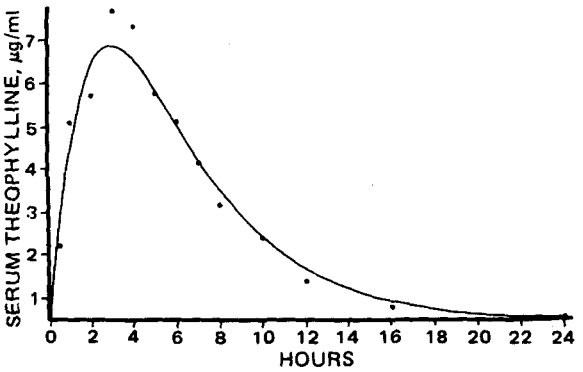

Figure 6—*Predicted serum theophylline level–time curve in Patient 1 after receiving Product C, theophylline anhydrous tablets plus 15 ml of antacid. Experimental values are indicated.*

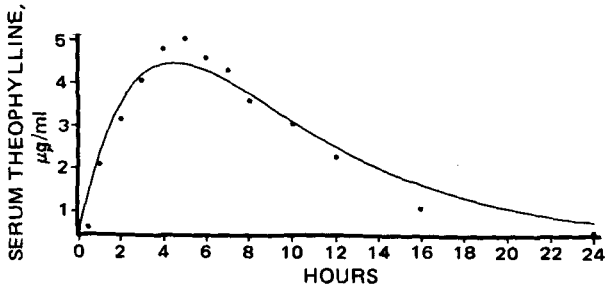

Figure 7—*Predicted serum theophylline level–time curve in Patient 1 after receiving Product D, theophylline anhydrous timed-release capsules plus 15 ml of antacid. Experimental values are indicated.*

droxide suspension with the rapid release theophylline anhydrous tablets did not affect theophylline bioavailability, as shown by the lack of any significant effect on the various pharmacokinetic parameters measured.

Antacid given with the theophylline anhydrous timed-release capsules increased the time for peak serum concentration, t_{max}, by ~13%. However, both the absorption rate constant, K_A, and the *AUC* for theophylline from the timed-release capsules were not affected by concurrent antacid administration. Therefore, the extent of theophylline bioavailability from the timed-release capsules was unaffected by antacid, and the theophylline bioavailability rate was affected only slightly.

A previous study (5) reported that 30 ml of magnesium aluminum hydroxide suspension significantly decreased the K_A for theophylline in volunteers given a single 200-mg dose of aminophylline tablets. This decrease may have been due to the fact that theophylline was given as the ethylenediamine salt (aminophylline) and in smaller doses compared to the present study. In addition, 30 ml of antacid was given compared to the 15 ml used in this study. In both studies, the elimination rate constant, K, *AUC*, and F/V values were in good agreement.

In conclusion, these data demonstrate that the concurrent administration of 15 ml of magnesium aluminum hydroxide suspension does not significantly affect the bioavailability of theophylline from theophylline anhydrous tablets or theophylline anhydrous timed-release capsules.

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Preparation and Antidiabetic Activity of New 3-Methyl-5-phenylpyrazolesulfonylurea Derivatives

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Received January 7, 1980, from the *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, and the ‡Department of Chemistry, Faculty of Science, University of Alexandria, Alexandria, Egypt. Accepted for publication September 26, 1980.

Abstract □ Two series of *p*-(3-methyl-5-phenylpyrazole-1)benzenesulfonylurea and *p*-(4-bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylurea derivatives were prepared for evaluation as hypoglycemic agents. Preliminary biological testing revealed that the new compounds possess potent antidiabetic activity.

Keyphrases □ 3-Methyl-5-phenylpyrazolesulfonylurea derivatives—preparation and evaluation for antidiabetic activity □ Structure–activity relationships—3-methyl-5-phenylpyrazolesulfonylurea derivatives and antidiabetic activity □ Antidiabetic activity—3-methyl-5-phenylpyrazolesulfonylurea derivatives synthesized and tested

Since 3,5-dimethylpyrazole and its active metabolite, 5-methylpyrazole-3-carboxylic acid, have potent hypoglycemic activity (1–5), studies have been performed on the synthesis of several new 3,5-disubstituted pyrazoles (6–8). In a continuation of previous work (8), many new substituted 3-methyl-5-phenylpyrazolesulfonylurea derivatives were prepared[1]. These compounds are analogous to, but vary in structure from, the aryl sulfonylurea derivatives.

The proposed compounds might provide valuable information concerning the structural requirements for

[1] Application for a patent was made for the compounds described in this report.

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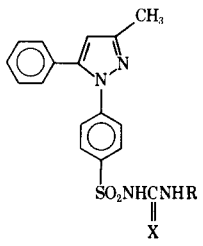


Table I—Substituted *p*-(3-Methyl-5-phenylpyrazole-1)benzenesulfonylurea (V) and Thiourea (VI) Derivatives

Compound	R	X	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
V*a*	C_2H_5	O	85	198°	$C_{19}H_{20}N_4O_3S$	C	59.4	59.8
						H	5.2	5.4
						N	14.6	14.8
						S	8.3	8.1
V*b*	$(CH_2)_2CH_3$	O	80	196°	$C_{20}H_{22}N_4O_3S$	C	60.3	60.4
						H	5.5	5.3
						N	14.1	14.2
						S	8.0	8.3
V*c*	$(CH_2)_3CH_3$	O	70	140°	$C_{21}H_{24}N_4O_3S$	C	61.2	61.3
						H	5.8	5.7
						N	13.6	13.7
						S	7.8	7.9
V*d*	C_6H_{11}	O	75	177°	$C_{23}H_{26}N_4O_3S$	C	63.0	63.1
						H	5.9	5.6
						N	12.8	12.7
						S	7.3	7.2
V*e*	C_6H_5	O	80	180°	$C_{23}H_{20}N_4O_3S$	C	63.9	64.0
						H	4.6	4.4
						N	13.0	13.2
						S	7.4	7.6
VI*a*	C_2H_5	S	80	187°	$C_{19}H_{20}N_4O_2S_2$	C	57.0	56.8
						H	5.0	5.3
						N	14.0	13.7
						S	16.0	16.0
VI*b*	$CH_2CH{=}CH_2$	S	70	174°	$C_{20}H_{20}N_4O_2S_2$	C	58.3	58.4
						H	4.9	4.9
						N	13.6	13.3
						S	15.5	15.3
VI*c*	$(CH_2)_3CH_3$	S	75	172°	$C_{21}H_{24}N_4O_2S_2$	C	58.9	59.2
						H	5.6	5.4
						N	13.1	13.3
						S	15.0	15.4
VI*d*	C_6H_{11}	S	70	186°	$C_{23}H_{26}N_4O_2S_2$	C	60.8	60.5
						H	5.7	5.5
						N	13.3	13.1
						S	14.1	14.4
VI*e*	$C_6H_5CH_2$	S	70	207°	$C_{24}H_{22}N_4O_2S_2$	C	62.3	62.4
						N	4.8	4.4
						N	12.1	12.0
						S	13.9	13.7
VI*f*	*p*-$CH_3C_6H_4$	S	75	210°	$C_{24}H_{22}N_4O_2S_2$	C	62.3	62.1
						H	4.8	4.8
						N	12.1	12.5
						S	13.9	14.0

hypoglycemic activity. Therefore, two main series of *p*-(3-methyl-5-phenylpyrazole-1)benzenesulfonylurea and *p*-(4-bromo -3- methyl-5-phenylpyrazole-1)benzenesulfonylurea derivatives were synthesized. Some synthesized compounds were tested for hypoglycemic activity. Preliminary biological testing revealed that the compounds possess potent antidiabetic activity.

DISCUSSION

The new pyrazoles are listed in Tables I and II. The antidiabetic activity of selected compounds is listed in Table III.

1-Phenylbutane-1,3-dione (1) reacts with aryl hydrazines to give a monohydrazone. On heating, this monohydrazone cyclizes to 1-aryl-3-methyl-5-phenylpyrazoles (9–12).

1-(*p*-Sulfamylphenyl)-3-methyl-5-phenylpyrazole (III) was prepared by treating *p*-sulfamylphenylhydrazine (II) with an equivalent amount of 1-phenylbutane-1,3-dione. Alkaline potassium permanganate oxidation of III afforded 1-(*p*-sulfamylphenyl)-5-phenylpyrazole-3-carboxylic acid (IV).

Bromination of III afforded 1-(*p*-sulfamylphenyl)-4-bromo-3-methyl-5-phenylpyrazole (VII). Acetylation of III with acetic anhydride afforded the monoacetyl derivative, as confirmed by microanalysis and IR and PMR spectra.

Substituted *p*-(3-methyl-5-phenylpyrazole-1)benzenesulfonylurea (V) and *p*-(4-bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylurea (VIII) derivatives were prepared by the reaction between III or VII and the appropriate isocyanate in dry acetone (13).

Substituted *p*-(3-methyl-5-phenylpyrazole-1)benzenesulfonylthiourea (VI) and *p*-(4-bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylthiourea (IX) derivatives were prepared by treatment of III or VII with the appropriate isothiocyanate.

EXPERIMENTAL[2]

1-(*p*-Sulfamylphenyl)-3-methyl-5-phenylpyrazole (III)—A mixture of *p*-sulfamylphenylhydrazine (18.7 g, 0.1 mole) and 1-phenylbutan-1,3-dione (16.6 g, 0.1 mole) in ethanol (150 ml) was refluxed for

[2] Melting points were determined on a Kofler block and are uncorrected. IR spectra were determined as Nujol mulls with a Beckman IR-4210 spectrometer. PMR spectra were recorded on a Varian A-60 A spectrometer. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, Egypt.

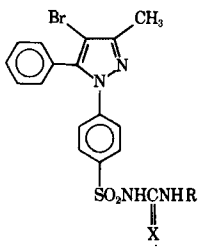


Table II—Substituted *p*-(4-Bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylurea (VIII) and Thiourea (IX) Derivatives

Compound	R	X	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
VIII*a*	C_2H_5	O	85	205°	$C_{29}H_{19}BrN_4O_3S$	C	49.2	49.3
						H	4.1	4.5
						Br	17.3	17.4
						N	12.1	12.1
						S	6.9	6.8
VIII*b*	$(CH_2)_2CH_3$	O	70	180°	$C_{20}H_{21}BrN_4O_3S$	C	50.3	50.1
						H	4.4	4.1
						Br	16.8	16.4
						N	11.7	11.6
						S	6.7	6.9
VIII*c*	$(CH_2)_3CH_3$	O	60	128°	$C_{21}H_{23}BrN_4O_3S$	C	51.3	51.3
						H	4.7	4.8
						Br	16.3	16.4
						N	11.4	11.3
						S	6.5	6.4
VIII*d*	C_6H_{11}	O	65	222°	$C_{23}H_{25}BrN_4O_3S$	C	53.4	53.5
						H	4.8	5.0
						Br	15.5	15.7
						N	10.8	10.7
						S	6.2	6.1
VIII*e*	C_6H_5	O	70	195°	$C_{23}H_{19}BrN_4O_3S$	C	54.0	54.3
						H	3.7	3.5
						Br	15.7	15.9
						N	11.0	10.7
						S	6.3	6.1
IX*a*	C_2H_5	S	70	192°	$C_{19}H_{19}BrN_4O_2S_2$	C	47.6	47.6
						H	4.0	3.8
						Br	16.7	16.5
						N	11.7	11.3
						S	13.4	13.4
IX*b*	$CH_2CH{=}CH_2$	S	60	126°	$C_{20}H_{19}BrN_4O_2S_2$	C	48.9	49.1
						H	3.9	4.0
						Br	16.3	16.1
						N	11.4	11.3
						S	13.0	13.3
IX*c*	$(CH_2)_3CH_3$	S	70	164°	$C_{21}H_{23}BrN_4O_2S_2$	C	49.7	50.0
						H	4.5	4.4
						Br	15.8	15.7
						N	11.0	11.3
						S	12.6	12.3
IX*d*	C_6H_{11}	S	60	188°	$C_{23}H_{25}BrN_4O_2S_2$	C	51.8	51.8
						H	4.7	4.6
						Br	15.0	14.7
						N	10.5	10.4
						S	12.0	12.0
IX*e*	$C_6H_5CH_2$	S	70	192°	$C_{24}H_{21}BrN_4O_2S_2$	C	53.2	53.6
						H	3.9	3.7
						Br	14.8	14.6
						N	10.4	10.4
						S	11.8	11.7
IX*f*	*p*-$CH_3C_6H_4$	S	65	230°	$C_{24}H_{21}BrN_4O_2S_2$	C	53.2	53.4
						H	3.9	4.0
						Br	14.8	14.5
						N	10.4	10.0
						S	11.8	11.6

4–6 hr on a steam bath, concentrated, and allowed to cool. The crude product was separated and recrystallized (75% yield) from ethanol, mp 198°.

Anal.—Calc. for $C_{16}H_{15}N_3O_2S$: C, 61.3; H, 4.8; N, 13.4; S, 10.2. Found: C, 61.4; H, 4.5; N, 13.2; S, 10.1.

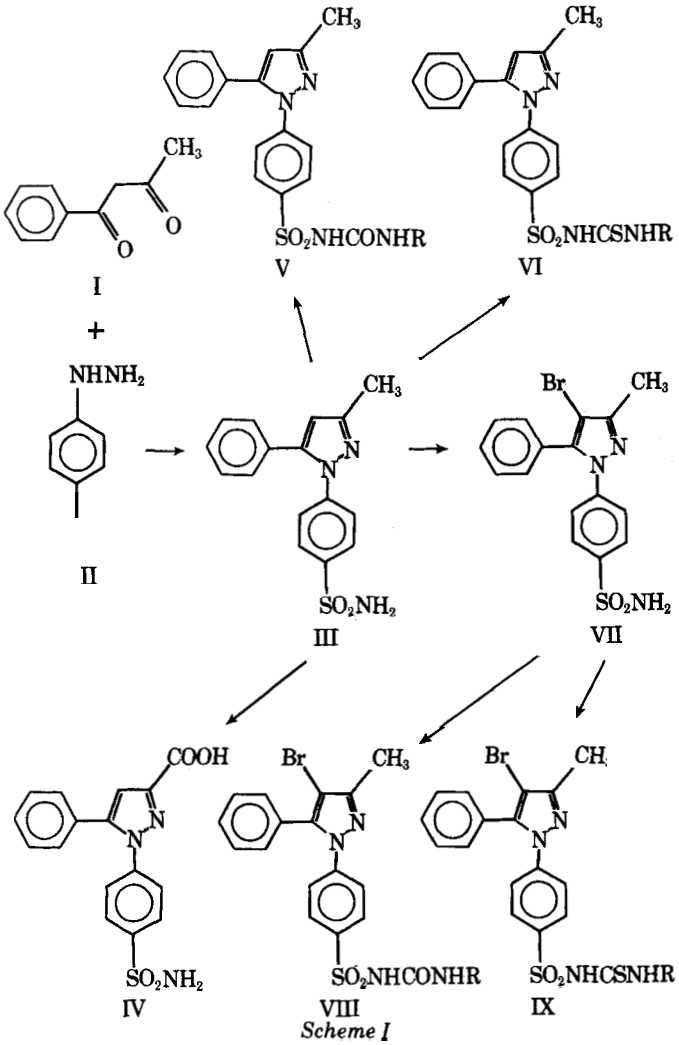
1-(*p*-Sulfamylphenyl)-5-phenylpyrazole-3-carboxylic Acid (IV)—A stirred mixture of III (0.1 mole) and sodium hydroxide (0.15 mole) in water (100 ml) was treated with powdered potassium permanganate (30 g) over 4 hr with stirring and cooling (temperature should not exceed 20°). Stirring was continued for 2 additional hr, and the mixture was left standing overnight. The mixture then was filtered and neutralized with 2 *N* HCl. The crude product was separated and crystallized from ethanol as colorless needles (65% yield), mp 185°.

Anal.—Calc. for $C_{16}H_{13}N_3O_4S$: C, 56.0; H, 3.8; N, 12.2; S, 9.3. Found: C, 55.7; H, 3.6; N, 12.0; S, 9.7.

1-(*p*-Sulfamylphenyl) -4- bromo-3-methyl-5-phenylpyrazole (VII)—A mixture of III (0.1 mole) in chloroform (100 ml) was stirred with bromine (0.1 mole) for 1 hr. The crude product that separated during stirring was filtered and recrystallized from ethanol as colorless needles (85% yield), mp 228°.

Anal.—Calc. for $C_{16}H_{14}BrN_3O_2S$: C, 49.0; H, 3.6; Br, 20.4; N, 10.7; S, 8.2. Found: C, 49.2; H, 3.4; Br, 20.6; N, 10.6; S, 8.4.

1-(*p*-Acetamidosulfonylphenyl)-3-methyl-5-phenylpyrazole—A mixture of III (0.01 mole), sodium acetate (0.02 mole), and acetic anhydride (10 ml) was refluxed for 3 hr. After cooling, the reaction mixture was poured onto water. The acetyl derivative was recrystallized from



Scheme I

methanol as white needles (65% yield), mp 172°.

Anal.—Calc. for $C_{18}H_{17}N_3O_3S$: C, 60.8; H, 4.8; N, 11.8; S, 9.0. Found: C, 61.1; H, 4.7; N, 11.5; S, 9.3.

The IR spectra of this acetyl derivative revealed a secondary carbonyl amide absorption at 1710 cm^{-1} in addition to the two bands of the SO_2N group at 1350 and 1170 cm^{-1}. The PMR spectra showed three singlets at δ 6.2, 2.3, and 1.8 for C-4, acetyl, and methyl protons, respectively, in addition to the aromatic protons at δ 7.9–7.1.

Substituted *p*-(3-Methyl-5-phenylpyrazole-1)benzenesulfonylurea (V) and *p*-(4-Bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylurea (VIII) Derivatives—A mixture of III or VII (0.05 mole) and anhydrous potassium carbonate (0.1 mole) in dry acetone (100 ml) was stirred and refluxed for 1.5 hr. At this temperature, a solution of the appropriate isocyanate (0.075 mole) in dry acetone (20 ml) was added dropwise. After the mixture was stirred and refluxed overnight, acetone was removed under reduced pressure, and the solid residue was dissolved in water. The crude product was isolated by acidification with 2 *N* HCl and purified by recrystallization from ethanol. The IR spectra of these compounds revealed two absorption bands at 1350–1330 and 1190–1170 cm^{-1}, indicative of the SO_2N group as well as a urea carbonyl band at 1660 cm^{-1}.

Substituted *p*-(3-Methyl-5-phenylpyrazole-1)benzenesulfonylthiourea (VI) and *p*-(4-Bromo-3-methyl-5-phenylpyrazole-1)benzenesulfonylthiourea (IX) Derivatives—A mixture of III or VII (0.05 mole) and anhydrous potassium carbonate (0.1 mole) in dry acetone (100 ml) was stirred and treated with the appropriate isothiocyanate (0.06 mole). After the mixture was stirred and refluxed for 10 hr, acetone was removed under reduced pressure. The solid mass thus obtained was dissolved in water and acidified with 2 *N* HCl. The crude product was purified by recrystallization from dilute ethanol.

The IR spectra of these compounds revealed two absorption bands at 1350–1335 and 1180–1170 cm^{-1}, indicative of the SO_2N group, and a band at 1200–1050 cm^{-1}, indicative of the C=S group, with the C–N absorption (III) at 1300 cm^{-1}.

1-[*p*-(2-Pyrimidinylsulfamyl)phenyl]-3-methyl-5-phenylpyrazole—A mixture of *p*-(2-pyrimidinylsulfamyl)phenylhydrazine (0.05 mole) and 1-phenylbutane-1,3-dione (0.05 mole) in ethanol (50 ml) was refluxed for 6 hr on a steam bath, concentrated, and allowed to cool. The crude product was recrystallized from ethanol as colorless crystals (75% yield), mp 265°.

Anal.—Calc. for $C_{20}H_{17}N_5O_2S$: C, 61.3; H, 4.3; N, 17.9; S, 8.2. Found: C, 60.9; H, 4.5; N, 17.5; S, 8.0.

Biological Testing Method—Compounds IV, V*b*–V*e*, VI*c*, VIII*d*, and IX*e* were tested for hypoglycemic activity using alloxan-treated female albino mice weighing 20 g. Alloxan, 100 mg/kg, was injected into the tail vein in a 10-mg/ml saline solution. Three days later, the mice were given the test compounds orally in suspension in 1% carboxymethylcellulose solution at the rate of 10 mg/kg.

Each day, a group of six mice was used as a control, and one group of six mice was given the standard, 100 mg of phenformin/kg. Up to six groups of six mice received the test compounds. Blood samples were collected into 0.04% NaF solution at 0, 1, and 3 hr.

Glucose was determined by the microcolorimetric copper reduction technique of Haslewood and Strookman (14). Results are expressed as a percentage reduction of the plasma glucose level compared to the control value.

Statistical significance was assessed by a Student *t* test. Statistical significance was accepted where the calculated *t* value exceeded the tabulated *t* value at $p = 0.05$.

From the data presented in Table III, it is obvious that V*b*–V*d* and VIII*d* possess marked hypoglycemic activity. The potency of these compounds is more than that of phenformin, and they are much more active than the parent compound, 3,5-dimethylpyrazole.

Table III—Antidiabetic Activity of Substituted *p*-(3-Methyl-5-phenylpyrazole-1)benzenesulfonylurea Derivatives

Compound	Reduction in Plasma Glucose Level, %	*p*
Phenformin	10	<0.01[a]
3,5-Dimethylpyrazole	4	<0.05[a]
IV	<1	0.05
V*b*	20	<0.01[a]
V*c*	21	<0.01[a]
V*d*	12.5	<0.01[a]
V*e*	4	0.05
VI*c*	2	0.05
VIII*d*	15	<0.01[a]
IX*e*	2	0.05

[a] Statistically significant.

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