Synthesis and Biological Activity of 1,5-Diphenyl-4-arylazopyrazoles and 5,5-Dimethylcyclohexane-1,2,3-trione Bishydrazones

HARI G. GARG[▲], ANU SINGHAL, and J. M. L. MATHUR

Abstract □ A series of 1,5-diphenyl-4-arylazopyrazoles was synthesized and evaluated for antimalarial activity. The compound possessing the best antimalarial activity of the entire study was 1,5-diphenyl-4-methoxyphenylazopyrazole. Another series of 5,5-dimethylcyclohexane-1,2,3-trione bishydrazones was prepared and tested as anthelmintics. No significant activity was observed.

Keyphrases □ 1,5-Diphenyl-4-arylazopyrazoles—synthesized and screened as potential antimalarial agents □ 5,5-Dimethylcyclohexane-1,2,3-trione bishydrazones—synthesized and screened as potential anthelmintics □ Anthelmintic agents, potential—synthesis and screening of 5,5-dimethylcyclohexane-1,2,3-trione bishydrazones □ Antimalarial agents, potential—synthesis and screening of 1,5-diphenyl-4-arylazopyrazoles

In a previous paper (1) the synthesis and biological data of N^1-substituted arylsulfonylpyrazoles (Ic) were reported. The test results on rodent malaria performed with some of these derivatives (Ic, X = 2-Cl, 4-OCH_3, or 4-NO_2) were not encouraging; the mean survival time of drug-treated, young female, noninbred ICR-HA swiss mice infected with a standard intraperitoneal inoculum of *Plasmodium berghei* (KBG-173) increased by 0.1 day compared to controls. In a search for efficient antimalarials, analogs of 1,5-diphenyl-4-arylazopyrazoles (Ia) were prepared and are reported in this article. The compounds were found to possess marked improvement in potencies over previous candidates.

In view of the anthelmintic activity displayed by Ic, a series of 5,5-dimethylcyclohexane-1,2,3-trione bishydrazones (IV) containing a few of these groupings was synthesized.

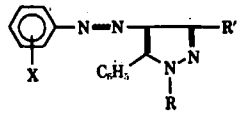


Table I—Chemical and Biological Properties of 1,5-Diphenyl-4-arylazopyrazoles[a]

Number	R	R′	X	Yield, %	Melting Point	Color[b]	Formula	Analysis, % Calc.	Analysis, % Found	Antimalarial Activity[c] D	TD	T/C	Remark
1	C_6H_5	H	H	60	180°	DR	$C_{21}H_{16}N_4$	C 77.77 H 4.93 N 17.28	77.72 4.95 17.24	320	2	3.9	Toxic
2	C_6H_5	H	4-Cl	50	195°	Y	$C_{21}H_{15}ClN_4$	C 70.29 H 4.18 N 15.62	70.24 4.28 15.41	320	2	3.9	Toxic
3	C_6H_5	H	2-OCH_3, 5-OCH_3	60	188°	B	$C_{23}H_{20}N_4O_2$	C 71.87 H 5.20 N 14.58	71.67 5.12 14.34	320	0	1.1	—
4	C_6H_5	H	4-CH_3	55	190°	Y	$C_{22}H_{18}N_4$	C 78.18 H 5.32 N 16.56	78.02 5.22 16.46	500	0	0.1	—
5	C_6H_5	H	4-OCH_3	70	206°	O	$C_{22}H_{18}N_4O$	C 74.57 H 5.08 N 15.81	74.56 5.01 15.61	320	3	4.4	Toxic
6	C_6H_5	H	2-OCH_3	65	193°	LY	$C_{22}H_{18}N_4O$	C 74.57 H 5.08 N 15.81	74.37 4.98 15.91	320	0	2.3	—
7	C_6H_5	H	2-NO_2	50	184°	O	$C_{21}H_{15}N_5O_2$	C 68.29 H 4.06 N 15.21	68.01 4.03 15.11	320	0	0.1	—
8	C_6H_5	H	4-OCH_2CH_3	50	170°	R	$C_{23}H_{20}N_4O$	C 75.00 H 5.43 N 15.21	74.92 5.31 15.11	320	3	3.9	Toxic
9	$C_6H_5CHOHCH_3$	CH_3	2-Br	—	101°[d]	—	—	—	—	320	0	0.3	—
10	$C_6H_5CHOHCH_3$	CH_3	2-NO_2	—	123°[d]	—	—	—	—	640	0	0.5	—
11	$C_6H_5CHOHCH_3$	CH_3	2-CH_3, 3-CH_3	—	78°[d]	—	—	—	—	640	0	0.3	—

[a] J. M. L. Mathur, M.S. thesis, University of Roorkee, Roorkee, India, 1971. Test data supplied by the Medicinal Chemistry Division, Walter Reed Army Institute for Research. [b] B = brown, Bk = brick, Bl = blood, Da = dark, D = dull, L = light, O = orange, R = red, and Y = yellow. [c] D = dose, mg./kg.; TD = toxic deaths attributed to drug toxicity when mice died 2–5 days postinfection of *P. berghei* (KBG-173); and T/C = increase in survival time of treated mice over controls. [d] *Reference 5.*

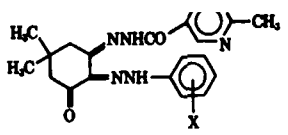


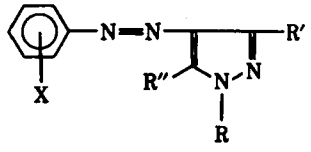
Table II—Chemical and Biological Properties Dimethylcyclohexane-1,2,3-trione Bishydrazones[a]

Number	X	Yield, %	Melting Point	Color[b]	Formula	Analysis, % Calc.	Analysis, % Found	Efficacy at Highest Tested Dose[c] T_g	N	C	O	Dose, mg./kg.
1	H	80	>270°[d]	DR	$C_{20}H_{22}N_6O_2$	C 60.91 H 5.58 N 21.31	60.72 5.34 21.41	—	0	75	0	300[e]
2	4-CH_3	78	>270°/	O	$C_{21}H_{24}N_6O_2$	C 61.76 H 5.88 N 20.58	61.56 5.82 20.68	—	0	0	0	300[e]
3	3-CH_3	75	137°	DaB	$C_{21}H_{24}N_6O_2$	C 61.76 H 5.88 N 20.68	61.66 5.85 20.60	—	—	—	—	—
4	4-OCH_3	78	264–266°/	LB	$C_{21}H_{24}N_6O_4$	C 59.43 H 5.66 N 19.81	59.23 5.43 19.79	—	0	0	0	100
5	2-OCH_3	65	152–154°/	DaB	$C_{21}H_{22}N_6O_4$	C 59.43 H 5.66 N 19.81	59.35 5.52 19.69	—	—	—	—	—
6	4-Cl	80	248–249°[d]	BlR	$C_{20}H_{21}ClN_6O_2$	C 56.00 H 4.60 N 19.60	56.20 4.59 19.42	—	—	—	—	—
7	4-Br	75	255–257°/	DaR	$C_{20}H_{21}BrN_6O_2$	C 50.73 H 4.43 N 17.75	50.53 4.22 17.55	—	0	0	0	100
8	3-NO_2	70	240–241°[d]	R	$C_{20}H_{21}N_7O_4$	C 54.66 H 4.78 N 22.32	54.46 4.52 22.22	0	0	0	0	100
9	2-NO_2	77	250–251°[d]	R	$C_{20}H_{21}N_7O_4$	C 54.66 H 4.78 N 22.32	54.56 4.42 22.30	0	0	0	50	100/400
10	2-Cl, 3-Cl	68	195–196°[d]	BkR	$C_{20}H_{20}Cl_2N_6O_2$	C 51.83 H 4.31 N 18.14	51.62 4.28 18.12	—	—	—	—	—
11	2-Cl, 4-Cl	70	180°	BkR	$C_{20}H_{20}Cl_2N_6O_2$	C 51.83 H 4.31 N 18.14	51.72 4.29 18.04	0	0	0	0	200
12	2-OCH_3, 4-OCH_3	72	215–217°	DaB	$C_{22}H_{26}N_6O_4$	C 58.14 H 5.72 N 18.50	58.04 5.70 18.48	—	—	—	—	—

[a] A. Singhal, M.S. thesis, University of Roorkee, Roorkee, India, 1971. Test data supplied by Dr. W. C. McGuire, Philips Roxane, Inc. [b] See *Footnote b* of Table I. [c] T_g = toxoplasma gondii-RH strain prevention of mortality in mice, N = nematodes, C = cestodes, and O = oxyurids. [d] Charring. [e] Approximate LD_{50}. / Decomposed.

Compounds of general structure I*a* were synthesized by the reaction of the sodium salt of oxymethyleneacetophenone (2) (II) with aryldiazonium salts to give III, which were then condensed with phenylhydrazine.

Bishydrazones (IV) were obtained by the condensation of 2-methyl-4-hydroxy-5-pyrimidylcarbohydrazide (V) with 5,5-dimethylcyclohexane-1,2,3-trione 2-arylhydrazones (VI). Compounds VI were prepared by the coupling of the diazotized anilines with 5,5-dimethylhexane-1,3-dione (3).



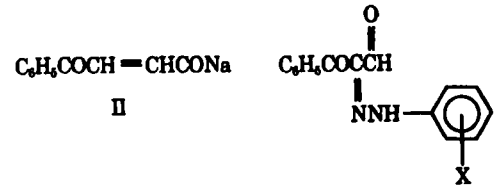
I*a*: R = R″ = C_6H_5, R′ = H

I*b*: R = $C_6H_5CHOHCH_2$, R′ = CH_3, R″ = C_6H_5

I*c*: R = —SO_2—(X), R′ = R″ = CH_3

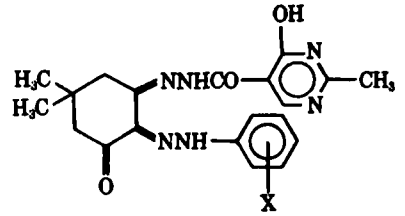
PHARMACOLOGY

Pyrazoles of series I*a* and I*b* appeared weakly active against *P. berghei* 173 in mice, increasing survival time up to 4.4 hr. over controls.

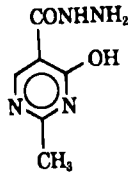


II

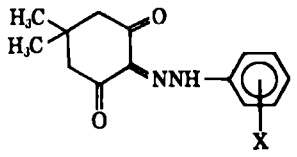
III



IV



V



VI

Anthelmintic activity testing of bishydrazone derivatives (IV) revealed that all were inactive except 2-phenyl and 2-(2-nitrophenyl) derivatives.

EXPERIMENTAL[1]

1,5-Diphenyl-4-arylazopyrazoles (Ia)—The appropriate aniline was diazotized as reported previously (4) and treated with sodium salt of oxymethyleneacetophenone (II). The precipitated arylhydrazone (III) (0.01 mole), on treatment with phenylhydrazine (0.01 mole) in ethanol and acetic acid followed by refluxing for several hours and finally cooling to room temperature, afforded pyrazole derivatives (Ia). All of these compounds were recrystallized from acetone (Table I).

5,5-Dimethylcyclohexane-1,2,3-trione, 1-(2-Methyl-n-hydroxy-5-pyrimidylcarbo)-2-(substituted phenyl) Bishydrazones (IV)—A solution of 2-arylhydrazone of 5,5-dimethylcyclohexane-1,2,3-trione (VI) (3) (0.005 mole) in ethanol (15 ml.) and 2-methyl-4-hydroxy-5-pyrimidylcarbohydrazide (V) (0.005 mole) in glacial acetic acid (1 ml.) was refluxed for 1 hr. On cooling, shining crystals of IV separated out and were recrystallized from dimethylformamide (Table II).

[1] All melting points were determined with a Kofler hot-stage-type apparatus and are uncorrected.

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Synthesis and CNS Depressant Activity of Imidazolinone Glyoxylates

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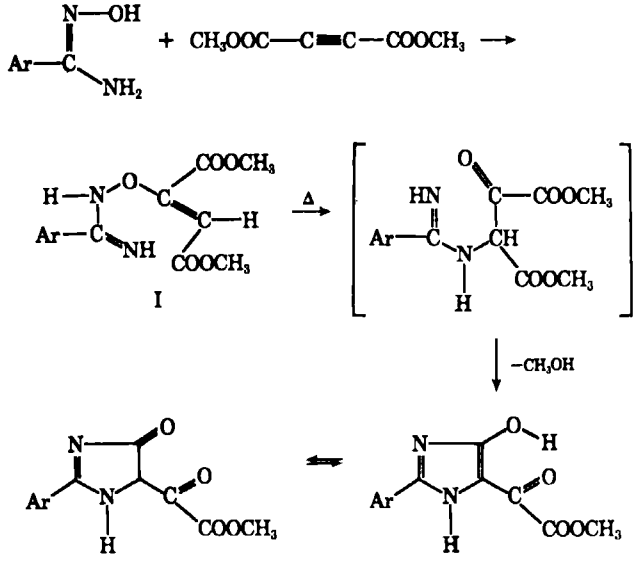
Abstract □ Six new imidazolinone glyoxylates, which exist in tautomeric equilibria with hydroxyimidazole glyoxylates, were synthesized by a new type of Claisen rearrangement and evaluated in a neuropharmacological mouse profile. CNS depression was observed in several members of the class.

Keyphrases □ Imidazolinone glyoxylates—synthesized and screened as potential CNS agents □ CNS agents, potential—synthesis and screening of imidazolinone glyoxylates □ Imidazoles—synthesis and CNS depressant activity of six imidazolinone glyoxylates

A recent publication (1) described the synthesis and characterization of a new type of imidazolinone glyoxylate (II) by the Claisen-like rearrangement of amide oxime–dimethyl acetylenedicarboxylate adducts (I). Pyrolysis of these adducts in refluxing diphenyl ether gave 41–68% yields of the tautomeric methyl 2-aryl-4-oxo-2-imidazoline-5-glyoxylates (II) (Scheme I). The impressive history of imidazoles as therapeutic agents (2, 3) and, more relevantly, the recent reports that several imidazoles function as centrally acting depressants (4–6) prompted this report of the evaluation of a new imidazole class in a primary Irwin neuropharmacological mouse profile (7).

The amide oximes utilized as starting materials were prepared by addition of hydroxylamine to aromatic nitriles. These amide oximes were condensed with dimethyl acetylenedicarboxylate to yield 1:1 adducts (I) in which —OH addition to the alkyne had occurred.



II

Scheme I