We interpret these data to indicate that all of the lipophilic analogues at the cellular level have an activity related to the amount of active species formed within the cell and that this activity may be essentially independent of the structural parameters of the parent compound. This property would be consistent with the random chemical reaction of the parent drug in the aqueous environment of the cell to liberate the active alkylating intermediate. The parent drug structure does not influence activity, which suggests that there is no significant binding of parent drug to cellular macromolecules in the cytotoxic process. Interactions of this type are expected to be structure specific. The observation that 1-(2-chloroethyl)-1-nitrosourea analogues have the same activity at the cellular level allows the observed differences in in vivo activity to be explained primarily by differences in biodistribution. For a better understanding of the structure–activity relationship at the cellular level, the amount of active species formed during the exposure period can be considered for agents that act through a common intermediate. This approach may provide new insight into the understanding of structure–activity relationships.

Experimental Section

Chemicals. BCNU, CCNU, PCNU, CNU, and chlorozotocin were obtained from Dr. Robert Engle of the Drug Development Branch, Division of Cancer Treatment, National Cancer Institute, and stored at −20 °C. Drug solutions were prepared immediately before use by dissolving samples in ethanol and then diluted to the desired volume with distilled water.

Cells. P388 and L1210 mouse leukemia cells were obtained from EG and G Mason Research Institute. The cell lines were maintained in suspension culture by using Fischers growth medium supplemented with 10% (v/v) horse serum, 100 μg/mL of streptomycin, and 100 units/mL of penicillin G. Stock cultures were grown in stationary bottles at 37 °C, under 5% CO_2/humidified air, and maintained by diluting to 5×10^4 cells/mL every 3 to 4 days with fresh media. Approximately 24 h prior to treatment, cells were planted in 250-mL spinner flasks at a density of 3×10^5 cells/mL. Experiments were performed on cells in log phase growth (P388 doubling time, 10 to 11 h; L1210 doubling time, 7 to 8 h).

Exposure of Cells to 1-(2-Chloroethyl)-1-nitrosoureas. Immediately prior to the experiment, the cells were counted on a hemocytometer and adjusted to a concentration of 1×10^6 cells/mL. Two different types of experiments were conducted, either varying the initial drug concentration at a defined exposure period or varying the exposure period, during which a defined initial drug concentration is incubated at 37 °C and pH 7.4. In the first set of experiments, 2.0 mL of cells was added to a series of sterile glass tubes capped with a rubber stopper. Drug was added in varying amounts to duplicate tubes and allowed to incubate for the given exposure period. No drug was added to the first four tubes; however, an amount of ethanol/water equivalent to that used in the drug solution was added for the incubation period (less than 0.1% ethanol). After the exposure period, a 0.27-mL aliquot of cells from each tube was diluted in 3.8 mL of fresh media to attain a final cell concentration of 6.6×10^4 cells/mL. Cells were incubated at 37 °C for 48 h and then counted on a Coulter counter. The fraction of cells killed after exposure to the drug relative to untreated cells is correlated to the initial concentration of drug and to the amount of active alkylating species formed in the exposure period. In the second set of experiments in which the exposure time rather than initial concentration was varied, a known concentration of drug was added to 18.9 mL of cells. At various time intervals, duplicate 0.27-mL aliquots were removed and added to 3.8 mL of fresh medium. Blanks were taken from the same cells before drug was added and diluted as described above. The fraction of cells killed after exposure to drug is correlated to the time of exposure for a given initial concentration and to the amount of active alkylating species formed during each exposure period.

1-(2-Chloroethyl)-1-nitrosourea Conversion to 2-Chloroethanol. A stock solution of chlorozotocin, BCNU, or CNU dissolved in Me_2SO was added to preheated (37 °C) 0.025 M phosphate buffer to give a final concentration of 7.5 mM. Reactions were carried out in a septum capped vial at 37 °C for 2.5 to 4 h or until 90% decomposition has occurred. Ethanol was used as an internal standard. At the end of the reaction period, an aliquot was removed and analyzed by gas chromatography. 2-Chloroethanol was quantified from the peak height ratios by reference to a standard 2-chloroethanol/ethanol curve.

Acknowledgment. This work was supported by the National Cancer Institute (Grant CA-26381) and the Purdue University Cancer Center Cell Culture Laboratory (Grant CA-23168). The authors thank Pablo Ruiz-Ramon and Mike Igo for technical assistance.

Registry No. 1-(2-Chloroethyl)-1-nitrosourea, 2365-30-2; 1,3-bis(2-chloroethyl)-1-nitrosourea, 154-93-8; 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea, 13909-02-9; 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, 13010-47-4; chlorozotocin, 54749-90-5.

Antidiabetic Activity of Some 1-Substituted 3,5-Dimethylpyrazoles

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Several new 1-substituted 3,5-dimethylpyrazoles were prepared for testing as hypoglycemic agents. A number of these containing para-substituted 1-carbonylphenylurea and para-substituted 1-carbamoylbenzenesulfonylurea derivatives were found to possess potent hypoglycemic activity.

At present, it has been estimated that the incidence of persons with diabetogenic genes stands at one in every four and that the rate of increase of diabetes is approximately three times that of the population in general.[1] If this trend continues, the problems of diagnosis and treatment of the disease and accompanying cardiovascular problems will also increase.

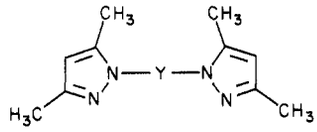
Grunwald[2] stated that there is still hope and need for oral hypoglycemic agents with mechanisms of action other than those of the compounds presently available. Preliminary work on animals revealed that 5-methylpyrazole-3-carboxylic acid derivatives very nearly approached this goal.[3-5]

† Faculty of Pharmacy.
‡ Faculty of Medicine.

(1) J. B. R. McKendry, *Appl. Ther.*, 9, 531 (1967).
(2) F. A. Grunwald, in "Medicinal Chemistry", 3rd ed., A. Burger, Ed., Wiley Interscience, New York, 1971, p 1182.

0022-2623/83/1826-1659$01.50/0

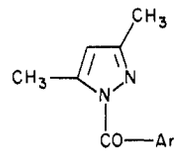
Table I. Bis[3,5-dimethylpyrazole] Derivatives



no.	Y	yield, %	mp, °C	formula	hypoglycemic act.[a]
2	CO	80	236	$C_{11}H_{14}N_4O$	2.5[b]
3	CH_2CO	70	170	$C_{12}H_{16}N_4O$	2.5[b]

[a] The reported hypoglycemic activities are the average levels at 1 and 3 h expressed as percentage reduction of the plasma glucose level compared to control value. See Experimental Section for details. 3,5-Dimethylpyrazole = $p < 0.05$, statistically significant. Phenformin = 2.5; $p < 0.05$, statistically significant. [b] Statistically significant, $p < 0.05$.

Table II. 1-Acyl-3,5-dimethylpyrazoles



no.	Ar	yield, %	mp, °C	formula	hypoglycemic act.[a]
23		80	>290	$C_{12}H_{12}N_2O_2$	<1
24		70	218–220	$C_{11}H_{11}N_3O$	<1
25		75	238–240	$C_{11}H_{11}N_3O$	<1

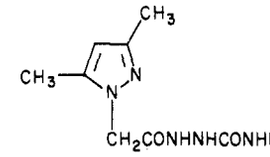
[a, b] See corresponding footnotes in Table I.

In previous work,[6] substituted 3,5-dimethylpyrazole sulfonylurea derivatives were synthesized and tested for their antidiabetic activity; some showed promising results. The present study was aimed at investigating the effect of different chemical groups substituted in position 1 of 3,5-dimethylpyrazole derivatives on antidiabetic action

Chemistry. The new pyrazoles that were prepared are listed on Tables I–VII, together with their antidiabetic activity. The majority of these compounds were prepared either by alkylation or acylation of 3,5-dimethylpyrazole or by cyclization of acyl hydrazides with 2,4-pentanedione

It has been reported that acyl hydrazides react with 1,3-diketones and ususally yield open-chain hydrazones.[7] The latter can be subsequently cyclized under the catalytic influence of phosphorus oxychloride at 0 °C to 1-acylpyrazoles in poor yields. In the present study, cyclization of 1,3-diketones with acyl hydrazides or semicarbazides could be achieved by fusion at 110 °C, in high yields (60–80%), in the absence of catalysts. This novel procedure was found useful in preparing 1-(*p*-aminobenzoyl)-3,5-dimethylpyrazole from *p*-aminobenzoic acid hydrazide and 2,4-pentanedione. This compound could not be prepared by the reported methods of cyclization because of the destructive effect of phosphorus oxychloride on the *p*-amino group of *p*-aminobenzoic acid.

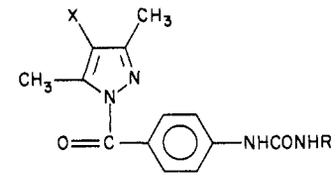
Table III. 3,5-Dimethylpyrazole-1-acetic Acid Semicarbazides



no.	R	yield, %	mp, °C	formula	hypoglycemic act.[a]
26	C_2H_5	60	187	$C_{10}H_{17}N_5O_2$	1.0
27	$(CH_2)_2CH_3$	65	175	$C_{11}H_{19}N_5O_2$	1.0
28	$(CH_2)_3CH_3$	65	161	$C_{12}H_{21}N_5O_2$	2.0
29	C_6H_{11}	70	181	$C_{14}H_{23}N_5O_2$	2.5[b]
30	$CH_2C_6H_5$	60	186	$C_{15}H_{19}N_5O_2$	<1

[a, b] See corresponding footnotes in Table I.

Table IV. [*p*-[(3,5-Dimethylpyrazol-1-yl)carbonyl]phenyl]urea Derivatives



no.	R	X	yield, %	mp, °C	formula	hypoglycemic act.[a]
31	$(CH_2)_2CH_3$	H	70	160	$C_{16}H_{20}N_4O_2$	8.0[b]
32	$(CH_2)_3CH_3$	H	75	155	$C_{17}H_{22}N_4O_2$	15.0[c]
33	C_6H_{11}	H	80	165	$C_{19}H_{24}N_4O_2$	20.0[c]
34	C_6H_5	H	72	218	$C_{19}H_{18}N_4O_2$	6.0[b]
35	$(CH_2)_2CH_3$	Br	78	112	$C_{16}H_{19}BrN_4O_2$	5.0[b]
36	$(CH_2)_3CH_3$	Br	75	195	$C_{17}H_{21}BrN_4O_2$	6.0[b]
37	C_6H_{11}	Br	80	152	$C_{19}H_{23}BrN_4O_2$	2.5[b]
38	C_6H_5	Br	60	250	$C_{19}H_{17}BrN_4O_2$	<1

[a, b] See corresponding footnotes *a* and *b* in Table I. [c] Statistically significant, $p < 0.01$.

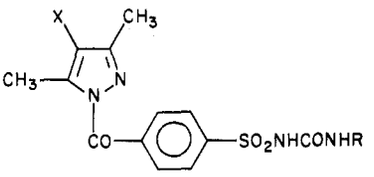
1,1′-Carbonylbis[3,5-dimethylpyrazole] (**2**) prepared by heating ethyl chloroformate with 2 equiv of 3,5-dimethylpyrazole in the presence of anhydrous potassium carbonate. 1-[(3,5-Dimethylpyrazol-1-yl)acetyl]-3,5-dimethylpyrazole (**3**) was prepared either by heating 3,5-dimethylpyrazole-1-acetic acid hydrazide with 2,4-pentanedione at 110 °C or by treating 3,5-dimethylpyrazole with half its equivalent of chloroacetyl chloride. *p*-[(3,5-Dimethylpyrazol-1-yl)carbonyl]benzenesulfonamide (**4**) was prepared by treating 3,5-dimethylpyrazole with *p*-sulfamidobenzoyl chloride (Scheme I). 1-(*p*-Aminobenzoyl)-3,5-dimethylpyrazole (**14**) was prepared by fusing *p*-aminobenzoic acid hydrazide with 2,4-pentanedione at 110 °C. *p*-[(3,5-Dimethylpyrazol-1-yl)carbamoyl]-benzenesulfonamide (**18**) was prepared by fusing *p*-sulfamylphenylsemicarbazide with 2,4-pentanedione at 110 °C (Scheme II). Treatment of compounds **4**, **14**, and **18** with the appropriate isocyanate afforded the corresponding urea derivatives. Similarly, treatment of compound **8** with the isocyanates gave the corresponding semicarbazide derivatives. Bromination of compounds **5**, **15**, **19**, and **21** afforded the corresponding 4-bromopyrazole derivatives.

Results and Discussion

From the data presented in Tables I–VII, it appears that substitution of 3,5-dimethylpyrazole in the 1-position with

(3) P. White, *Med. Clin. North Am.*, **49**, 857 (1965).
(4) D. L. Smith, A. A. Forist, and W. E. Dulin, *J. Med. Chem.*, **8**, 350 (1965).
(5) G. C. Gerritsen and W. E. Dulin, *J. Pharmacol. Exp. Ther.*, **150**, 491 (1965).
(6) R. Soliman, *J. Med. Chem.*, **22**, 321 (1979).
(7) Auwers and Dietrich, *J. Prakt. Chem.*, **139**, 65 (1934).

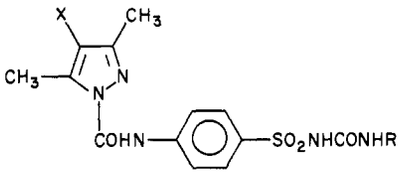
Table V. [[(3,5-Dimethylpyrazol-1-yl)benzoyl]sulfonyl]urea Derivatives



no.	R	X	yield, %	mp, °C	formula	hypoglycemic act.[a]
39	C_2H_5	H	66	226-227	$C_{15}H_{18}N_4O_4S$	<1
40	$(CH_2)_2CH_3$	H	64	151-152	$C_{16}H_{20}N_4O_4S$	<1
41	$(CH_2)_3CH_3$	H	70	186-188	$C_{17}H_{22}N_4O_4S$	2.0
42	C_6H_{11}	H	75	165-166	$C_{19}H_{24}N_4O_4S$	<1
43	C_6H_5	H	60	238-240	$C_{19}H_{18}N_4O_4S$	2.0
44	$CH_2C_6H_5$	H	68	189-190	$C_{20}H_{20}N_4O_4S$	<1
45	C_2H_5	Br	70	191-192	$C_{15}H_{17}BrN_4O_4S$	1.0
46	C_6H_{11}	Br	80	143-144	$C_{19}H_{23}BrN_4O_4S$	1.0
47	C_6H_5	Br	65	280 dec	$C_{19}H_{17}BrN_4O_4S$	3.0[b]
48	$CH_2C_6H_5$	Br	70	168-169	$C_{20}H_{19}BrN_4O_4S$	2.0

[a, b] See corresponding footnotes in Table I.

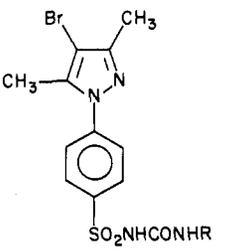
Table VI. [[[(3,5-Dimethylpyrazol-1-yl)carbamoyl]phenyl]sulfonyl]urea Derivatives



no.	R	X	yield, %	mp, °C	formula	hypoglycemic act.[a]
49	C_2H_5	H	66	170-171	$C_{15}H_{19}N_5O_4S$	4.0[b]
50	$(CH_2)_2CH_3$	H	65	148-149	$C_{16}H_{21}N_5O_4S$	6.0[c]
51	$(CH_2)_3CH_3$	H	68	80-81	$C_{17}H_{23}N_5O_4S$	7.5[c]
52	C_6H_{11}	H	75	225-226	$C_{19}H_{25}N_5O_4S$	9.0[c]
53	C_6H_5	H	60	230-231	$C_{19}H_{19}N_5O_4S$	2.0
54	$CH_2C_6H_5$	H	70	236-237	$C_{20}H_{21}N_5O_4S$	1.0
55	C_2H_5	Br	72	188-190	$C_{15}H_{18}BrN_5O_4S$	<1
56	$(CH_2)_2CH_3$	Br	70	161-162	$C_{16}H_{20}BrN_5O_4S$	1.0
57	$(CH_2)_3CH_3$	Br	75	175-176	$C_{17}H_{22}BrN_5O_4S$	2.0
58	C_6H_{11}	Br	77	200-201	$C_{18}H_{24}BrN_5O_4S$	4.0[b]

[a, b] See corresponding footnotes in Table I. [c] Statistically significant, $p < 0.01$.

Table VII. [(3,5-Dimethyl-4-bromopyrazol-1-yl)sulfonyl]urea Derivatives



no.	R	yield, %	mp, °C	formula	hypoglycemic act.[a]
59	C_2H_5	70	195-196	$C_{14}H_{17}BrN_4O_3S$	<1
60	$(CH_2)_2CH_3$	73	181-182	$C_{15}H_{19}BrN_4O_3S$	2.0
61	$(CH_2)_3CH_3$	70	176-177	$C_{16}H_{21}BrN_4O_3S$	3.0[b]
62	C_6H_{11}	75	200-201	$C_{18}H_{23}BrN_4O_3S$	2.5[b]
63	C_6H_5	68	260-261	$C_{18}H_{17}BrN_4O_3S$	<1

[a, b] See corresponding footnotes in Table I.

groups that are easily cleaved, such as carbonyl or carbamoyl, increase hypoglycemic efficacy. Accordingly, the most active of the compounds tested, **31–34**, 36, and **50–52**, are all para-substituted 1-carbonylphenylurea and para-substituted 1-carbamoylbenzenesulfonylurea derivatives. These preliminary results show that certain 1-substituted 3,5-dimethylpyrazoles produce a larger decrease in blood glucose than 3,5-dimethylpyrazole or phenformin.

Experimental Section

Melting points were taken in open tubes and are uncorrected. Infrared spectra were measured as Nujol mulls with a Beckman IR-4210. ^1H NMR spectra were determined with a Varian EM-390 90-MHz spectrometer. Mass spectra were determined with a Perkin-Elmer R 12 spectrometer. Microanalyses were performed by the Microanalytical Unit, Faculty of Science, Cairo, Egypt.

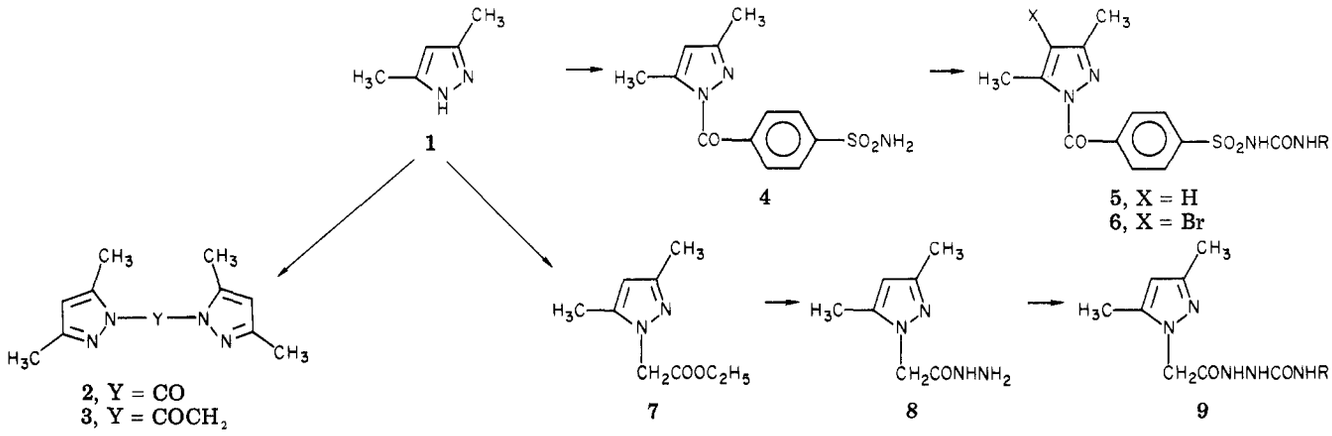
1-Acyl-3,5-dimethylpyrazoles (12). Method A. A mixture of 2,4-pentanedione (0.01 mol) and acyl hydrazide (0.01 mol) was heated at 110 °C for 0.5 h, cooled, and crystallized from the proper solvent (Table II).

Method B. To a stirred mixture of 3,5-dimethylpyrazole[8] (1; 0.1 mol), anhydrous potassium carbonate (0.1 mol), and dry benzene (75 mL) was added gradually, with cooling, the appropriate acyl chloride (0.1 mol). The reaction mixture was then heated under reflux for 0.5 h and filtered, and the filtrate was concentrated and allowed to crystallize.

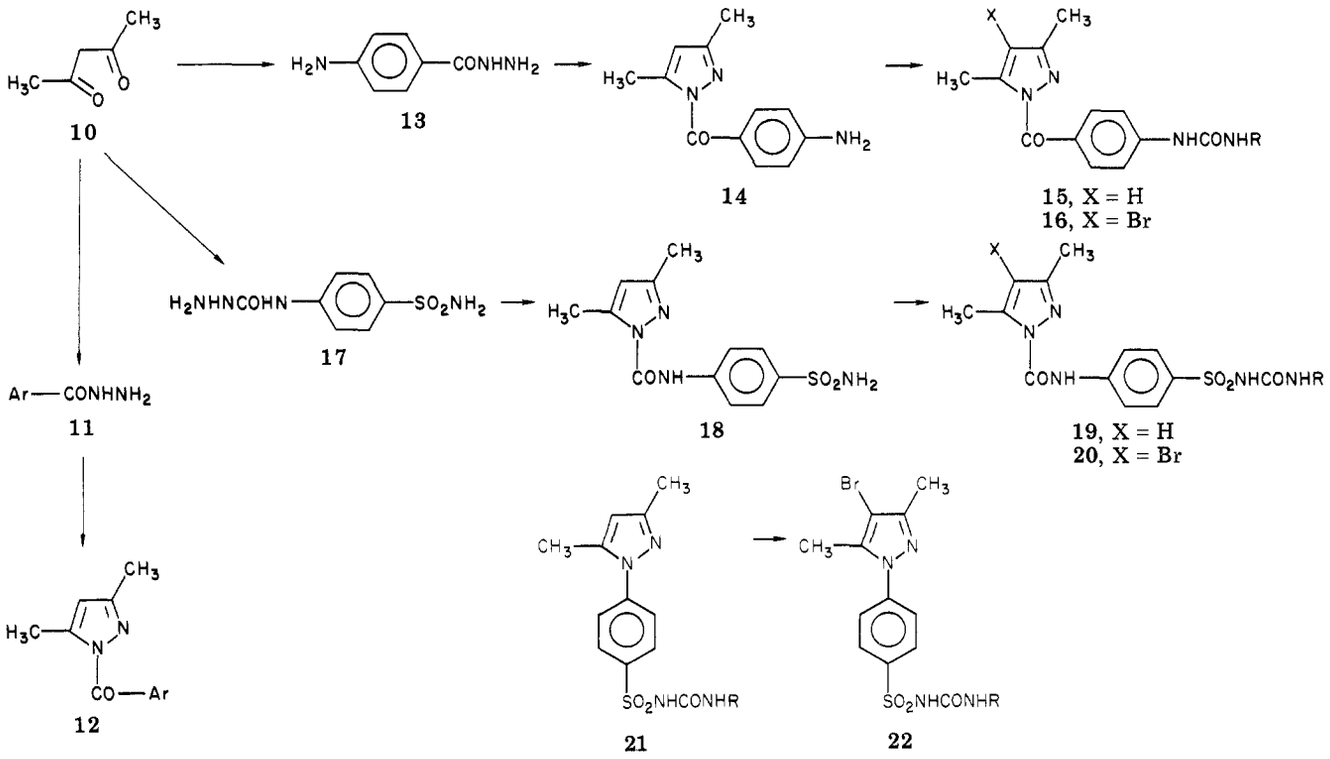
1,1′-Carbonylbis[3,5-dimethylpyrazole] (2). To a stirred mixture of 3,5-dimethylpyrazole (0.1 mol), anhydrous potassium carbonate (0.1 mol), and dry benzene (100 mL) was added

(8) R. H. Wiley, and P. E. Hexner, in "Organic Syntheses", Collect. Vol. IV, Wiley, New York, 1963, p 351.

Scheme I



Scheme II



gradually, with cooling, ethyl chloroformate (0.05 mol). The reaction mixture was then heated under reflux for 2 h and filtered hot and the filtrate was concentrated and allowed to crystallize (Table I).

Ethyl 3,5-Dimethylpyrazole-1-acetate (7). To a mixture of 1 (0.1 mol), anhydrous potassium carbonate (0.1 mol), and dry benzene (60 mL) was added gradually, with stirring, ethyl chloroacetate (0.1 mol). The reaction mixture was then refluxed for 1 h and filtered, and the filtrate was concentrated and allowed to crystallize: mp 60 °C; yield 75%.

3,5-Dimethylpyrazole-1-acetic Acid Hydrazide (8). To stirred solution of 7 (0.1 mol) in absolute ethanol (60 mL) was added 100% hydrazine hydrate (0.2 mol), and the reaction mixture was refluxed for 1 h. The crude product that separated on cooling was filtered and crystallized from ethanol: mp 198–199 °C; yield 50%.

3,5-Dimethylpyrazole-1-acetic Acid Semicarbazides (9). To a solution of 8 (0.01 mol) in anhydrous benzene (25 mL) was added, with stirring, a solution of the appropriate isocyanate (0.012 mol) in anhydrous benzene (5 mL). After the solution was stirred and refluxed for 2 h, benzene was removed under reduced pressure, and the solid residue was recrystallized from benzene (Table III).

1-[(3,5-Dimethylpyrazol-1-yl)acetyl]-3,5-dimethylpyrazole (3) was prepared either by heating 3,5-dimethylpyrazole-1-acetic acid hydrazide with an equivalent amount of 2,4-pentanedione at 110 °C for 0.5 h and purifying the crude product obtained by crystallization from ethanol or by heating 3,5-dimethylpyrazole with half its equivalent of chloroacetyl chloride in anhydrous benzene in the presence of anhydrous potassium carbonate. The reaction mixture was stirred and refluxed for 1 h and filtered hot, and the filtrate was concentrated and allowed to crystallize (Table I).

***p*-Aminobenzoic Acid Hydrazide (13).** Ethyl *p*-aminobenzoate (0.1 mol) and 100% hydrazine hydrate (0.2 mol) were fused at 110 °C for 1 h. Recrystallization from ethanol yielded 13 as needles: mp 220 °C (lit.[9] mp 220 °C); yield 90%.

1-(*p*-Aminobenzoyl)-3,5-dimethylpyrazole (14). A mixture of 13 (0.1 mol) and pentanedione (0.1 mol) was heated with stirring at 110 °C for 1 h. The crude product thus obtained was purified by recrystallization from absolute ethanol: mp 150 °C; yield 65%.

Substituted [*p*-[(3,5-Dimethylpyrazol-1-yl)carbonyl]-phenyl]urea Derivatives (15). A mixture of 14 (0.01 mol) and the appropriate isocyanate (0.012 mol) in dry benzene (30 mL) was stirred and refluxed for 2 h. The solvent was removed under

(9) "Dictionary of Organic Compounds", vol. 1, Oxford University Press, New York, p 87.

reduced pressure, and the crude product left was purified by recrystallization from ethanol (Table IV, **31–35**).

***p*-[(3,5-Dimethylpyrazol-1-yl)carbonyl]benzenesulfonamide (4).** To a stirred mixture of 3,5-dimethylpyrazole (0.1 mol), anhydrous potassium carbonate (0.1 mol), and dry benzene (100 mL) was added gradually, with cooling, *p*-sulfonamidobenzoyl chloride (0.1 mol). The reaction mixture was heated under reflux for 0.5 h and filtered hot, and the filtrate was concentrated and allowed to crystallize. Colorless crystals were obtained: mp 234–236 °C; yield 75%.

4-(*p*-Sulfamylphenyl)semicarbazide (17). To a stirred mixture of ethyl *p*-sulfamylphenylcarbamate, obtained from the reaction of sulfanilamide and ethyl chloroformate (0.1 mol) in absolute ethanol (100 mL), was added gradually, with cooling, 100% hydrazine hydrate (0.2 mol). After stirring and refluxing for 2 h, the reaction mixture was filtered, and the filtrate was concentrated and allowed to crystallize. The crude product thus obtained was filtered, washed several times with cold water to remove excess hydrazine, and recrystallized from ethanol as colorless needles, mp 232–233 °C; yield 70%.

***p*-[(3,5-Dimethylpyrazol-1-yl)carbamoyl]benzenesulfonamide (18).** A mixture of **17** (0.1 mol) and 2,4-pentanedione (0.1 mol) was stirred and fused at 110 °C for 1 h, cooled, and crystallized from ethanol: colorless crystals; mp 218 °C; yield 75%.

Substituted [(3,5-Dimethylpyrazol-1-yl)sulfonyl]urea Derivatives (5 and 19). A mixture of **4** or **18** (0.05 mol) and anhydrous potassium carbonate (0.1 mol) and dry acetone (100 mL) was stirred, and a solution of the appropriate isocyanate (0.075 mol) in dry acetone (10 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 obtained on acidification with 2 N hydrochloric acid was purified by recrystallization from ethanol/benzene (table V, **39–44** and VI, **49–54**).

1-Substituted 3,5-Dimethyl-4-bromopyrazole Derivatives (6, 16, 20, and 22). A mixture of **5**, **15**, **19**, or **21**[6] (0.05 mol) in chloroform (50 mL) was stirred with bromine (0.05 mol) for 1 h and allowed to stand for overnight. The crude product that separated was filtered and recrystallized from ethanol as colorless crystals (Tables IV, **35–38**; V, **45–48**; VI, **55–58**; and VII, **59–63**).

Biological Testing Method. The compounds in Tables I–VII were tested for hypoglycemic activity with alloxan-diabetic female albino mice weighing 20 g. Alloxan, 100 mg/kg of body weight, was injected into the tail vein in 10 mg/mL of saline solution. Six days later the mice were given test compounds (0.04 mmol/kg body weight) orally in suspension in 1% carboxymethylcellulose solution.

Each day, two groups of six mice were used as controls, and one group of six mice was given the standard drug phenformin in a dose of 100 mg (0.4 mmol/kg of body weight). Up to six groups of six mice received test compounds. Blood samples were taken at 0, 1, and 3 h. Blood glucose levels were measured at 0 h, directly after oral administration of the compound, to assess the effect of alloxan. Animals that did not show blood glucose levels of at least 125 mg/dL were excluded from the test.[10] Blood was collected into 0.04% NaF solution. Glucose was determined by the microcolorimetric copper reduction technique of Haslewood and Strookman.[11] The reported hypoglycemic activities are the average glucose levels at 1 and 3 h.

Statistical significance was assessed by means of Student's *t* test. Statistical significance was accepted where the calculated value for *t* exceeded the tabulated value for *t* at the 0.05 level of *p*.

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Registry No. **1**, 67-51-6; **2**, 50476-17-0; **3**, 87013-78-3; **4**, 36140-81-5; **7**, 10199-60-7; **8**, 64019-58-5; **13**, 5351-17-7; **14**, 87013-79-4; **17**, 87013-80-7; **18**, 87013-81-8; **23**, 56983-69-8; **24**, 17605-86-6; **25**, 42329-05-5; **26**, 87013-82-9; **27**, 87013-83-0; **28**, 87013-84-1; **29**, 87013-85-2; **30**, 87013-86-3; **31**, 87013-87-4; **32**, 87013-88-5; **33**, 87013-89-6; **34**, 87013-90-9; **35**, 87013-91-0; **36**, 87013-92-1; **37**, 87039-26-7; **38**, 87013-93-2; **39**, 87013-94-3; **40**, 87013-95-4; **41**, 87013-96-5; **42**, 87013-97-6; **43**, 87013-98-7; **44**, 87013-99-8; **45**, 87014-00-4; **46**, 87014-01-5; **47**, 87014-02-6; **48**, 87014-03-7; **49**, 87014-04-8; **50**, 87014-05-9; **51**, 87014-06-0; **52**, 86404-56-0; **53**, 87014-07-1; **54**, 87014-08-2; **55**, 87039-27-8; **56**, 87014-09-3; **57**, 87014-10-6; **58**, 87014-11-7; **59**, 87014-12-8; **60**, 87014-13-9; **61**, 87014-14-0; **62**, 87014-15-1; **63**, 87014-16-2; ethyl chloroacetate, 105-39-5; ethyl *p*-aminobenzoate, 94-09-7; *p*-sulfonamidobenzoyl chloride, 51594-97-9; ethyl *p*-sulfamylphenylcarbamate, 41104-55-6; ethyl chloroformate, 541-41-3; 2,4-pentanedione, 123-54-6; chloroacetyl chloride, 79-04-9.

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