For the above transformation, the spline function would still be fit to the untransformed response data. An alternative that might be necessary if the final concentrations are close to zero is to fit the spline function to a transformed response variable (3). However, the situation is more complicated[2] since the AUC becomes a nonlinear function of the spline parameters. In this case, the weighted jackknife (17) should be employed. Also note that this discussion relates to the within-experimental group analysis. The necessity for transformation for purposes of comparisons between experimental groups is a separate consideration. For instance, in the analysis of the study data, a log transformation was employed in the hope of achieving homogeneity of the within-infestation group variance for the liver fluke data. However, the results were similar to the untransformed case and, thus, were not reported.

The jackknife estimate of variance is known to be slightly inflated in theory (24)[1]. However, this is a minor defect since the standard error estimates from nonlinear regression procedures are often optimistically low (25)[1], and the jackknife precision estimates are closer to reality because they are data based. The results of a study which examined the jackknife estimation of rate constants for multiexponential functions fitted to biochemical data seemed to corroborate this claim (26).

The chief drawback to the widespread use of the jackknife has been concern about computational issues. However, with growing sophistication of computers, software packages, and more efficient jackknife procedures (18, 27), this may no longer be an issue. As noted above, the entire model estimation procedure developed in this paper can be automatically perfomed with a SAS macro (21).

In summary, the model-independent approach gave reasonable AUC estimates and allowed for intergroup comparisons in this study (type A design, two groups studied). Careful application of this procedure should prove to be a valuable technique for type A studies. This method should also be investigated for other parameters that can be computed by model-independent methods.

REFERENCES

(1) E. L. Frome and G. J. Yakatan, *Commun. Stat. Simula. Comput.*, **B9**, 201 (1980).

(2) K. C. Yeh and K. C. Kwan, *J. Pharmacokinet. Biopharm.*, **6**, 79 (1978).

(3) S. Wold, *Technometrics*, **16**, 1 (1974).

(4) F. Mosteller and J. W. Tukey, "Data Analysis and Regression," Addison-Wesley, Reading, Mass., 1977, pp. 133–162.

(5) M. Schulman, D. Valentino, S. Cifelli, and D. Ostlind, *J. Parasitol.*, **68**, 603 (1982).

(6) J. Ahlberg, F. N. Nilson, and J. L. Walsh, "The Theory of Splines and Other Applications," Academic, New York, N.Y., 1967, pp. 9–108.

(7) P. L. Smith, *Am. Statist.*, **33**, 57 (1979).

(8) T. P. Capizzi and R. D. Small, "1978 Proceedings of Stat. Comput. Sec.," American Statistical Association, Washington, D.C., 1978, pp. 218–222.

(9) L. G. Dunfield and J. F. Read, *J. Chem. Phys.*, **57**, 2178 (1971).

(10) K. C. Yeh and K. C. Kwan, *J. Pharm. Sci.*, **68**, 1120 (1979).

(11) S. Wold, *J. Phys. Chem.*, **76**, 369 (1972).

(12) P. Veng-Pedersen, *J. Pharm. Sci.*, **69**, 305 (1980).

(13) N. Draper and H. Smith, "Applied Regression Analysis," Wiley, New York, N.Y., 1981, pp. 70–124.

(14) M. J. Quenouille, *Biometrika*, **43**, 353 (1956).

(15) J. W. Tukey, *Ann. Math. Stat.*, **29**, 614 (1958).

(16) R. G. Miller, *Biometrika*, **61**, 1 (1974).

(17) D. V. Hinkley, *Technometrics*, **19**, 285 (1977).

(18) L. Oppenheimer, T. Capizzi, and G. Miwa, *Biochem. J.*, **197**, 721 (1981).

(19) B. E. Rodda, C. B. Sampson, and D. W. Smith, *J. R. Stat. Soc., C*, **24**, 309 (1975).

(20) SAS Users Guide, SAS Institute, Raleigh, N.C., 1979.

(21) H. Mehta, T. Capizzi, and L. Oppenheimer, "Proceedings of the Sixth Annual SAS Users Group International Conference," SAS Institute, Raleigh, N.C., 1981, pp. 211–216.

(22) T. P. Capizzi and R. D. Small, *Biometrics*, **35**, 855 (1979).

(23) B. Gladen, *J. Am. Stat. Assoc.*, **74**, 278 (1979).

(24) B. Efron and C. Stein, *Ann Stat.*, **9**, 586 (1981).

(25) H. Boxenbaum, S. Riegelman, and R. M. Elashoff, *J. Pharmacokinet., Biopharm.*, **2**, 123 (1974).

(26) I. A. Nimmo, A. Bauermeister, and J. E. Dale, *Anal. Biochem.*, **110**, 407 (1981).

(27) T. Fox, D. Hinkley, and K. Larntz, *Technometrics*, **22**, 29 (1980).

ACKNOWLEDGMENTS

Parts of this paper were presented at the Sixth Annual SAS Users Group International Conference, February 1980 and were included in the Conference Proceedings.

The authors thank an anonymous referee for an insightful review and for several suggestions which have been incorporated in this paper. The authors also thank B. Rodda, M. Tsianco, and K. C. Yeh for their thoughtful and helpful comments on previous drafts of the manuscript.

[2] As noted by a referee.

Synthesis and Antidiabetic Activity of Some Sulfonylurea Derivatives of 3,5-Disubstituted 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 □ Two series of 3,5-disubstituted pyrazolesulfonylurea derivatives were prepared and evaluated as hypoglycemic agents. Preliminary biological testing revealed that the new compounds possess potent hypoglycemic activity.

Keyphrases □ 3,5-Disubstituted pyrazolesulfonylurea derivatives—synthesis, potential hypoglycemic agents □ Potential hypoglycemic agents—preparation, antidiabetic activity of 3,5-disubstituted pyrazolesulfonylurea derivatives

Previous work showed that 3,5-dimethylpyrazole and its active metabolite, 5-methylpyrazole-3-carboxylic acid, had potent hypoglycemic activity (1–5). The present study, which is a continuation of previous work (6–11), describes the preparation of derivatives of 3,5-disubstituted pyrazolesulfonylureas and their evaluation as potential hypoglycemic agents.

Derivatives of *p*-[3-ethoxycarbonyl-5-α-phenyl-*p*-chlorostyryl)-1-pyrazolyl]benzenesulfonylurea and *p*-[3 - ethoxycarbonyl-5-(α-phenyl-*p*-methoxystyryl)-1-

0022-3549/83/0900-0999$01.00/0

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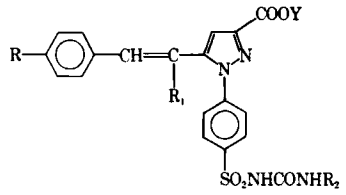
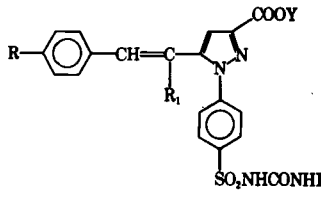
Table I—Physical and Analytical Data for the 3-Carboxy-5-substituted Styrylpyrazolylsulfonylurea Derivatives



Compound	R	R_1	Y	R_2	Yield, %	Melting Point, °	Formula	Analysis, %	Calc.	Found
V*a*	H	H	C_2H_5	$(CH_2)_3CH_3$	80	205[a]	—		—	
V*b*	H	CH_3	C_2H_5	C_6H_{11}	80	225[a]	—		—	
V*c*	H	C_6H_5	C_2H_5	$(CH_2)_3CH_3$	75	128[a]	—		—	
V*d*	Cl	C_6H_5	C_2H_5	C_2H_5	70	199[b]	$C_{29}H_{27}ClN_4O_5S$	C	60.2	60.3
								H	4.7	5.0
								Cl	6.1	6.2
								N	9.7	9.7
V*e*	Cl	C_6H_5	C_2H_5	$(CH_2)_2CH_3$	75	102[c]	$C_{30}H_{29}ClN_4O_5S$	C	60.8	61.0
								H	4.9	5.0
								Cl	6.0	6.2
								N	9.5	9.5
V*f*	Cl	C_6H_5	C_2H_5	$(CH_2)_3CH_3$	70	209[d]	$C_{31}H_{31}ClN_4O_5S$	C	61.3	61.5
								H	5.1	5.1
								Cl	5.9	6.0
								N	9.2	9.2
V*g*	Cl	C_6H_5	C_2H_5	C_6H_{11}	80	229[e]	$C_{33}H_{33}ClN_4O_5S$	C	62.6	62.5
								H	5.2	5.5
								Cl	5.6	5.8
								N	8.9	9.0
V*h*	Cl	C_6H_5	C_2H_5	C_6H_5	78	238[e]	$C_{33}H_{27}ClN_4O_5S$	C	63.2	63.3
								H	4.3	4.5
								Cl	5.7	5.8
								N	8.9	9.0
VII*a*	Cl	C_6H_5	H	C_2H_5	75	200	$C_{27}H_{23}ClN_4O_5S$	C	58.9	59.1
								H	4.2	4.2
								Cl	6.4	6.3
								N	10.2	10.1
VII*b*	Cl	C_6H_5	H	$(CH_2)_2CH_3$	70	160	$C_{28}H_{23}ClN_4O_5S$	C	59.5	59.5
								H	4.4	4.5
								Cl	6.3	6.4
								N	9.9	10.0
VII*c*	Cl	C_6H_5	H	$(CH_2)_3CH_3$	68	218	$C_{29}H_{27}ClN_4O_5S$	C	60.2	60.1
								H	4.7	4.6
								Cl	6.1	6.0
								N	9.7	9.7
VII*d*	Cl	C_6H_5	H	C_6H_{11}	72	228	$C_{31}H_{29}ClN_4O_5S$	C	61.5	61.5
								H	4.8	5.0
								Cl	5.9	6.0
								N	9.3	9.5
VII*e*	Cl	C_6H_5	H	C_6H_5	78	230	$C_{31}H_{23}ClN_4O_5S$	C	62.2	62.4
								H	3.8	4.0
								Cl	5.9	6.0
								N	9.4	9.5
V*i*	OCH_3	C_6H_5	C_2H_5	C_2H_5	70	215[d]	$C_{30}H_{30}N_4O_6S$	C	62.7	63.0
								H	5.2	5.3
								N	9.8	10.0
								S	5.6	5.6
V*j*	OCH_3	C_6H_5	C_2H_5	$(CH_2)_2CH_3$	75	181[b]	$C_{31}H_{32}N_4O_6S$	C	63.3	63.5
								H	5.4	5.5
								N	9.5	9.5
								S	5.4	5.5
V*k*	OCH_3	C_6H_5	C_2H_5	$(CH_2)_3CH_3$	70	175[b]	$C_{32}H_{34}N_4O_6S$	C	63.8	63.6
								H	5.3	5.4
								N	9.3	9.5
								S	5.3	5.2
V*l*	OCH_3	C_6H_5	C_2H_5	C_6H_{11}	75	228[e]	$C_{34}H_{36}N_4O_6S$	C	65.0	65.0
								H	5.7	5.7
								N	8.9	9.0
								S	5.1	5.0
V*m*	OCH_3	C_6H_5	C_2H_5	C_6H_5	80	240[e]	$C_{34}H_{30}N_4O_6S$	C	65.6	65.7
								H	4.8	4.7
								N	9.0	9.1
								S	5.1	5.0
VII*f*	OCH_3	C_6H_5	H	C_2H_5	68	184	$C_{28}H_{26}N_4O_6S$	C	61.5	61.5
								H	4.8	5.0
								N	10.3	10.2
								S	5.9	6.0

continued

Table I—*continued*



Compound	R	R_1	Y	R_2	Yield, %	Melting Point, °	Formula	Analysis, %	Calc.	Found
VII*g*	OCH_3	C_6H_5	H	$(CH_2)_2CH_3$	72	158	$C_{29}H_{28}N_4O_6S$	C	62.1	62.2
								H	5.0	5.0
								N	10.0	10.1
								S	5.7	5.9
VII*h*	OCH_3	C_6H_5	H	$(CH_2)_3CH_3$	75	190	$C_{30}H_{30}N_4O_6S$	C	62.7	63.0
								H	5.2	5.1
								N	9.8	10.0
								S	5.6	5.5
VII*i*	OCH_3	C_6H_5	H	C_6H_{11}	73	224	$C_{32}H_{32}N_4O_6S$	C	64.0	64.2
								H	5.3	5.1
								N	9.3	9.5
								S	5.3	5.4
VII*j*	OCH_3	C_6H_5	H	C_6H_5	78	236	$C_{32}H_{26}N_4O_6S$	C	64.6	64.7
								H	4.4	4.5
								N	9.4	9.3
								S	5.4	5.5

[a] Taken from Ref. 11. [b] Crystallized in ethanol–water. [c] Crystallized in benzene–petroleum ether. [d] Crystallized in chloroform–methanol. [e] Crystallized in methanol–benzene.

pyrazolyl]benzenesulfonylurea were prepared, and some were evaluated for hypoglycemic activity. Preliminary biological testing revealed that the new compounds possess potent hypoglycemic activity.

BACKGROUND

The pyrazole esters (III) were prepared by condensation of the appropriate ethyl 2,4-dioxo-6-(*p*-substituted phenyl)-5-phenyl-hex-5-enoate (I) with *p*-sulfamylphenylhydrazine (II). The resulting benzenesulfonamides (II), on treatment with the appropriate isocyanate or isothiocyanate in dry acetone, afforded the corresponding pyrazolesulfonylurea or thiourea derivatives (V and VI). Alkaline hydrolysis of the pyrazole esters III, V, or VI with ethanolic 2 *N* potassium hydroxide solution, afforded the corresponding pyrazole-3-carboxylic acids.

The physical and analytical data of these new pyrazoles are listed in Tables I and II. The antidiabetic activity of some of these compounds are given in Table III.

EXPERIMENTAL[1]

1 - (*p*-Sulfamylphenyl) -3- ethoxycarbonyl-5-(α-phenyl-*p*-chlorostyryl)pyrazole (III*a*)—A mixture of *p*-sulfamylphenylhydrazine (II) (0.1 mole) and ethyl 2,4-dioxo-6-(*p*-chlorophenyl)-5-phenyl-hex-5-enoate (I) (0.1 mole) in ethanol (150 ml) was refluxed for 6 hr on a steam bath, concentrated, and allowed to cool. The crude product was separated and recrystallized (65% yield) from ethanol, mp 196°.

The ^{1}H-NMR spectrum of III*a* showed absorption at 7.0–7.8 (m, aromatic H), 6.8 (s, 1, pyrazole H), 6.3 (s, 1, styryl H), 5.3 (s, 2, SO_2NH_2), 4.3 (q, J = 7.0 Hz, 2, $CO_2CH_2CH_3$), and 1.2 ppm (t, J = 7.0 Hz, 3 $CO_2CH_2CH_3$).

Anal.—Calc. for $C_{26}H_{22}ClN_3O_4S$: C, 61.5; H, 4.3; Cl, 7.0; N, 8.3. Found: C, 61.6; H, 4.5; Cl, 7.3; N, 8.0.

1-(*p*-Sulfamylphenyl)-3-carboxy-5-(α-phenyl-*p*-chlorostyryl)-pyrazole—A mixture of III*a* (1 g) in an ethanolic solution 2 *N* potassium hydroxide (25 ml) was refluxed for 1 hr. After concentration, cooling, and acidification with dilute hydrochloric acid, the crude pyrazole carboxylic acid crystallized. Recrystallization from ethanol gave the carboxylic acid (80% yield), mp 210°. IR showed bands at 1700–1725 (C=O), 1330–1350, and 1170–1190 cm^{-1} (SO_2N).

Anal.—Calc. for $C_{24}H_{18}ClN_3O_4S$: C, 60.1; H, 3.3; Cl, 7.4; N, 8.8. Found: C, 60.0; H, 3.5; Cl, 7.6; N, 9.1.

1 - (*p*-Sulfamylphenyl) -3- ethoxycarbonyl-5-(α-phenyl-*p*-methoxystyryl)pyrazole (III*b*)—A mixture of II (0.1 mole) and ethyl 2,4-dioxo-6-(*p*-methoxyphenyl)-5-phenyl-hex-5-enoate (0.1 mole) in ethanol (150 ml) was refluxed for 6 hr on a steam bath, concentrated, and allowed to cool. The crude product was separated and recrystallized (70% yield) from ethanol, mp 185°.

The ^{1}H-NMR spectrum of III*b* showed absorption at 6.8–7.7 (m, aromatic H), 6.7 (s, 1, pyrazole H), 6.4 (s, 1, styryl H), 5.0 (s, 2, SO_2NH_2), 4.3 (q, 2, $CO_2CH_2CH_3$), and 3.6 ppm (s, 3, OCH_3).

Anal.—Calc. for $C_{27}H_{25}N_3O_5S$: C, 64.4; H, 5.0; N, 8.3; S, 6.4. Found: C, 64.5; H, 5.0; N, 8.5; S, 6.5.

1 - (*p*-Sulfamylphenyl)-3-carboxy -5- (α-phenyl-*p*-methoxystyryl)pyrazole—A mixture of III*b* (1 g) in an ethanolic solution of potassium hydroxide (25 ml) was refluxed for 1 hr. After concentration, cooling, and acidification with dilute hydrochloric acid, the crude pyrazole carboxylic crystallized. Recrystallization from ethanol gave the carboxylic acid (78% yield), mp 108°. IR showed bands at 1700–1730 (C=O), 1330–1350, and 1170–1190 cm^{-1} (SO_2N).

Anal.—Calc. for $C_{25}H_{21}N_3O_5S$: C, 63.2; H, 4.4; N, 8.8; S, 6.7. Found: C, 63.4; H, 4.5; N, 9.0; S, 6.6.

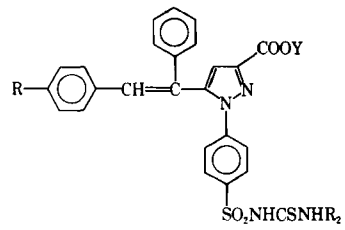
***p*-[3-Ethoxycarbonyl -5- (α-phenyl-*p*-chlorostyryl) -1- pyrazolyl]benzenesulfonylurea Derivatives (V*d–h*)**—A mixture of III*a* (0.005 mole) and anhydrous potassium carbonate (0.01 mole) in dry acetone (50 ml) was stirred at reflux for 1.5 hr. At this temperature, a solution of the appropriate isocyanate (0.01 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. The resulting solid material was dissolved in water, and the solution was acidified with 2 *N* hydrochloric acid. Recrystallization of the resulting solid from the appropriate solvent (12) gave V*d–h*.

***p* - [3-Ethoxycarbonyl -5- (α-phenyl -*p*- methoxystyryl)-1-pyrazolyl]benzenesulfonylurea Derivatives (V*i–m*)**—A mixture of III*b* (0.005 mole) and anhydrous potassium carbonate (0.01 mole) in dry acetone (50 ml) was treated with the appropriate isocyanate (0.01 mole) in dry acetone (10 ml) and completed as mentioned above.

***p*-[3-Ethoxycarbonyl -5- (α-phenyl -*p*- chlorostyryl)-1-pyrazolyl]benzenesulfonylthiourea Derivatives (VI*a–e*)**—A mixture of III*a* (0.005 mole) and anhydrous potassium carbonate (0.01 mole) in dry acetone (50 ml) was stirred and treated with the appropriate isothiocyanate (0.006 mole). The mixture was stirred at reflux for 10 hr, and the acetone was removed under reduced pressure. The resulting solid was dissolved in water, and the mixture was acidified with 2 *N* hydrochloric acid. The

[1] Melting points were determined in open glass capillaries and are uncorrected. UV spectra were measured with a Perkin-Elmer 550 S spectrophotometer. 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.

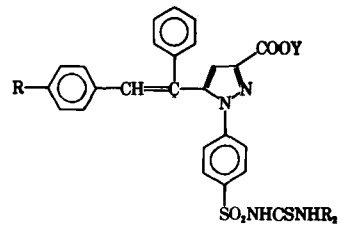
Table II—Physical and Analytical Data for the 3-Carboxy-5-substituted Styrylpyrazolylsulfonylthiourea Derivatives



Compound[a]	R	Y	R_2	Yield, %	Melting Point, °	Formula	Analysis, %	Calc.	Found
VI*a*	Cl	C_2H_5	$(CH_2)_3CH_3$	80	220	$C_{31}H_{31}ClN_4O_4S_2$	C	59.8	60.0
							H	5.0	5.1
							Cl	5.7	5.6
							N	9.0	8.9
VI*b*	Cl	C_2H_5	C_6H_{11}	82	224	$C_{33}H_{33}ClN_4O_4S_2$	C	61.1	61.0
							H	5.1	5.1
							Cl	5.5	5.4
							N	8.6	8.8
VI*c*	Cl	C_2H_5	C_6H_5	78	162	$C_{33}H_{27}ClN_4O_4S_2$	C	61.6	61.8
							H	4.2	4.5
							Cl	5.5	5.5
							N	8.7	8.5
VI*d*	Cl	C_2H_5	$C_6H_5CH_2$	80	217	$C_{34}H_{29}ClN_4O_4S_2$	C	62.1	62.3
							H	4.4	4.5
							Cl	5.4	5.3
							N	8.5	8.7
VI*e*	Cl	C_2H_5	*p*-$CH_3C_6H_4$	75	185	$C_{34}H_{29}ClN_4O_4S_2$	C	62.1	62.0
							H	4.4	4.3
							Cl	5.4	5.5
							N	8.5	8.5
VIII*a*	Cl	H	$(CH_2)_3CH_3$	70	185	$C_{29}H_{27}ClN_4O_4S_2$	C	58.5	58.7
							H	4.5	4.6
							Cl	6.0	6.1
							N	9.4	9.2
VIII*b*	Cl	H	C_6H_{11}	75	230	$C_{31}H_{29}ClN_4O_4S_2$	C	60.0	60.0
							H	4.7	4.5
							Cl	5.7	5.9
							N	9.0	8.9
VIII*c*	Cl	H	C_6H_5	73	135	$C_{31}H_{23}ClN_4O_4S_2$	C	60.5	60.3
							H	3.7	3.8
							Cl	5.8	6.0
							N	9.1	9.0
VIII*d*	Cl	H	$C_6H_5CH_2$	78	>300	$C_{32}H_{25}ClN_4O_4S_2$	C	61.1	61.0
							H	4.0	4.0
							Cl	5.6	5.7
							N	8.9	9.0
VIII*e*	Cl	H	*p*-$CH_3C_6H_4$	80	>300	$C_{32}H_{25}ClN_4O_4S_2$	C	61.1	61.3
							H	4.0	3.9
							Cl	5.6	5.5
							N	8.9	9.0
VI*f*	OCH_3	C_2H_5	$(CH_2)_3CH_3$	70	228	$C_{32}H_{34}N_4O_5S_2$	C	62.1	62.0
							H	5.5	5.4
							N	9.1	9.3
							S	10.4	10.2
VI*g*	OCH_3	C_2H_5	C_6H_{11}	76	120	$C_{34}H_{36}N_4O_5S_2$	C	63.4	63.7
							H	5.6	5.8
							N	8.7	8.6
							S	9.9	10.0
VI*h*	OCH_3	C_2H_5	C_6H_5	73	176	$C_{34}H_{30}N_4O_5S_2$	C	63.9	64.0
							H	4.7	4.5
							N	8.8	8.9
							S	10.0	9.8
VI*i*	OCH_3	C_2H_5	$C_6H_5CH_2$	78	233	$C_{35}H_{32}N_4O_5S_2$	C	64.4	64.5
							H	4.9	5.0
							N	8.6	8.7
							S	9.8	9.6
VI*j*	OCH_3	C_2H_5	*p*-$CH_3C_6H_4$	80	170	$C_{35}H_{32}N_4O_5S_2$	C	64.4	64.7
							H	4.9	4.8
							N	8.6	8.5
							S	9.8	10.0
VIII*f*	OCH_3	H	$(CH_2)_3CH_3$	77	190	$C_{30}H_{30}N_4O_5S_2$	C	61.0	60.8
							H	5.1	5.1
							N	9.5	9.3
							S	10.8	10.6
VIII*g*	OCH_3	H	C_6H_{11}	80	165	$C_{32}H_{32}N_4O_5S_2$	C	62.3	62.1
							H	5.2	5.3
							N	9.1	9.0
							S	10.4	10.5

continued

Table II—*continued*



Compound[a]	R	Y	R_2	Yield, %	Melting Point, °	Formula	Analysis, %	Calc.	Found
VIII*h*	OCH_3	H	C_6H_5	75	160	$C_{32}H_{26}N_4O_5S_2$	C	63.0	62.7
							H	4.3	4.4
							N	9.2	9.1
							S	10.5	10.5
VIII*i*	OCH_3	H	$C_6H_5CH_2$	72	195	$C_{33}H_{28}N_4O_5S_2$	C	63.5	63.2
							H	4.5	4.5
							N	9.0	8.8
							S	10.3	10.5
VIII*j*	OCH_3	H	p-$CH_3C_6H_4$	78	>300	$C_{33}H_{28}N_4O_5S_2$	C	63.5	63.4
							H	4.5	4.6
							N	9.0	9.2
							S	10.3	10.1

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

crude product was purified by recrystallization from the appropriate solvent.

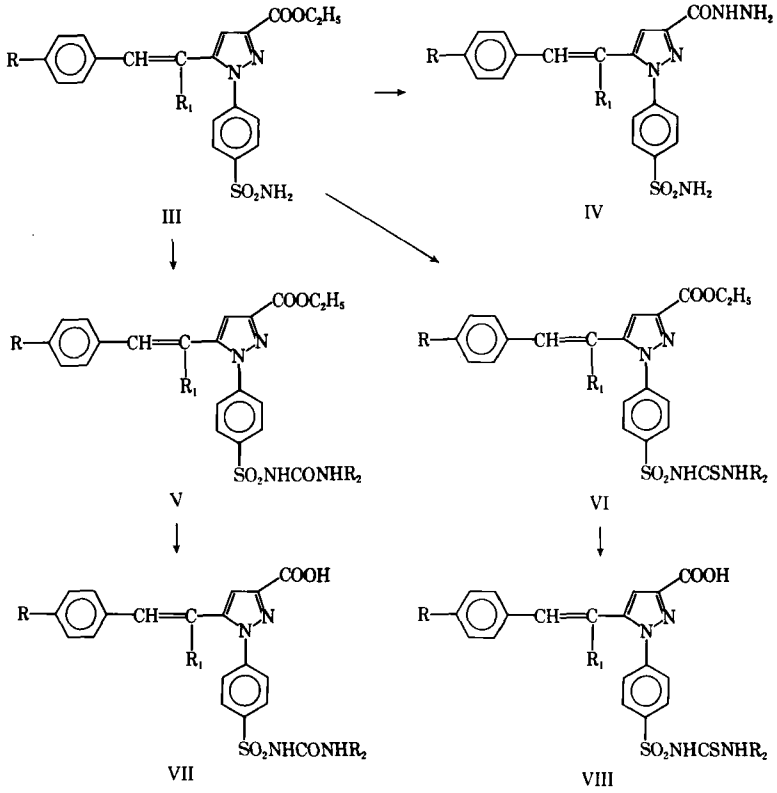
***p*-[3-Ethoxycarbonyl-5-(α-phenyl-*p*-methoxystyryl)-1-pyrazolyl]benzenesulfonylthiourea Derivatives (VI*f–j*)**—A mixture of III*b* (0.005 mole) and anhydrous potassium carbonate (0.01 mole) in dry acetone (50 ml) was stirred and treated with the appropriate isothiocyanate (0.006 mole) and completed as mentioned above.

***p*-[3-Carboxy-5-(α-phenyl-*p*-substituted styryl)-1-pyrazolyl]-benzenesulfonylurea (VII) or -thiourea (VIII) Derivatives**—A mixture of V or VI (1 g) in an ethanolic solution of 2 *N* potassium hydroxide (20 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 dilute ethanol gave either VII or VIII.

Spectra of V–VIII—The UV spectra of V–VIII showed absorption at 228–235 and 268–277 nm. The IR spectra of V–VIII showed absorption at 1700–1725 (C=O) and 1330–1360 cm^{-1} (2 bands) (SO_2N); compounds V and VII showed additional carbonyl absorption at 1650–1660 cm^{-1}, whereas compounds VI and VIII showed absorption at 1050–1200 cm^{-1}, indicative of the C=S group.

The ^1H-NMR spectrum of V*g* showed absorption at 7.8–8.2 (aromatic H), 6.8 (pyrazole H), 6.2 (s, styryl H), 4.2 (q, CH_2 of the ester), 1.5 (m, methylene H), and 1.0 ppm (t, CH_3 of the ester).

Biological Testing Method—Compounds IV, V*a–g,k,l*, VI*b,h*, VII*d,e,h* and VIII*a,g* 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



Scheme I

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.

REFERENCES

(1) J. B. Wright, W. E. Dulin, and J. H. Markillie, *J. Med. Chem.*, **7**, 102 (1964).

(2) G. C. Gerritsen and W. E. Dulin, *Diabetes*, **14**, 507 (1965).

(3) D. L. Smith, A. A. Forist, and W. E. Dulin, *J. Med. Chem.*, **8**, 350 (1965).

(4) G. C. Gerritsen and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491 (1965).

(5) D. L. Smith, A. A. Forist, and G. C. Gerritsen, *J. Pharmacol. Exp. Ther.*, **150**, 316 (1965).

(6) R. Soliman, H. Mokhtar, and E. S. El Ashry, *Pharmazie*, **33**, 184 (1978).

(7) H. Mokhtar and R. Soliman, *Pharmazie*, **33**, 649 (1978).

(8) R. Soliman, *J. Med. Chem.*, **22**, 321 (1979).

(9) R. Soliman and H. M. Feid-Allah, *J. Pharm. Sci.*, **70**, 602 (1981).

(10) R. Soliman, H. M. Feid-Allah, S. K. El Sadany, and H. F. Mohamed, *J. Pharm. Sci.*, **70**, 606 (1981).

(11) H. M. Feid-Allah, H. Mokhtar, and R. Soliman, *J. Heterocycl. Chem.*, **18**, 1561 (1981).

(12) F. J. Marshall, M. V. Sigal, and M. A. Root, *J. Med. Chem.*, **6**, 60 (1963).

(13) G. A. D. Haslewood and T. A. Strookman, *Biochem. J.*, **33**, 920 (1939).

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

0022-3549/83/0900-1004$01.00/0

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