32.2			100	52.0						
	100	34.5										
33	25	35.2	100	21.0	300	49.0	25	44.3	100	31.5	1000	1000
	50	33.8										
	100	51.3										
tolazamide	10	28.1	100	33.5	100	0	10	75.8	25	29.4	1000	1000
	25	50.0	125	26.7			20	85.6				
	250	42.9	150	30.4								
	500	51.1	160	25.0								
phenformin	100	0	25	46.0	100	62.0			80	25.3	160	900
									120	52.9		
buformin	100	0	30	50.0	300	21.9	350	42.2	300	25.9	140	300

[a] Hypoglycemia measured 2 h after drug administration. [b] Hypoglycemia measured 5 h after drug administration. [c] Milligrams of active moiety, excluding weight of base or acid. [d] $p < 0.05$ by two-tailed students' t test.

methyl 5-methylpyrazole-3-carboxylate and 5.3 g (0.05 mol) of $(C_2H_5)_3N$ in 75 mL of dry CH_3CN was added 7.5 g (0.05 mol) of *N*-ethylbenzimidoyl chloride over a period of 0.5 h. After the addition was completed, the mixture was heated to reflux for a period of 5 h. The $(C_2H_5)_3N{\cdot}HCl$ was removed by filtration; concentration of the CH_3CN layer and distillation of the residue afforded 1-(*N*-ethylbenzimidoyl)-3-carbomethoxy-5-methylpyrazole: yield 5 g (37%); bp 130–132 °C (1 mm); n^{25}_D 1.55.

1-(2-Methyl-*N*-phenylbenzimidoyl)-3-carbomethoxy-5-(4-chlorophenyl)pyrazole (24). Method B. To a suspension of 1.6 g (0.048 mol) of 50% NaH in 100 mL of dry DMF was added 7.8 g (0.03 mol) of 3-carbomethoxy-5-(4-chlorophenyl)pyrazole over a period of 15 min. After the evolution of H_2 gas had ceased, 7.6 g (0.03 mol) of 2-methyl-*N*-phenylbenzimidoyl chloride was added dropwise into the reaction mixture. The reaction mixture was heated at 100 °C for a period of 24 h, allowed to cool, and vacuum filtered. The filtrate was evaporated in vacuo, the residue was dissolved in H_2O, and the organic material was extracted with ether. Concentration of the dried ether layer yielded 6 g of crude product. The crude product was recrystallized twice from *n*-heptane to afford 1-(2-methyl-*N*-phenylbenzimidoyl)-3-carbomethoxy-5-(4-chlorophenyl)pyrazole: yield 2.5 g (17%); mp 138–140 °C.

1-(*N*-Isobutylbenzimidoyl)-3,5-dimethylpyrazole (1). Method C. To a suspension of 7.8 g (0.2 mol) of $NaNH_2$ in 130 mL of dry toluene was added dropwise 9.8 g (0.1 mol) of 3,5-dimethylpyrazole over a period of 10 min. The reaction mixture was heated under reflux for 3 h and then cooled. To the cooled solution was added dropwise 19.5 g (0.1 mol) of *N*-isobutylbenzimidoyl chloride, and the resulting solution was refluxed for 4 h. H_2O, 200 mL, was added to the reaction mixture, and the organic layer was separated from the aqueous fraction. Concentration of the dried toluene layer and distillation of the residue (25 g) afforded 1-(*N*-isobutylbenzimidoyl)-3,5-dimethylpyrazole: yield 11 g (43%); bp 102–106 °C (0.02 mm); n^{25}_D 1.5390.

Pharmacological Methods. Glucose-Primed, Fasted Rat. The primary screen employed to test these compounds was the method described by Dulin[14] using glucose-primed, fasted rats. Groups of six male Sprague–Dawley rats, weighing 140–150 g, were fasted for 16 h. Each animal then received 100 mg of glucose subcutaneously in a volume of 0.5 mL of isotonic sodium chloride. An aqueous carboxymethylcellulose suspension of the test compound (0.5 mL) was administered orally immediately thereafter. Untreated control animals received the vehicle (0.5 mL). Tolazamide [1-(hexahydro-1*H*-azepin-1-yl)-3-(*p*-tolylsulfonyl)urea], phenformin (1-phenethylbiguanide), and buformin (1-butylbiguanide) were orally administered to additional groups of rats as positive controls. After 2 h the rats were lightly anesthetized with ether, and blood was withdrawn by cardiac puncture. Blood glucose concentrations were determined by the Autoanalyzer modification[15] of the method described by Hoffman[16] and are found in Tables I and II.

Normal, Fasted Guinea Pig. Male and female Hartley guinea pigs (450–500 g) were separated into groups of four by sex and deprived of food, but not water, for a period of 18 h. Blood samples for glucose determinations were obtained by cardiac puncture. Immediately after taking the zero time or control blood sample, the animals were administered the test compound orally. Blood samples were again withdrawn 5 h after the drugs were given. The results are expressed as percent change in blood glucose as compared to the pretreatment blood glucose values as shown in Table II.

Alloxanized, Diabetic Rat.[17] Male rats of the Sprague–Dawley strain (180–220 g) were made diabetic by the intraabdominal injection of 225 mg/kg alloxan monohydrate. Three days later the urine of each rat was tested for the presence of glucose using Clinistix reagent strips. Those showing glucose in the urine were segregated into groups of six rats each. After we obtained control blood samples from the tail vein of all rats, the test compounds were administered orally. Blood samples were again obtained for glucose assay 5 h after compound administration. The results are expressed as percent change in blood glucose as

(17) E. H. Kass and B. A. Weisbren, *Proc. Soc. Exp. Biol. Med.*, 60, 303 (1945).

compared to the pretreatment blood glucose values as shown in Table II.
to the pretreatment blood glucose values as shown in Table II.

Glucose-Primed, Adrenalectomized Rat.[14] The hypoglycemic activity of 13, 33, and the control drugs was measured in male Sprague–Dawley rats that were adrenalectomized 7 days prior to testing. At the end of 7 days, the rats were deprived of food for 16 h and then injected subcutaneously with 100 mg of glucose per rat. Immediately thereafter, the treatment groups received the test drug orally, and the control group was administered an equal volume of saline. Blood samples were withdrawn after 2 h by cardiac puncture. The results are expressed as percent change in blood glucose as compared to the pretreatment blood glucose values as shown in Table II.

Non-Glucose-Primed Rat.[18] Male Sprague–Dawley rats (120–160 g) were fasted for a period of 18 h prior to and during treatment. Blood samples were obtained from the tail vein. The drug was administered at zero time, and blood samples were drawn 3 and 5 h after drug administration. The results are expressed as percent change in blood glucose as compared to the pretreatment blood glucose values as shown in Table II.

Acute Toxicity Determinations. Male and female Carworth Farms CF-1 strain mice, weighing 16–25 g, were used. Four mice per dose level were used in this procedure. LD_{50}'s (the dose that produces lethality in 50% of mice dosed) for all drugs were determined following oral and intraperitoneal routes of administration. Drugs were dissolved in distilled water or suspended in 0.5% carboxymethylcellulose or 0.5% gelatin mixtures. Drugs were also solubilized by pH adjustment with 1 N HCl or 1 N NaOH if the drugs were not affected by such treatment. Dosages were logarithmically spaced and the mice were observed for 7 days after drug administration. The determination of the LD_{50}'s was based on the method of Bliss.[19]

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(19) C. I. Bliss, *Q. J. Pharm. Pharmacol.*, 11, 192 (1938).

Efficient Synthesis of 14-Hydroxymorphinans from Codeine

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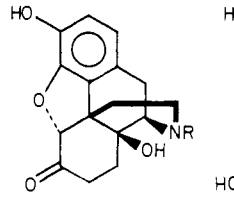
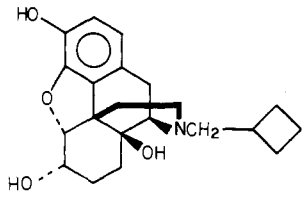
Codeine is converted to 7,8-dihydro-14-hydroxynorcodeinone (noroxycodone) in six steps and 52% overall yield or to noroxymorphone in seven steps and 43% overall yield. N-Demethylation and oxidation of codeine afford *N*-(ethoxycarbonyl)norcodeinone, which is converted to its dienol acetate derivative and oxidized with singlet oxygen to give *N*-(ethoxycarbonyl)-14-hydroxynorcodeinone in the key step. Hydrogenation of the latter affords *N*-(ethoxycarbonyl)noroxycodone, which upon acid hydrolysis yields noroxycodone. Alternatively, O-demethylation of *N*-(ethoxycarbonyl)noroxycodone with boron tribromide and subsequent acid hydrolysis gives noroxymorphone. The results of the singlet oxygen oxidation of the pyrrolidine dienamine derived from *N*-(ethoxycarbonyl)norcodeinone are also described.

14-Hydroxymorphinans, such as naloxone (**1a**), naltrexone (**1b**), and nalbuphine (**2**), have become important morphine derivatives due to their behavior as potent analgesics and/or narcotic antagonists.[1] The currently most practical synthetic route to these pharmaceuticals requires thebaine (**3**) as starting material and centers on oxidation of **3** to 14-hydroxycodeinone (**4**) with hydrogen peroxide–formic acid[2] or *m*-chloroperbenzoic acid in acetic acid–trifluoroacetic acid;[3] subsequent hydrogenation of **4**, followed by application of O- and N-demethylation procedures, then affords the essential intermediate noroxymorphone (**1c**)[4] in six steps overall from thebaine. In view of the relative scarcity of natural thebaine, however, alternate practical synthetic routes to noroxymorphone have been sought.



1a, R = $CH_2CH{=}CH_2$
b, R = $CH_2CH(CH_2)_2$
c, R = H



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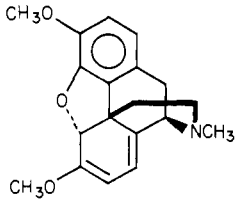

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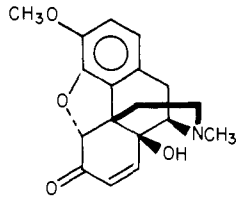

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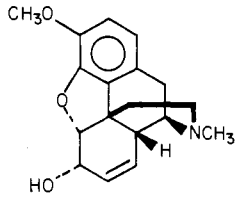

5

Codeine (**5**) is an attractive and readily available potential precursor to noroxymorphone, the required key transformation being oxidation at the allylic position to give the corresponding 14-hydroxy derivative. The direct allylic oxidation of codeine has met with only limited success, however. Treatment of codeine with chromic anhydride in sulfuric acid,[5] with manganese dioxide,[6] or

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