Preparation and Antidiabetic Activity of New Substituted 3,5-Diarylpyrazolesulfonylurea Derivatives

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Abstract □ Four series of *p*-(3,5-diphenylpyrazole-1)-, *p*-[5-(*p*-chlorophenyl)-3-phenylpyrazole-1]-, *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazolin-1-yl]-, and *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenylpyrazole-1]benzenesulfonylurea derivatives were prepared for evaluation as hypoglycemic agents. Preliminary biological testing revealed that the new compounds possess potent hypoglycemic activity.

Keyphrases □ 3,5-Diarylpyrazolesulfonylurea derivatives, substituted—preparation and evaluation for antidiabetic activity □ Structure–activity relationships—substituted 3,5-diarylpyrazolesulfonylurea derivatives and antidiabetic activity □ Antidiabetic activity—substituted 3,5-diarylpyrazolesulfonylurea derivatives synthesized and tested

Since several 3,5-dimethylpyrazoles possess hypoglycemic activities as great as 100 times that of tolbutamide in glucose-primed intact rats (1–5), studies have been conducted on the synthesis of new 3,5-disubstituted pyrazoles (6–9). In continuation of previous work (8, 9), many new substituted 3,5-diarylpyrazolesulfonylurea derivatives were prepared[1].

In light of the biological data reported in this paper and previously (8, 9), a possible structure–activity relationship for hypoglycemic activity may result.

Four series of *p*-(3,5-diphenylpyrazole-1)-, *p*-[5-(*p*-chlorophenyl)-3-phenylpyrazole-1]-, *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazolin-1-yl]-, and *p*-[5-(*p*-chlorophenyl)-4-hydroxy -3- phenylpyrazole-1]benzenesulfonylurea derivatives were synthesized. Some compounds were tested for hypoglycemic activity. Preliminary biological testing revealed that the compounds showed potent antidiabetic activity.

DISCUSSION

The new pyrazoles are listed in Tables I and II. The compounds listed in Table III were tested for antidiabetic activity.

1-(*p*-Sulfamylphenyl)-3,5-diphenylpyrazole (III) was prepared by treating *p*-sulfamylphenylhydrazine (I) with an equivalent amount of epoxybenzalacetophenone (II) (Scheme I). Acetylation of III with acetic anhydride afforded the monoacetyl derivative (IV*a*). Similarly, benzoylation of III with benzoyl chloride or *p*-methoxybenzoyl chloride in pyridine afforded the corresponding monobenzoyl (IV*b*) and the *p*-methoxybenzoyl (IV*c*) derivatives, respectively, as affirmed by microanalysis and IR spectra.

Condensation of I with an equivalent amount of epoxy-*p*-chlorobenzalacetophenone (VII) afforded a mixture of 1-(*p*-sulfamylphenyl)-5-(*p*-chlorophenyl)-3-phenylpyrazole (VIII) and 1-(*p*-sulfamylphenyl)-5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazoline (IX). Compound IX, on oxidation with bromine water, gave 1-(*p*-sulfamylphenyl)-5-(*p*-chlorophenyl)-4-hydroxy-3-phenylpyrazole (X). Benzoylation of VIII and IX afforded the corresponding benzamidosulfonyl derivatives (Scheme II).

Substituted *p*-(3,5-diphenylpyrazole-1)- (V), substituted *p*-[5-(*p*-chlorophenyl)-3-phenylpyrazole-1]- (XII), substituted *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazolin-1-yl]- (XIII), and substituted *p*-[5-(*p*-chlorophenyl) -4- hydroxy-3-phenylpyrazole-1]benzenesulfonylurea (XIV) derivatives were prepared by the reaction between III, VIII, IX, or X and the appropriate isocyanate in dry acetone (10).

Substituted *p*-(3,5-diphenylpyrazole-1)- (VI), substituted *p*-[5-(*p*-chlorophenyl)-3-phenylpyrazole-1]- (XII), substituted *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazolin-1-yl]- (XIII), and substituted *p*-[5-(*p*-chlorophenyl)-4-hydroxy -3- phenylpyrazole-1]benzenesulfonylthiourea (XIV) derivatives were prepared by the reaction between III, VIII, IX, or X and the appropriate isothiocyanates in dry acetone.

Substituted *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenylpyrazole-1]-benzenesulfonylurea and thiourea derivatives were also prepared by direct oxidation of the corresponding 2-pyrazoline derivatives (XIII*a*–XIII*f*) using bromine water.

EXPERIMENTAL[2]

1-(*p*-Sulfamylphenyl)-3,5-diphenylpyrazole (III)—A mixture of *p*-sulfamylphenylhydrazine (I, 0.1 mole) and epoxybenzalacetophenone (II, 0.1 mole) in absolute ethanol (50 ml) was refluxed for 3 hr on a steam bath, concentrated, and allowed to cool. The crude product was filtered and recrystallized from ethanol as colorless prismatic needles (75% yield), mp 172°. The IR spectrum of III revealed two characteristic bands at 1365 and 1170 cm^{-1}, indicative of the SO_2N group, and two bands at 3170 and 3350 cm^{-1}, indicative of the NH_2 group.

Anal.—Calc. for $C_{21}H_{17}N_3O_2S$: C, 67.2; H, 4.5; N, 11.2; S, 8.5. Found: C, 67.2; H, 4.4; N, 11.3; S, 8.4.

1-(*p*-Acetamidosulfonylphenyl)-3,5-diphenylpyrazole (IV*a*)—A mixture of III (0.01 mole), sodium acetate (0.02 mole), and acetic anhydride (10 ml) was refluxed for 4 hr. After cooling, the reaction mixture was diluted with water. The crude acetyl derivative was recrystallized from dilute methanol in yellow needles (65% yield), mp 98°. The IR spectrum of IV*a* revealed a secondary carbonyl amide absorption at 1720 cm^{-1} and an NH band at 3090 cm^{-1} in addition to the two bands of the SO_2N group at 1365 and 1170 cm^{-1}.

Anal.—Calc. for $C_{23}H_{19}N_3O_3S$: C, 66.2; H, 4.6; N, 10.1; S, 7.7. Found: C, 66.0; H, 4.8; N, 10.3; S, 7.9.

1-(*p*-Benzamidosulfonylphenyl)-3,5-diphenylpyrazole (IV*b*)—A solution of III (0.001 mole) in pyridine (5 ml) was heated with benzoyl chloride (0.001 mole) for 20 min. The reaction mixture was left at room temperature for 6 hr and then diluted with ice-cold water. The crude product was purified by recrystallization from dilute methanol to give white needles (70% yield), mp 135°. The IR spectrum of IV*b* revealed a secondary carbonyl amide absorption at 1705 cm^{-1} and an NH band at 3100 cm^{-1}, in addition to the two bands of the SO_2N group at 1365 and 1170 cm^{-1}.

Anal.—Calc. for $C_{28}H_{21}N_3O_3S$: C, 70.1; H, 4.4; N, 8.8; S, 6.7. Found: C, 69.8; H, 4.2; N, 9.0; S, 6.7.

1-[*p*-(*p*-Methoxybenzamido)sulfonylphenyl]-3,5-diphenylpyrazole (IV*c*)—A solution of III (0.001 mole) in pyridine (5 ml) was heated with *p*-methoxybenzoyl chloride (0.001 mole) for 20 min. The reaction mixture then was left at room temperature for 6 hr and diluted with ice-cold water. The crude product was purified by recrystallization from dilute methanol to give white needles (70% yield), mp 225°. The IR spectrum of IV*c* revealed a secondary carbonyl amide absorption at 1700 cm^{-1} and an NH band at 3090 cm^{-1} in addition to the two bands of the SO_2N group at 1365 and 1170 cm^{-1}.

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

[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.

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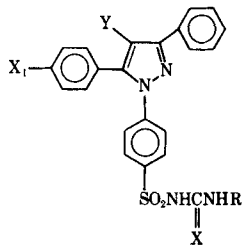


Table I—Substituted *p*-(3,5-Diarylpyrazole-1)benzenesulfonylurea Derivatives

Compound	R	X	X_1	Y	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
V*a*	C_2H_5	O	H	H	70	208°	$C_{24}H_{22}N_4O_3S$	C	64.6	64.2
								H	4.9	4.7
								N	12.6	12.5
								S	7.2	7.2
V*b*	$CH_3(CH_2)_2$	O	H	H	65	205°	$C_{25}H_{24}N_4O_3S$	C	65.2	65.5
								H	5.2	5.4
								N	12.2	12.6
								S	7.0	7.1
V*c*	$CH_3(CH_2)_3$	O	H	H	60	235°	$C_{26}H_{26}N_4O_3S$	C	65.8	66.1
								H	5.5	5.4
								N	11.8	12.2
								S	6.8	6.7
V*d*	C_6H_{11}	O	H	H	80	212°	$C_{28}H_{28}N_4O_3S$	C	67.2	67.5
								H	5.6	5.2
								N	11.2	11.1
								S	6.4	6.4
V*e*	C_6H_5	O	H	H	70	220°	$C_{28}H_{22}N_4O_3S$	C	68.0	68.2
								H	4.5	4.5
								N	11.3	11.6
								S	6.5	6.5
VI*a*	C_2H_5	S	H	H	65	175°	$C_{24}H_{22}N_4O_2S_2$	C	62.3	62.1
								H	4.8	4.8
								N	12.1	12.5
								S	13.9	13.7
VI*b*	$CH_3(CH_2)_3$	S	H	H	60	162°	$C_{26}H_{26}N_4O_2S_2$	C	63.6	64.0
								H	5.3	5.3
								N	11.4	11.2
								S	13.1	13.3
VI*c*	C_6H_{11}	S	H	H	70	210°	$C_{28}H_{28}N_4O_2S_2$	C	65.1	64.9
								H	5.4	5.7
								N	10.8	10.4
								S	12.4	12.3
VI*d*	*p*-$CH_3C_6H_4$	S	H	H	65	214°	$C_{29}H_{24}N_4O_2S_2$	C	66.4	66.2
								H	4.6	4.5
								N	10.7	10.3
								S	12.2	12.1
VI*e*	$C_6H_5CH_2$	S	H	H	65	158°	$C_{29}H_{24}N_4O_2S_2$	C	66.4	66.4
								H	4.6	4.8
								N	10.7	10.6
								S	12.2	12.6
XII*a*	C_2H_5	O	Cl	H	70	215°	$C_{24}H_{21}ClN_4O_3S$	C	59.9	60.0
								H	4.4	4.3
								Cl	7.4	7.1
								N	11.7	11.8
								S	6.7	6.7
XII*b*	$CH_3(CH_2)_2$	O	Cl	H	65	222°	$C_{25}H_{23}ClN_4O_3S$	C	60.7	61.1
								H	4.7	4.9
								Cl	7.2	7.0
								N	11.3	11.0
								S	6.5	6.3
XII*c*	$CH_3(CH_2)_3$	O	Cl	H	60	205°	$C_{26}H_{25}ClN_4O_3S$	C	61.4	61.6
								H	4.9	5.2
								Cl	7.0	7.3
XII*d*	C_6H_{11}	O	Cl	H	70	220°	$C_{28}H_{27}ClN_4O_3S$	C	62.7	63.0
								H	5.1	5.0
								Cl	6.6	7.0
								N	10.5	10.7
								S	6.0	5.7
XII*e*	C_6H_5	O	Cl	H	65	223°	$C_{28}H_{21}ClN_4O_3S$	C	63.6	63.4
								H	4.0	4.2
								Cl	6.7	6.5
								N	10.6	10.6
								S	6.1	6.2
XII*f*	C_6H_{11}	S	Cl	H	70	210°	$C_{28}H_{27}ClN_4O_2S_2$	C	61.0	61.3
								H	4.9	4.8
								Cl	6.4	6.2
								N	10.2	10.4
								S	11.6	11.9

(*continued*)

Table I—*Continued*

Compound	R	X	X_1	Y	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
XIV*a*	C_2H_5	O	Cl	OH	60	195°	$C_{24}H_{21}ClN_4O_4S$	C	58.0	58.0
								H	4.2	4.6
								Cl	7.2	7.3
								N	11.2	11.0
XIV*b*	C_6H_5	O	Cl	OH	65	282°	$C_{28}H_{21}ClN_4O_4S$	C	61.7	62.1
								H	4.0	4.1
								N	10.3	10.2
								S	5.9	5.9
XIV*c*	C_2H_5	S	Cl	OH	70	175°	$C_{24}H_{21}ClN_4O_3S_2$	C	56.2	56.5
								H	4.1	4.3
								Cl	6.9	6.5
								N	10.9	10.8
								S	12.5	12.5
XIV*d*	C_6H_{11}	S	Cl	OH	60	185°	$C_{28}H_{27}ClN_4O_3S_2$	C	59.3	59.2
								H	4.8	5.2
								Cl	6.3	6.1
								N	9.9	10.0
								S	11.3	11.1

Anal.—Calc. for $C_{29}H_{23}N_3O_4S$: C, 68.4; H, 4.5; N, 8.3; S, 6.3. Found: C, 68.4; H, 4.2; N, 8.3; S, 6.4.

1 - (*p* - Sulfamylphenyl)-5-(*p*-chlorophenyl)-3-phenylpyrazole (VIII)—A mixture of *p*-sulfamylphenylhydrazine (0.1 mole) and epoxy-*p*-chlorobenzalacetophenone (0.1 mole) in absolute ethanol (50 ml) was refluxed for 3 hr on a steam bath, concentrated, and allowed to cool. The crude product was filtered and recrystallized from a mixture of benzene and ethanol to give yellow needles (60% yield), mp 275°. The IR spectrum of VIII revealed two characteristic bands at 1360 and 1150 cm^{-1}, indicative of the SO_2N group, and two bands at 3170 and 3320 cm^{-1}, indicative of the NH_2 group.

Anal.—Calc. for $C_{21}H_{16}ClN_3O_2S$: C, 61.5; H, 3.9; Cl, 8.7; N, 10.3; S, 7.8. Found: C, 61.4; H, 3.5; Cl, 8.5; N, 10.1; S, 7.7.

1-(*p*-Sulfamylphenyl)-5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazoline (IX)—When the mother liquor of the previous reaction was left to evaporate slowly, the pyrazoline derivative separated out. It was recrystallized from methanol as colorless plates (40% yield), mp 225°. The IR spectrum of IX revealed a band at 3400 cm^{-1}, indicative of an OH group, and two bands at 3220 and 3280 cm^{-1}, indicative of the NH_2 group.

Anal.—Calc. for $C_{21}H_{18}ClN_3O_3S$: C, 58.9; H, 4.2; Cl, 8.3; N, 9.8; S, 7.5. Found: C, 59.2; H, 4.5; Cl, 8.1; N, 10.1; S, 7.6.

1 - [*p*-(*p*-Methoxybenzamido)sulfonylphenyl]-5-(*p*-chlorophenyl)-3-phenylpyrazole (XI)—A solution of VIII (0.001 mole) in pyridine (5 ml) was heated with *p*-methoxybenzoyl chloride (0.001 mole) for 20 min. The mixture was left at room temperature for 6 hr and then diluted with ice-cold water. The crude product was purified by recrystallization (50% yield) from dilute methanol, mp 242°. The IR spectrum of XI re-

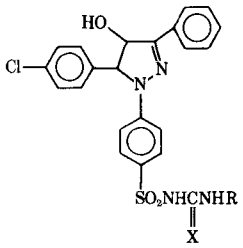
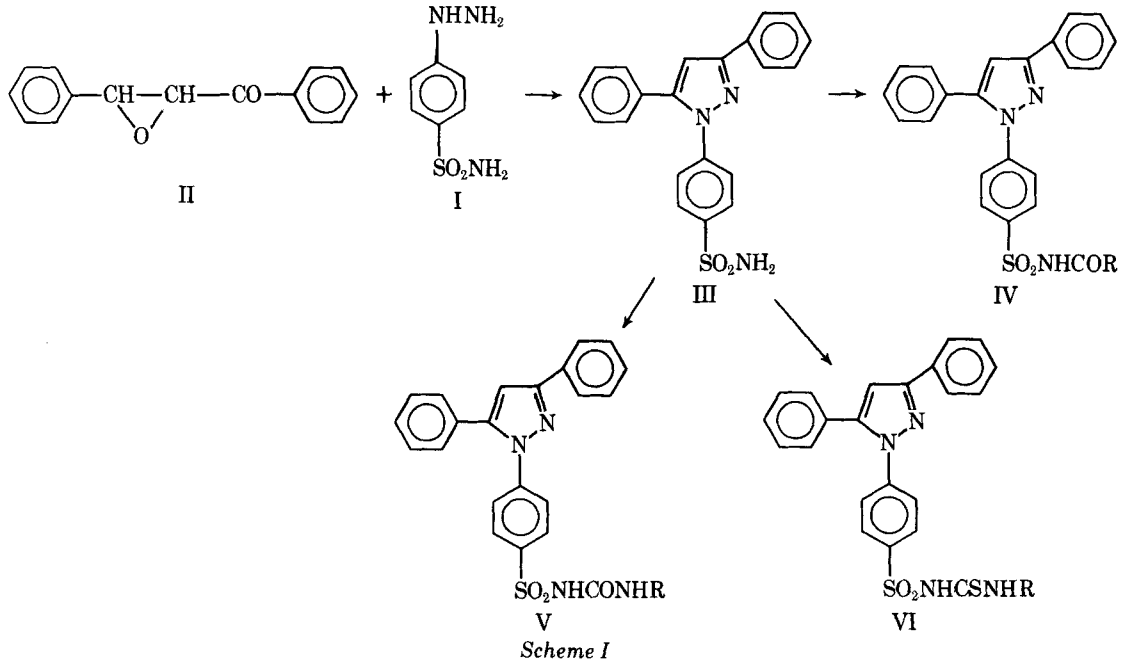


Table II—Substituted *p*-[5-(*p*-Chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazolin-1-yl]benzenesulfonylurea Derivatives

Compound	R	X	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
XIII*a*	C_2H_5	O	65	215°	$C_{24}H_{23}ClN_4O_4S$	C	57.8	58.0
						H	4.6	4.6
						Cl	7.1	7.3
						N	11.2	11.1
						S	6.4	6.4
XIII*b*	C_6H_{11}	O	70	230°	$C_{28}H_{29}ClN_4O_4S$	C	60.8	60.5
						H	5.3	5.4
						Cl	6.4	6.0
						N	10.1	10.3
						S	5.7	5.8
XIII*c*	C_6H_5	O	60	172°	$C_{28}H_{23}ClN_4O_4S$	C	61.5	61.5
						H	4.2	4.4
						Cl	6.5	6.4
						N	10.2	10.5
						S	5.9	5.9
XIII*d*	C_2H_5	S	65	195°	$C_{24}H_{23}ClN_4O_3S_2$	C	56.0	55.9
						H	4.5	4.1
						Cl	6.9	6.5
						N	10.9	10.8
						S	12.5	12.5
XIII*e*	C_6H_{11}	S	70	218°	$C_{28}H_{29}ClN_4O_3S_2$	C	59.1	59.2
						H	5.1	5.3
						Cl	6.2	6.1
						N	9.9	9.5
XIII*f*	$C_6H_5CH_2$	S	65	142°	$C_{29}H_{25}ClN_4O_3S_2$	C	60.4	60.7
						H	4.3	4.3
						Cl	6.2	6.1
						N	9.7	10.1
						S	11.1	11.5



Scheme I

vealed a secondary carbonyl amide band at 1705 cm^{-1} and an NH band at 3090 cm^{-1}.

Anal.—Calc. for $C_{29}H_{22}ClN_3O_4S$: C, 64.0; H, 4.0; Cl, 6.5; N, 7.7; S, 5.9. Found: C, 64.4; H, 4.1; Cl, 6.4; N, 7.9; S, 5.5.

1-(*p*-Benzamidosulfonylphenyl)-5-(*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazoline—A solution of IX (0.001 mole) in pyridine (5 ml) was heated with benzoyl chloride (0.001 mole) for 20 min. The reaction mixture then was left at room temperature for 6 hr and diluted with ice-cold water. The crude product was purified by recrystallization from methanol to give white needles (75% yield), mp 162°. The IR spectrum revealed a band at 3380 cm^{-1}, indicative of an OH group, a secondary carbonyl amide band at 1710 cm^{-1}, and an NH band at 3100 cm^{-1}.

Anal.—Calc. for $C_{28}H_{22}ClN_3O_4S$: C, 63.2; H, 4.1; Cl, 6.7; N, 7.9; S, 6.0. Found: C, 63.4; H, 4.5; Cl, 6.8; N, 7.7; S, 6.0.

1-[*p*-(*p*-Methoxybenzamido)sulfonylphenyl] -5- (*p*-chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazoline—A solution of IX (0.001 mole) in pyridine (5 ml) was heated with *p*-methoxybenzoyl chloride (0.001 mole) for 20 min. The reaction mixture then was left at room temperature for 6 hr and diluted with ice-cold water. The crude product was purified by recrystallization from ethanol to give white needles (70% yield), mp 190°. The IR spectrum revealed a band at 3350 cm^{-1}, indicative of an OH group, a secondary carbonyl amide band at 1715 cm^{-1}, and an NH band at 3100 cm^{-1}.

Anal.—Calc. for $C_{29}H_{24}ClN_3O_5S$: C, 62.0; H, 4.3; Cl, 6.3; N, 7.5; S, 5.7. Found: C, 62.2; H, 4.3; Cl, 6.1; N, 7.6; S, 5.8.

1 - (*p* - Sulfamylphenyl)-5-(*p*-chlorophenyl)-4-hydroxy-3-phenylpyrazole (X)—A suspension of IX (0.01 mole) in water (10 ml) was treated with 5% bromine water until a faint-yellow color developed with stirring. Stirring continued for 2 hr, and the crude pyrazole was filtered and recrystallized from methanol as colorless needles (45% yield), mp 252°. The IR spectrum of X showed a band at 3400 cm^{-1}, indicative of an OH group, and two bands at 3230 and 3290 cm^{-1}, indicative of an NH_2 group.

Anal.—Calc. for $C_{21}H_{16}ClN_3O_3S$: C, 59.2; H, 3.8; Cl, 8.3; N, 9.9; S, 7.5. Found: C, 59.1; H, 3.9; Cl, 8.1; N, 10.1; S, 7.5.

Substituted *p*-(3,5-Diarylpyrazole-1)benzenesulfonylurea (V, XII, and XIV) Derivatives—A mixture of III, VIII, or X (0.01 mole) and anhydrous potassium carbonate (0.02 mole) in dry acetone (25 ml) was stirred and refluxed for 1 hr. At this temperature, a solution of the appropriate isocyanate (0.015 mole) in dry acetone (5 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 (Table I).

Substituted *p*-(3,5-Diarylpyrazole-1)benzenesulfonylthiorea (VI, XII, and XIV) Derivatives—A mixture of III, VIII, or X (0.01 mole) and anhydrous potassium carbonate (0.02 mole) in dry acetone (25 ml) was stirred and treated with the appropriate isothiocyanate (0.012 mole). After the mixture was stirred and refluxed for 10 hr, acetone was removed under reduced pressure, and the solid mass was dissolved in water and acidified with 2 *N* HCl. The crude product was purified by recrystallization from dilute ethanol (Table I).

Substituted *p*-[5-(*p*-Chlorophenyl)-4-hydroxy-3-phenyl-2-pyrazolin-1-yl]benzenesulfonylurea and Thiourea (XIIIa–XIIIf) Derivatives—Compounds XIII*a*–XIII*f* were prepared by the same procedures used in the preparation of substituted *p*-(3,5-diarylpyrazole-1)benzenesulfonylurea and thiourea derivatives.

Substituted *p*-[5-(*p*-chlorophenyl)-4-hydroxy-3-phenylpyrazole-1]-benzenesulfonylurea and thiourea (XIV*a*–XIV*d*) derivatives could also be prepared by bromine water oxidation of their corresponding pyrazoline derivatives (XIII*a*–XIII*f*).

The IR spectra of V*a*–V*e* showed a band at 1660–1680 cm^{-1}, indicative of C=O, and a band at 3110–3080 cm^{-1}, indicative of an NH group. Compounds VI*a*–VI*e* showed a characteristic band in the region of 1100–1140 cm^{-1}, indicative of a C=S group, and a band in the region of 3100–3080 cm^{-1}, indicative of an NH group. Compounds XII*a*–XII*e* showed a characteristic band at 1660–1640 cm^{-1}, indicative of a secondary carbonyl amide, in addition to the two bands of the SO_2N group at 1360–1330 and 1180–1150 cm^{-1}. Compounds XIII*a*–XIII*c* showed two characteristic bands at 3400–3380 cm^{-1}, indicative of an OH group, and at 1665–1650 cm^{-1}, indicative of a carbonyl group. Compounds XIII*d* and XIII*e* showed a characteristic band at 1100–1220 cm^{-1}, indicative of a C=S group, in addition to the band of an OH group at 3450–3400 cm^{-1}.

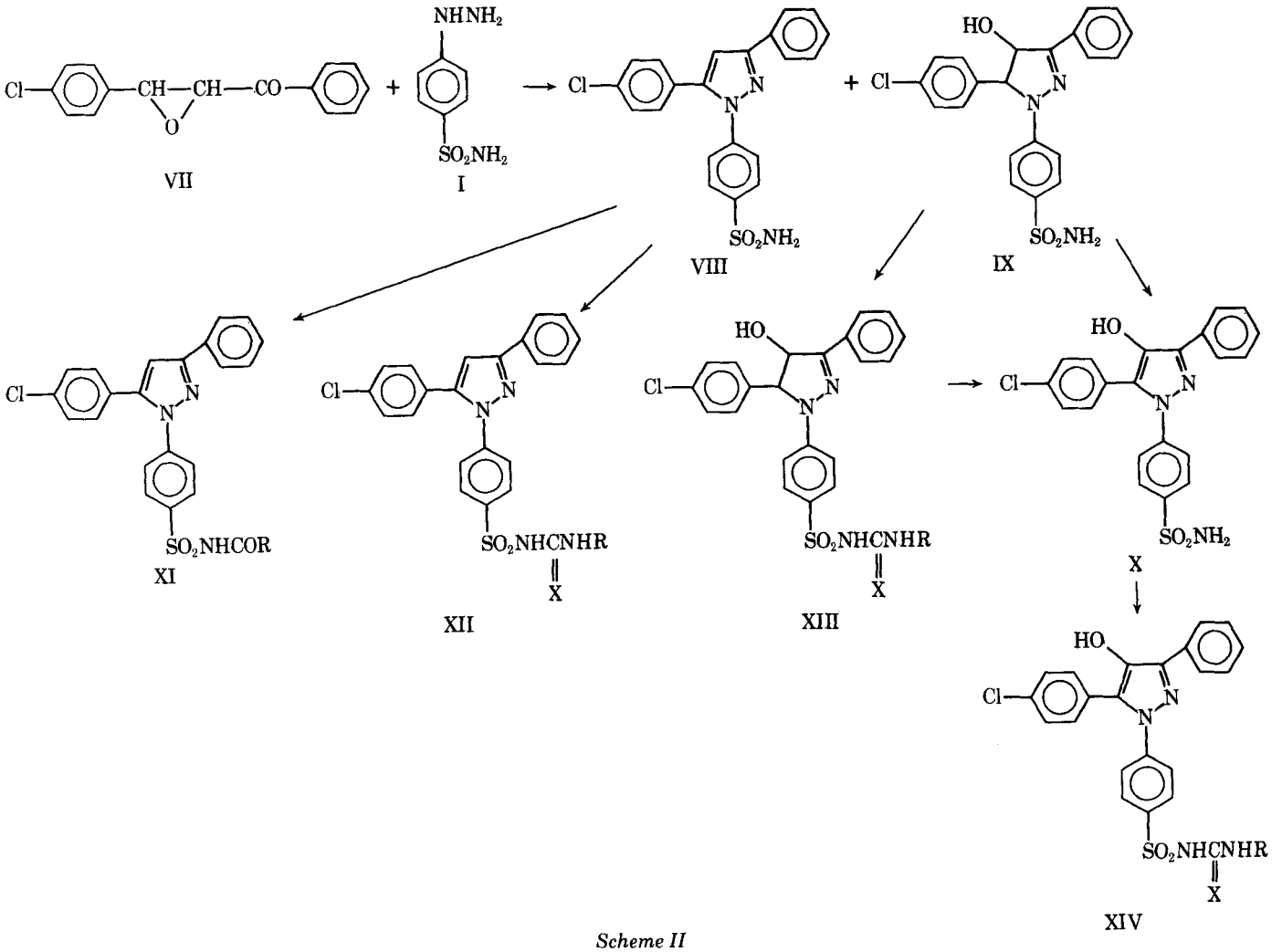
The PMR spectra of VI*c* showed aromatic protons at δ 7.2–8.0, a multiplet at δ 0.5–1.9 for the cyclohexyl protons, and a singlet at δ 6.9 due to the C-4 proton.

The PMR spectra of XIII*d* showed a multiplet in the region of δ 8.1–8.8 for the aromatic protons with the two NH protons, a triplet at δ 1.1 for the CH_3 of the ethyl group, and a quartet at δ 3.7 for the CH_2 of the ethyl group. The C-4 and C-5 protons appeared as a triplet and doublet at δ

Table III—Antidiabetic Activity of Substituted 3,5-Diarylpyrazole-1-benzenesulfonylurea Derivatives

Compound	Reduction in Plasma Glucose Level, %	*p*
Phenformin	10	<0.01[a]
III	<1	0.05
V*c*	12	<0.01[a]
V*d*	10	<0.01[a]
VI*c*	7.5	<0.01[a]
XII*c*	3	0.01[a]
XII*f*	2	0.01[a]
XIII*b*	7	<0.01[a]
XIV*b*	10	<0.01[a]

[a] Statistically significant.



Scheme II

3.3 and 1.5, respectively. The signal at δ 6.5 was due to the OH group.

Biological Testing Method—Compounds III, Vc, Vd, VIc, XIIc, XII*f*, XIII*b*, and XIV*b* 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 0.2 mmole/kg.

Each day, a group of four mice was used as the control, and one group of four mice was given the standard, 100 mg (0.4 mmole) of phenformin/kg. Up to six groups of four 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 (11). Results are expressed as a percentage reduction of plasma glucose levels compared to the control value.

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

RESULTS

Compounds Vc, Vd, VIc, XIII*b*, and XIV*b* possess marked hypoglycemic activity (Table III). The potency of these compounds, however, is more than that of phenformin (0.2 mmole of test compound/kg compared to 0.4 mmole of phenformin/kg) and much more active than 3,5-dimethylpyrazole.

From the data presented previously (8, 9) and in this study, it is obvious that many 3,5-disubstituted pyrazolebenzenesulfonylurea derivatives possess marked hypoglycemic activity. Thiourea derivatives are much less active. Introduction of a bromine atom at position 4 of the pyrazole ring increases the hypoglycemic activity of the sulfonylurea derivative. The 3-methyl-5-phenylpyrazole derivatives are much more active than their corresponding 3,5-dimethylpyrazole analogs. 3,5-Diarylpyrazolesulfonylurea derivatives are quite active as antidiabetic agents. 3,5-Diphenylpyrazole derivatives are much more active than their corresponding 3-phenyl-5-(*p*-chlorophenyl)pyrazole analogs. The presence of an hydroxy group in position 4 of the pyrazole ring of benzenesulfonylurea derivatives increases hypoglycemic activity.

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