Table IV—Elemental Analyses of Compounds I–III and Their Derivatives

Compound	Formula	Analysis, %—Calc.	Found
I Free alcohol	$C_{29}H_{50}O$	C 83.99	84.26
		H 12.15	12.33
I Acetate	$C_{31}H_{52}O_2$	C 81.52	81.72
		H 11.48	11.55
II Free alcohol	$C_{30}H_{50}O$	C 84.40	84.92
		H 11.80	11.78
II Acetate	$C_{32}H_{52}O_2$	C 81.99	81.95
		H 11.18	11.26
III	$C_{30}H_{50}O \cdot H_2O$	C 81.02	81.26
		H 11.79	11.80

of this fraction on silicic acid yielded β-sitosterol. TLC on alumina of several fractions eluted from the silicic acid column yielded cycloartenol. Acetylation of a fraction from the alumina column yielded, after preparative TLC, β-amyrin acetate. Examination of a petroleum ether extract of the plant which was not subjected to harsh saponification methods indicated that β-amyrin also occurs as the acetate.

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Potential Antidiabetics XII: N^1-Phenylcarbamoyl-4-arylazo(3- and/or 5-substituted)pyrazoles and Their Biological Activities

H. G. GARG▲ and CHANDRA PRAKASH

Abstract □ The promising antidiabetic candidates N^1-phenylcarbamoyl-4-arylazo-3,5-dimethylpyrazoles, N^1-phenylcarbamoyl-4-arylazo-3-methyl-5-phenylpyrazoles, and N^1-phenylcarbamoyl-4-arylazo-3,5-diphenylpyrazoles were prepared in 55–70% yield by the cyclization of 2,3,4-pentanetrione-2-arylhydrazones, 1-phenyl-2-arylhydrazono-1,2,3-butanetriones, and 1,3-diphenyl-2-arylhydrazono-1,2,3-propanetriones, respectively, with 4-phenylsemicarbazide. No significant antidiabetic effects were observed in pharmacological testing of these compounds except for N^1-phenylcarbamoyl-4-(2,3-dimethylphenylazo)-3,5-dimethylpyrazole.

Keyphrases □ Antidiabetic agents, potential—synthesis and biological activity of N^1-phenylcarbamoyl-4-arylazo(3- and/or 5-substituted)pyrazoles □ Pyrazoles, N^1-phenylcarbamoyl-4-arylazo(3- and/or 5-substituted)—synthesis as potential antidiabetic agents, biological activity □ N^1-Phenylcarbamoyl-4-arylazo(3- and/or 5-substituted)pyrazoles—synthesis as potential antidiabetic agents, biological activity

The facts that N^1-phenylcarbamoyl-3,5-dimethylpyrazole possesses hypoglycemic activity 20–30 times that of tolbutamide (1) and that certain arylazohydroxyquinolines are diabetogenic (2) led to the synthesis of N^1-phenylcarbamoyl-4-arylazo-3,5-dimethylpyrazoles, N^1-phenylcarbamoyl-4-arylazo-3-methyl-5-phenylpy-

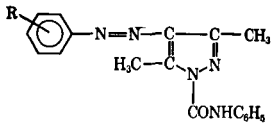

Table I—N^1-Phenylcarbamoyl-3,5-dimethyl-4-arylazopyrazoles

Compound Number	R	Yield, %	Melting Point	Color[a]	Formula	Analysis, % Calc.	Found
1	3-NO_2	58	155°	LtBN	$C_{18}H_{16}N_6O$	N 23.07	22.80
2	4-NO_2	60	183°	OP	$C_{18}H_{16}N_6O$	N 23.07	22.78
3	3-Cl	63	214°	LtON	$C_{18}H_{16}ClN_5O$	N 19.80	19.53
4	4-Cl	60	166°	YN	$C_{18}H_{16}ClN_5O$	Cl 10.04	9.84
5	2-Br	55	117°	DYP	$C_{18}H_{16}BrN_5O$	N 17.59	17.28
6	4-Br	60	123–125°	YN	$C_{18}H_{16}BrN_5O$	N 17.59	17.31
7	2-CH_3	63	108° dec.	YP	$C_{19}H_{19}N_5O$	N 21.02	20.68
8	2-CH_3O	56	138°	LtYP	$C_{19}H_{19}N_5O_2$	N 20.05	20.24
9	3-CH_3O	55	232°	YN	$C_{19}H_{19}N_5O_2$	N 20.05	19.82
10	4-CH_3O	66	169°	YN	$C_{19}H_{19}N_5O_2$	N 20.05	19.83
11	4-CH_3CH_2O	60	148°	BN	$C_{20}H_{21}N_5O_2$	N 19.28	19.02
12	2-Cl; 3-Cl	66	167°	YP	$C_{18}H_{15}Cl_2N_5O$	N 18.04 Cl 18.29	17.74 18.09
13	2-Cl; 5-Cl	60	148°	BP	$C_{18}H_{15}Cl_2N_5O$	Cl 18.92	18.19
14	2-Br; 5-Br	63	219°	YP	$C_{18}H_{15}Br_2N_5O$	Br 33.54	33.2

[a] B, brown; D, dark; Lt, light; N, needles; O, orange; P, plates; and Y, yellow.

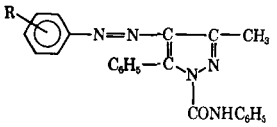

Table II—N^1-Phenylcarbamoyl-3-methyl-5-phenyl-4-arylazopyrazoles

Compound Number	R	Yield, %	Melting Point	Color[a]	Formula	Analysis, % Calc.	Found
1	2-NO_2	63	176°	ON	$C_{23}H_{18}N_6O_3$	N 19.90	19.58
2	4-NO_2	65	174°	YP	$C_{23}H_{18}N_6O_3$	N 19.90	19.49
3	3-Cl	58	293°	LtYP	$C_{23}H_{18}ClN_5O$	Cl 8.54	8.23
4	2-Br	58	190–192°	LtYP	$C_{23}H_{18}BrN_5O$	Br 17.39	17.03
5	2-CH_3	55	296°	LtBP	$C_{24}H_{21}N_5O$	N 17.72	17.93
6	4-CH_3	59	198° dec.	YP	$C_{24}H_{21}N_5O$	N 17.72	17.54
7	2-CH_3O	60	165°	YP	$C_{24}H_{21}N_5O_2$	N 17.03	17.12
8	3-CH_3O	58	243° dec.	OP	$C_{24}H_{21}N_5O_2$	N 17.03	17.31
9	2-CH_3CH_2O	63	139°	YP	$C_{25}H_{23}N_5O_2$	N 16.47	16.18
10	2-Cl; 4-Cl	60	145°	LtBP	$C_{23}H_{17}Cl_2N_5O$	Cl 15.77	15.56
11	2-Br; 4-Br	63	183°	LtOP	$C_{23}H_{17}Br_2N_5O$	Br 29.68	29.52
12	2-Br; 5-Br	58	178°	YN	$C_{23}H_{17}Br_2N_5O$	Br 29.68	29.42
13	2-CH_3; 3-CH_3	56	136°	DYP	$C_{25}H_{23}N_5O$	N 17.11	16.82
14	2-CH_3; 4-CH_3	60	121°	ON	$C_{25}H_{23}N_5O$	N 17.11	16.91
15	2-CH_3; 5-CH_3	59	146°	LtOP	$C_{25}H_{23}N_5O$	N 17.11	16.82
16	3-CH_3; 5-CH_3	59	186°	DYP	$C_{25}H_{23}N_5O$	N 17.11	17.32

[a] B, brown; D, dark; Lt, light; N, needles; O, orange; P, plates; and Y, yellow.

razoles, and N^1-phenylcarbamoyl-4-arylazo-3,5-diphenylpyrazoles. These are obtained by the condensation of 4-phenylsemicarbazide with 2,3,4-pentanetrione-3-arylhydrazone (3), 1-phenyl-2-arylhydrazono-1,2,3-butanetriones (4), and 1,3-diphenyl-2-arylhydrazono-1,2,3-propanetriones (5), respectively.

The structural evidence obtained by IR spectroscopy is in complete agreement with their assignments. The most characteristic bands are in the regions of 1515–1520 (C=C—N=N—) (6), 1640–1660 (aryl C=C) (6), and 3000–3100 (—NH—) $cm.^{-1}$.

PHARMACOLOGY

These compounds were evaluated for their antidiabetic activity in mice. Doses of 0.25–1.5 mmoles/kg. of the compounds were administered in carboxymethyl cellulose suspensions. Controls received an equal volume of the vehicle. The blood samples (0.05 ml.) obtained from retrobulbarplexuses at 0, 3, and 4 hr. after dosing were analyzed for blood sugar with the aid of an analyzing unit[1] using the modified method of Hoffman (7). No appreciable antidiabetic activity was observed for the following compounds: 4-(4-chlorophenylazo)-, 4-(4-methoxyphenylazo)-, and 4-(4-chloro-2,5-dimethoxyphenylazo)-N^1-phenylcarbamoyl-3-methyl-5-phenylpyrazoles. N^1-Phenylcarbamoyl-4-(2,3-dimethylphenylazo)-3,5-dimethylpyrazole showed hypoglycemic activity in the single preliminary test.

EXPERIMENTAL[2]

2,3,4-Pentanetrione 3-arylhydrazones (3), 1-phenyl-2-arylhydrazono-1,2,3-butanetriones (4), and 1,3-diphenyl-2-arylhydrazono-1,2,3-triones (5) were prepared according to literature routes.

[1] Technicon AutoAnalyzer.

[2] Melting points were determined on Kofler hot-stage apparatus. IR spectra were recorded on a Perkin-Elmer model 137 spectrometer.

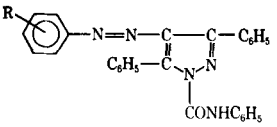

Table III—N^1-Phenylcarbamoyl-3,5-diphenyl-4-arylazopyrazoles

Compound Number	R	Yield, %	Melting Point	Color[a]	Formula	Analysis, % Calc.	Found
1	2-NO_2	60	163–165°	DYP	$C_{28}H_{20}N_6O_3$	N 17.21	17.02
2	3-NO_2	63	184°	LtON	$C_{28}H_{20}N_6O_3$	N 17.21	16.93
3	4-NO_2	60	171°	ON	$C_{28}N_{20}N_6O_3$	N 17.21	16.93
4	4-Cl	55	166°	YN	$C_{28}H_{20}ClN_5O$	Cl 7.43	7.14
5	4-Br	58	159°	YP	$C_{28}H_{20}BrN_5O$	Br 15.32	15.53
6	2-CH_3	55	175–176°	DYN	$C_{29}H_{23}N_5O$	N 15.31	15.03
7	3-CH_3	55	203°	BN	$C_{29}H_{23}N_5O$	N 15.31	15.14
8	4-CH_3	58	197°	ON	$C_{29}H_{13}N_5O$	N 15.31	14.84
9	3-CH_3O	68	157–159°	DYP	$C_{29}H_{23}N_5O_2$	N 14.79	14.63
10	4-CH_3CH_2O	63	199–201°	LtOP	$C_{30}H_{25}N_5O_2$	N 14.37	14.14
11	4-SO_2NH_2	63	154°	LtOP	$C_{28}H_{22}N_6O_3S$	N 16.09 S 6.13	15.82 5.84
12	2-Cl; 4-Cl	56	172–174°	DYP	$C_{28}H_{19}Cl_2N_5O$	Cl 13.86	13.64
13	2-Br; 4-Br	57	189°	LtON	$C_{28}H_{19}Br_2N_5O$	Br 26.62	26.42
14	2-CH_3; 5-CH_3	55	151°	YP	$C_{30}H_{25}N_5O$	N 14.83	14.73
15	3-CH_3; 5-CH_3	60	176°	LtYN	$C_{30}H_{25}N_5O$	N 14.86	14.72
16	2-CH_3CH_2O; 5-CH_3CH_2O	63	192°	OP	$C_{32}H_{29}N_5O_3$	N 13.18	13.31

[a] B, brown; D, dark; Lt, light; N, needles; O, orange; P, plates; and Y, yellow.

N^1-Phenylcarbamoyl-4-phenylazo-3,5-dimethylpyrazole—To a hot solution of 2,3,4-pentanetrione 3-phenylhydrazone (0.005 mole) in ethanol (25 ml.) was added an aqueous ethanolic solution of 4-phenylsemicarbazide (0.005 mole). The contents were shaken well and left at room temperature for 1 hr. The yellow precipitate so obtained was recrystallized from ethanol to give light-yellow plates (63%), m.p. 269°.

Anal.—Calc. for $C_{18}H_{17}N_5O$: C, 67.70; H, 5.32; N, 21.94. Found: C, 67.30; H, 5.02; N, 21.63.

The characteristics of other N^1-phenylcarbamoyl-4-arylazo-3,5-dimethylpyrazoles, prepared by a similar procedure, are given in Table I.

N^1-Phenylcarbamoyl-4-phenylazo-3-methyl-5-phenylpyrazole—An aqueous alcoholic solution of 4-phenylsemicarbazide (0.005 mole) was treated with 1-phenyl-2-phenylhydrazono-1,2,3-butanetrione (0.005 mole) in hot ethanol (25 ml.). The mixture was heated for 20 min. on a steam bath. The yellow crystals, which separated out on cooling, were filtered and washed with ethanol and recrystallized from ethanol to give yellow plates (58%), m.p. 194–195°.

Anal.—Calc. for $C_{23}H_{19}N_5O$: C, 72.44; H, 4.98; N, 18.37. Found: C, 72.22; H, 4.68; N, 18.29.

The characteristics of other N^1-phenylcarbamoyl-4-arylazo-3-methyl-5-phenylpyrazoles are given in Table II.

N^1-Phenylcarbamoyl-4-phenylazo-3,5-diphenylpyrazole—A mixture of 1,3-diphenyl-2-phenylhydrazono-1,2,3-propanetrione (0.005 mole) in ethanol (30 ml.) and an aqueous solution of 4-phenylsemicarbazide (0.005 mole) was heated under reflux for 1 hr. on a steam bath. On cooling, the shining yellow crystals separated out and were recrystallized from ethanol (65%), m.p. 181°.

Anal.—Calc. for $C_{28}H_{21}N_5O$: C, 75.87; H, 4.74; N, 15.80. Found: C, 75.59; H, 4.49; N, 15.63.

The characteristics of other N^1-phenylcarbamoyl-4-arylazo-3,5-diphenylpyrazoles are given in Table III.

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