Table III—Antidiabetic Activity of 3-Carboxy-5-substituted Styrylpyrazolylsulfonylurea Derivatives

Compound	Reduction in Plasma Glucose Level[a], %
IV	12[b]
Va	18[b]
Vb	9[b]
Vc	8[b]
Vd	6.5[c]
Ve	3
Vf	4
Vg	3.5
Vk	2.5
Vl	6.5[c]
VIb	3.5
VIh	4
VIId	5[c]
VIIe	4.5
VIIh	4
VIIIa	2
VIIIg	1

[a] Tested using alloxan-treated mice (100 mg/kg). Phenformin (0.4 mmole/kg) was used as the positive control; the hypoglycemic activity of phenformin was 10% reduction (statistically significant when compared with the untreated controls, $p < 0.01$). [b] Statistically significantly different when compared with the untreated controls at $p < 0.01$. [c] Statistically significantly different when compared with the untreated controls at $p < 0.05$.

in 1% carboxymethylcellulose at the rate of 0.4 mmole/kg. On each day of the experiment, a group of four mice was used as the control; one group of four mice was given the standard 100 mg (0.4 mmole) of phenformin/kg. Up to five groups of four mice each received the test compounds. Blood samples were collected into 0.04% NaF solution at 0, 1, and 3 hr.

Glucose was determined by a microcolorimetric copper reduction technique used previously (13). Results are expressed as a percentage reduction of plasma glucose levels compared with the control value. Statistical significance was assessed by Student's t test, where the calculated t value exceeded the tabulated t value at the $p = 0.05$ level.

Compounds IV, Va,b,c,l, and VIIe possess marked hypoglycemic activity. The most active members are the α-unsubstituted styrylpyrazolesulfonylurea derivatives. The activity decreases from the α-methylstyryl to α-phenylstyryl analogues. Surprisingly, α-unsubstituted styrylpyrazolylsulfonamide-3-carbohydrazide showed marked hypoglycemic activity.

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Synthesis and Antidiabetic Activity of Some Sulfonylurea Derivatives of 3,4,5-Trisubstituted Pyrazoles

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Received August 26, 1981, from the **Department of Pharmaceutical Chemistry*, the ‡*Department of Pharmacology, Faculty of Pharmacy*, and the §*Department of Chemistry Faculty of Science, University of Alexandria, Alexandria, Egypt.* Accepted for publication May 21, 1982.

Abstract □ Three series of 3,4,5-trisubstituted pyrazolesulfonylurea derivatives were prepared and evaluated as hypoglycemic agents. Preliminary biological testing revealed that the new compounds possess moderate hypoglycemic activity.

Keyphrases □ Pyrazolesulfonylurea derivatives—preparation, potential hypoglycemic agents □ Potential hypoglycemic agents—preparation of new trisubstituted pyrazolesulfonylurea derivatives

Since previous studies indicated that several substituted 3,5-dimethylpyrazoles possessed potent hypoglycemic activity (1–5), additional compounds were synthesized (6–10). The present study, which is a continuation of previous work (8–10), describes the preparation of derivatives of 3,4,5-trisubstituted pyrazolesulfonylureas and their evaluation as potential hypoglycemic agents.

Derivatives of *p*-(3,5-dimethyl-4-ethoxycarbonyl-1-pyrazolyl)-benzenesulfonylurea, *p*-(3-methyl-5-phenyl-4-carboxy-1-pyrazolyl)-benzenesulfonylurea, and *p*-(3-methyl - 5 - phenyl - 1 - pyrazolylcarbamoylbenzenesulfonylurea (in addition to the corresponding 4-bromo derivative) were prepared and some were evaluated for hypoglycemic activity. Preliminary biological testing revealed that the new compounds possess moderate hypoglycemic activity.

BACKGROUND

1-(*p*-Sulfamylphenyl)-3,5-dimethyl-4-ethoxycarbonylpyrazole (III) was prepared by treating *p*-sulfamylphenylhydrazine (II) with an equivalent amount of 3-ethoxycarbonyl-2,4-pentanedione (I). Similarly, 1 - (*p* - sulfamylphenyl) - 3 - methyl - 5 - phenyl - 4 - ethoxycarbonylpyrazole (VII) was prepared by treating *p*-sulfamylphenylhydrazine (II), with 1-phenyl-2-ethoxycarbonylbutane-1,3-dione (VI).

The IR absorption spectra of these trisubstituted pyrazoles (III and VII) showed an absorption band at 1700–1725 cm^{-1} due to the carbonyl of the ester group and two bands at 1330–1350 cm^{-1} and 1170–1190 cm^{-1} due to the $—SO_2N$ group.

Alkaline hydrolysis of the pyrazole esters (IV and VII) with ethanolic 2 *N* potassium hydroxide solution afforded the corresponding pyrazole-3-carboxylic acids (V and VIII). The IR spectra of the pyrazolylcarboxylic acid (VIII) showed an absorption band at 1675 cm^{-1} for the —COOH group.

p - (3,5 - Dimethyl - 4 - ethoxycarbonyl - 1 - pyrazolyl)benzenesulfonylurea (IV) and *p*-(4-carboxy-3-methyl-5-phenyl-1-pyrazolyl)benzenesulfonylurea (IX) derivatives were prepared by the reaction between III or VIII with the appropriate isocyanate in dry acetone (11). The

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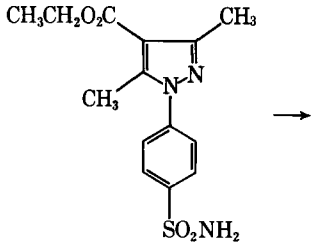
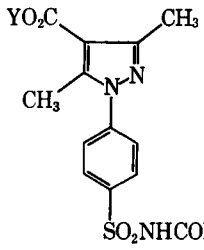
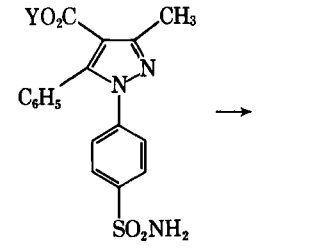


III

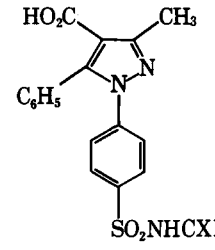


IVa: Y = CH_2CH_3, R = CH_2CH_3 Va: Y = H, R = CH_2CH_3
b: Y = CH_2CH_3, R = $(CH_2)_2CH_3$ b: Y = H, R = $(CH_2)_2CH_3$
c: Y = CH_2CH_3, R = $(CH_2)_3CH_3$ c: Y = H, R = $(CH_2)_3CH_3$
d: Y = CH_2CH_3, R = C_6H_{11} d: Y = H, R = C_6H_{11}
e: Y = CH_2CH_3, R = C_6H_5 e: Y = H, R = C_6H_5

Scheme I



VII: Y = CH_2CH_3
VIII: Y = H



IXa: X = O, R = $(CH_2)_2CH_3$ Xa: X = S, R = $CH_2CH{=}CH_2$
b: X = O, R = $(CH_2)_3CH_3$ b: X = S, R = $(CH_2)_3CH_3$
c: X = O, C_6H_{11} c: X = S, R = C_6H_{11}
d: X = S, R = C_6H_5
e: X = S, R = $CH_2C_6H_5$

Scheme II

thiourea derivatives (X) were prepared in a similar manner treating VIII with the appropriate isothiocyanate in dry acetone.

p-(3-Methyl-5-phenylpyrazol-1-yl-carbamoyl)benzenesulfonamide (XIII) was prepared by fusing *p*-sulfamylphenylsemicarbazide (XII) with 1-phenylbutane-1,3-dione (XI) at 110°. Treatment of XIII with the appropriate isocyanate afforded *p*-(3-methyl-5-phenyl-1-pyrazolyl)carbamoylbenzenesulfonylurea (XIV), which on bromination with bromine in chloroform gave the corresponding 4-bromo derivatives. The IR spectra of these compounds revealed two absorption bands at 1350–1330 cm^{-1} and 1190–1170 cm^{-1} indicative of the $-SO_2N$ group as well as a urea carbonyl band at 1660 cm^{-1}.

The physical and analytical data of these new pyrazoles, as well as the antidiabetic activity of some of the compounds are listed in Table I.

EXPERIMENTAL[1]

1 - (*p* - Sulfamylphenyl) - 3,5 - dimethyl - 4 - ethoxycarbonylpyrazole (III)—A mixture of *p*-sulfamylphenylhydrazine (18.7 g, 0.1 mole) and 3-ethoxycarbonyl-2,4-pentanedione (17 g, 0.1 mole) in ethanol (150 ml) was refluxed for 4 hr on a steam bath, concentrated, and allowed to cool. The crude product was separated and recrystallized (65% yield) from ethanol, mp 232°.

Anal.—Calc. for $C_{12}H_{17}N_3O_4S$: C, 48.2; H, 5.7; N, 14.0; S, 10.7. Found: C, 48.4; H, 5.6; N, 14.1; S, 11.0.

Substituted *p*-(3,5-Dimethyl-4-ethoxycarbonyl-1-pyrazolyl)-benzenesulfonylurea Derivatives (IV)—A mixture of III (0.025 mole) and anhydrous potassium carbonate (0.05 mole) in dry acetone (50 ml) was stirred at reflux for 1.5 hr. At this temperature, a solution of the appropriate isocyanate (0.04 mole) in dry acetone (10 ml) was added, in a dropwise manner, the mixture was stirred at reflux overnight, the acetone was removed under reduced pressure, and the resulting solid residue was dissolved in water. The crude product was isolated by acidification with 2 *N* hydrochloric acid and purified by recrystallization from ethanol.

Substituted *p*-(4-Carboxy-3,5-dimethyl-1-pyrazolyl)benzenesulfonylurea Derivatives (V)—A mixture of IV (1 g) in an alcoholic solution of 2 *N* potassium hydroxide (25 ml) was refluxed for 1 hr. The mixture was concentrated, cooled, and acidified with dilute hydrochloric acid to give crystalline material.

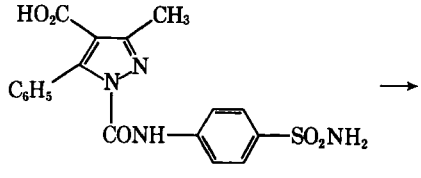
1-(*p*-Sulfamylphenyl)-3-methyl-5-phenyl-4-ethoxycarbonylpyrazole (VII)—A mixture of *p*-sulfamylphenylhydrazine (18.7 g, 0.1 mole) and 1-phenyl-2-ethoxycarbonylbutane-1,3-dione (23.6 g, 0.1 mole) in ethanol (150 ml) was refluxed for 4–6 hr on a steam bath, concentrated, and allowed to cool. The crude product was separated and recrystallized (70% yield) from ethanol, mp 232°.

Anal.—Calc. for $C_{17}H_{19}N_3O_4S$: C, 56.5; H, 5.3; N, 11.6; S, 8.9. Found: C, 56.5; H, 5.5; N, 11.8; S, 9.1.

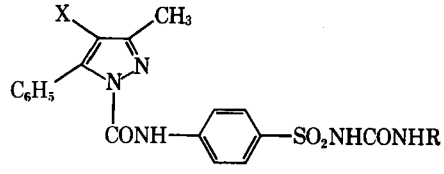
1 - (*p* - Sulfamylphenyl) - 3 - methyl - 5 - phenyl - 4 - carboxypyrazole (VIII)—A mixture of VII (5 g) in alcoholic solution of 2 *N* potassium hydroxide (100 ml) was refluxed for 1 hr. The mixture was concentrated, cooled, and then acidified with dilute hydrochloric acid to give a crystalline material. Recrystallization from ethanol, gave VIII (80% yield) mp 250°.

Anal.—Calc. for $C_{15}H_{15}N_3O_4S$: C, 54.1; H, 4.5; N, 12.6; S, 9.6. Found: C, 54.4; H, 4.4; N, 12.5; S, 9.8.

Substituted *p*-(4-Carboxy-3-methyl-5-phenyl-1-pyrazolyl)-benzenesulfonylurea Derivatives (IX)—A mixture of VIII (0.025 mole) and anhydrous potassium carbonate (0.05 mole) in dry acetone (50 ml) was refluxed for 1.5 hr. At this temperature, a solution of the appropriate isocyanate (0.04 mole) in dry acetone (10 ml) was added in a dropwise manner. After the mixture was stirred and refluxed overnight, the acetone was removed under reduced pressure, and the solid residue was dissolved in water. The crude product precipitated when the mixture was acidified with 2 *N* hydrochloric acid. Recrystallization from ethanol afforded the purified material.



XIII



XIVa: X = H, R = CH_2CH_3 XVa: X = Br, R = $(CH_2)_2CH_3$
XIVb: X = H, R = $(CH_2)_2CH_3$ XVb: X = Br, R = $(CH_2)_3CH_3$
XIVc: X = H, R = $(CH_2)_3CH_3$ XVc: X = Br, R = C_6H_5
XIVd: X = H, R = C_6H_5

Scheme III

[1] Melting points were determined in open glass capillaries and are uncorrected. UV spectra were measured with a Perkin-Elmer 550 S spectrophotometer. The IR spectra were determined as Nujol mulls with a Beckman IR-4210 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-360 60-Hz, NMR spectrophotometer. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, University of Cairo, Cairo, Egypt.

Table I—Physical and Analytical Data and Hypoglycemic Activity of the Substituted Pyrazolesulfonylureas

Compound	Yield, %	Melting Point,°	Formula		Analysis, % Calc.	Found	Reduction in Plasma Glucose Level %,[a]
IV*a*	65	195	$C_{17}H_{22}N_4O_5S$	C	51.8	52.0	
				H	5.6	5.7	
				N	14.2	14.0	
				S	8.1	8.3	
IV*b*	60	145	$C_{18}N_{24}N_4O_5S$	C	52.9	53.1	
				H	5.9	6.2	
				N	13.7	13.5	
				S	7.8	8.0	
IV*c*	70	77	$C_{19}H_{26}N_4O_5S$	C	54.0	53.9	5[b]
				H	6.2	6.4	
				N	13.3	13.1	
				S	7.6	7.8	
IV*d*	73	204	$C_{21}H_{28}N_4O_5S$	C	56.3	56.1	
				H	6.3	6.4	
				N	12.5	12.5	
				S	7.1	7.0	
IV*e*	70	226	$C_{21}H_{22}N_4O_5S$	C	57.0	56.9	4[b]
				H	5.0	5.1	
				N	12.7	12.5	
				S	7.2	7.4	
V*a*	70	178	$C_{15}H_{18}N_4O_5S$	C	49.2	49.0	
				H	4.9	5.0	
				N	15.3	15.4	
				S	8.7	9.0	
V*b*	68	134	$C_{16}H_{20}N_4O_5S$	C	50.5	50.6	
				H	5.3	5.1	
				N	14.7	14.8	
				S	8.4	8.4	
V*c*	65	89	$C_{17}H_{22}N_4O_5S$	C	51.8	51.7	5
				H	5.6	5.8	
				N	14.2	14.0	
				S	8.1	8.3	
V*d*	72	218	$C_{19}H_{24}N_4O_5S$	C	54.3	54.1	3
				H	5.7	5.8	
				N	13.3	13.3	
				S	7.6	7.4	
V*e*	75	235	$C_{19}H_{18}N_4O_5S$	C	55.1	55.0	
				H	4.3	4.5	
				N	13.5	13.4	
				S	7.7	7.7	
IX*a*	65	170	$C_{21}H_{22}N_4O_5S$	C	57.0	57.1	2
				H	5.0	4.9	
				N	12.7	13.0	
				S	7.2	7.3	
IX*b*	70	72	$C_{22}H_{24}N_4O_5S$	C	57.8	58.0	
				H	5.3	5.4	
				N	12.3	12.5	
				S	7.0	7.1	
IX*c*	75	195	$C_{24}H_{26}N_4O_5S$	C	59.8	60.0	2
				H	5.4	5.5	
				N	11.6	11.8	
				S	6.6	6.5	
X*a*	65	140	$C_{21}H_{20}N_4O_4S_2$	C	55.3	55.5	
				H	4.4	4.5	
				N	12.3	12.4	
				S	14.0	13.8	
X*b*	68	239	$C_{22}H_{24}N_4O_4S_2$	C	55.9	56.1	
				H	5.1	5.0	
				N	11.9	12.1	
				S	13.6	13.3	
X*c*	66	255	$C_{24}H_{26}N_4O_4S_2$	C	57.8	58.1	3
				H	5.2	5.1	
				N	11.2	11.5	
				S	12.9	13.0	
X*d*	70	152	$C_{24}H_{20}N_4O_4S_2$	C	58.5	58.4	1
				H	4.1	4.1	
				N	11.4	11.6	
				S	13.0	12.9	
X*e*	65	252	$C_{25}H_{22}N_4O_4S_2$	C	59.3	59.5	
				H	4.3	4.4	
				N	11.1	11.2	
				S	12.6	12.5	
XIV*a*	70	128	$C_{20}H_{21}N_5O_4S$	C	56.2	56.0	
				H	4.9	5.0	
				N	16.4	16.5	
				S	7.5	7.4	
XIV*b*	65	108	$C_{21}H_{23}N_5O_4S$	C	57.1	57.0	
				H	5.2	5.1	
				N	15.9	16.1	
				S	7.3	7.3	

continued

Table I—*continued*

Compound	Yield, %	Melting Point,°	Formula		Analysis, % Calc.	Found	Reduction in Plasma Glucose Level %,[a]
XIV*c*	73	70	$C_{22}H_{25}N_5O_4S$	C	58.0	57.9	
				H	5.5	5.6	
				N	15.4	15.2	
				S	7.0	7.1	
XIV*d*	65	230	$C_{24}H_{21}N_5O_4S$	C	60.6	60.9	10[c]
				H	4.4	4.6	
				N	14.7	14.4	
				S	6.7	6.8	
XV*a*	80	100	$C_{21}H_{22}BrN_5O_4S$	C	48.5	48.4	
				H	4.2	4.1	
				Br	15.4	15.6	
				N	13.5	13.3	
XV*b*	88	74	$C_{22}H_{24}BrN_5O_4S$	C	49.4	49.1	8[c]
				H	4.5	4.5	
				Br	15.0	14.8	
				N	13.1	13.0	
XV*c*	84	220	$C_{24}H_{20}BrN_5O_4S$	C	52.0	52.1	
				H	3.6	3.8	
				Br	14.4	14.3	
				N	12.6	12.6	

[a] Tested using alloxan-treated mice (100 mg/kg). Phenformin (0.4 mmole/kg) was used as the positive control; the hypoglycemic activity of phenformin was 10% reduction (statistically significant when compared with the untreated controls at $p < 0.01$). [b] Statistically significantly different from the untreated controls at $p < 0.05$. [c] Statistically significantly different from the untreated controls at $p < 0.01$.

Substituted *p*-(4-Carboxy-3-methyl-5-phenyl-1-pyrazolyl)-benzenesulfonylthiourea Derivatives (X)—A mixture of VIII (0.025 mole) and anhydrous potassium carbonate (0.05 mole) in dry acetone (100 ml) was stirred and treated with the appropriate isothiocyanate (0.03 mole). The mixture was stirred at reflux for 10 hr, and then the acetone was removed under reduced pressure; the resulting solid residue was dissolved in water. Acidification with 2 *N* hydrochloric acid, followed by recrystallization of the resulting solid from dilute ethanol gave X.

***p*-(3-Methyl-5-phenyl-1-pyrazolyl)carbamoylbenzenesulfonamide (XIII)**—A mixture of XII (22.9 g, 0.1 mole) and 1-phenylbutane-1,3-dione (16.6 g, 0.1 mole) was stirred and fused at 110° for 1 hr, cooled, and crystallized from ethanol to give colorless crystals, mp 190°.

Anal.—Calc. for $C_{17}H_{16}N_4O_3S$: C, 57.3; H, 4.5; N, 15.7; S, 9.0. Found: C, 57.5; H, 4.5; N, 16.0; S, 8.8.

***p*-(3-Methyl-5-phenyl-1-pyrazolyl)carbamoylbenzenesulfonylurea (XIV)**—A mixture of XIII (0.025 mole) and anhydrous potassium carbonate (0.05 mole) in dry acetone (50 ml) was stirred at reflux for 1.5 hr. At this temperature, a solution of the appropriate isocyanate (0.04 mole) in dry acetone (10 ml) was added in a dropwise manner. The mixture was stirred at reflux overnight, and then the acetone was removed under reduced pressure to give a solid material. This material was dissolved in water, and the solution was acidified with 2 *N* hydrochloric acid. Recrystallization from methanol–benzene gave XIV.

***p*-(4-Bromo-3-methyl-5-phenyl-1-pyrazolyl)carbamoylbenzenesulfonylurea Derivatives (XV)**—A mixture of XIV (0.01 mole) in chloroform (10 ml) was stirred at room temperature and a solution of bromine was added with chloroform (0.011 mole) for a 1-hr period. The mixture was allowed to stand at room temperature overnight and the resulting solid was removed by filtration. Recrystallization from dilute ethanol gave colorless crystals of XV.

Spectra—The UV spectrum of IV showed two peaks at λ_{max} 230–237 and 272–277 nm. Compound IX showed two peaks at λ_{max} 210–214 and 260–268 nm. The IR spectra revealed bands at 1700–1730 (C=O), 1330–1350, and 1170–1190 cm^{-1} (SO_2N), whereas XIV and XV showed bands at 1650–1660 (amide), 1330–1350, and 1170–1190 cm^{-1} (SO_2N).

The ^{1}H-NMR spectrum of III showed absorption at 7.1–7.7 (m, aromatic H), 5.6 (s, 2, SO_2NH_2), 4.2 (q, J = 7.0 Hz, $CO_2CH_2CH_3$), 1.8 (s, CH_3), and 1.2 ppm (t, J = 7.0 Hz, $CO_2CH_2CH_3$). The ^{1}H-NMR spectrum of XIV*d* showed absorption at 7.6–8.2 (m aromatic H), 6.6 (s, 1, pyrazole H), and 1.6 ppm (s, CH_3).

Biological Testing Method—Compounds IV*c*,*e*, V*c*,*d*, IX*a*,*c*, X*c*,*d*, XIV*d*, and XV*b* were tested for hypoglycemic activity using alloxan-treated female albino mice with an average weight of 20 g. Alloxan (100 mg/kg) in a 10-mg/ml saline solution was injected into the tail vein. Three days later, the mice were given the test compounds orally in suspension in 1% carboxymethylcellulose at the rate of 0.4 mmole/kg. Each day of the experiment, a group of four mice was used as the control; one group of four mice was given the standard, 100 mg (0.4 mmole) of phenformin/kg. Up to five groups of four mice each received the test compounds. Blood samples were collected into 0.04% NaF solution at 0, 1, and 3 hr.

Glucose was determined by a previously used microcolorimetric copper reduction technique (12). Results are expressed as a percentage reduction of plasma glucose levels compared with the control value. Statistical significance was assessed by Student's t test, where the calculated t value exceeded the tabulated t value at the p = 0.05 level.

Compound XIV*d* possesses marked hypoglycemic activity (Table I); its potency is comparable with phenformin. The other compounds showed moderate hypoglycemic activity.

From the data presented previously (8–10) and in this report, it is obvious that pyrazole-3-carboxylic acids are much more potent hypoglycemics than the corresponding 4-carboxylic acid derivatives. 3,5-Disubstituted pyrazolebenzenesulfonylurea derivatives are much more active than the corresponding trisubstituted pyrazoles. The presence of a 4-ethoxycarbonyl or carboxy group in the pyrazole ring reduces the hypoglycemic activity. Generally, pyrazolesulfonylurea derivatives are much more active than the corresponding thiourea analogues.

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