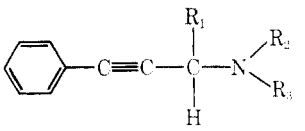
TABLE I



Compd	R_1	R_2	R_3	Mp (HCl), °C dec[a]	Yield, %	Formula	Anal[b]	Method	pK_a
I	H	H	H	216–217	51.6	$C_9H_{10}NCl$	C, H, N[c]	A	8.42
II	H	H	Me	165–166	58	$C_{10}H_{12}NCl$	C, H, N	A	8.10
III	H	H	Et	180–180.5	57	$C_{11}H_{14}NCl$	C, H, N[d]	A	8.30
IV	H	Me	Me	162–163	35.6	$C_{11}H_{14}NCl$	C, H, N	B	7.27
V	H	Et	Et	137–138	39	$C_{13}H_{18}NCl$	C, H, N	B[e,f]	8.46
VI[g]	Me	H	H	178–178.5	60	$C_{10}H_{12}NCl$	C, H, N	A[h]	7.93
VII	Me	H	Me	152.5–153	65	$C_{11}H_{14}NCl$	C, H, N	A[h]	8.21
VIII	Me	H	Et	178.5–179	60	$C_{12}H_{16}NCl$	C, H, N	A[h]	8.67
IX	Me	Me	Me	205–205.5	66	$C_{12}H_{16}NCl$	C, H, N[i]	A[h,j]	7.55
X	Me	Et	Et	134–135	55	$C_{14}H_{20}NCl$	C, H, N[k]	A[h,l]	7.57

[a] Melting points (uncorr) were taken in open capillary tubes. [b] Microanalyses were performed by Dr. C. Daessle, Organic Microanalysis, Montreal. [b] N: calcd, 8.36; found, 7.72. [d] C: calcd, 67.5; found, 68.4. [e] Water bath, 90 min. [f] Reagent II, Et_2N (Experimental Section). [g] Compounds VI–X were not resolved. [h] Reagent I, 1-phenyl-3-bromo-1-butyne (Experimental Section). [i] C: Calcd 68.7, found 69.14. [j] Five min. [k] C: Calcd 70.7, found 70.25. [l] Three days, room temperature.

ser for 30 hr. Work-up in the usual manner gave 31.7 g of the free base. Treatment of the base with HCl gas in Et_2O gave a solid which was recrystd (Me_2CO).

Antifungal Activity and Geometric Isomerism. Anilides of *o*-Coumarinic Acid

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The report by Schultz[1] that anilides of *o*-coumaric acid possessed some antifungal properties prompted the preparation of several cis analogs, anilides of *o*-coumarinic acid, for biological evaluation. Screening against *Trychophyton mentagrophytes*, *T. rubrum*, and *Candida albicans* by known methods,[2] however, showed these compounds to be inactive.

Experimental Section[3]

***o*-Hydroxy-*cis*-cinnamanilide.**—To a PhH solution of *o*-acetoxycoumarinyl chloride, prepared from 10.3 g (0.05 mole) of *o*-acetoxycoumarinic acid,[4] there was added 9.3 g (0.1 mole) of $C_6H_5NH_2$ at room temperature. After allowing the mixture to evaporate to dryness it was treated with 5% HCl. The solid obtained was then treated with 0.1 *N* NaOH for 30 min at 40–45°. Filtration and rapid acidification of the cooled filtrate (HCl) gave 5.9 g (49%) of product. Purification was effected by solution in cold EtOH and precipitation with crushed ice. Several repetitions gave mp 114–115° (trans isomer, mp 186–187°[1]). *Anal.* ($C_{15}H_{13}NO_2$) C, H.

A 1-g sample was refluxed in 95% EtOH for 1 hr. The product obtained after recrystallizing twice (EtOH 50%), melted at 186–188° (reported[1] mp 186–188°). A mixture melting point with an authentic sample of 2-hydroxycinnamanilide gave no depression; the ir spectra were identical.[5]

Acknowledgment.—Acknowledgment is made to Messrs. P. Skolnick and P. Rost who participated in this study as senior students. The author wishes to thank Mr. Leo Greenberg for his assistance with the screening of the compounds and the supply of pathogens.

(1) H. W. Schultz, *J. Pharm. Sci.*, **52**, 503 (1963).

(2) A. M. Kligman and E. J. Rosenweig, *J. Invest. Dermatol.*, **10**, 51 (1948).

(3) Melting points were determined on a Thomas-Hoover Uni-Melt and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 337 (KBr); uv spectra on a Hitachi-Coleman 124 (95% EtOH). Elemental analyses were performed by F. B. Strauss, Oxford, England.

(4) R. Stoermer and B. Ladewig, *Ber.*, **44**, 651 (1911).

(5) The 2′-methyl- and 3′-methyl-*o*-hydroxy-*cis*-cinnamanilides were also prepared. However, repeated purifications failed to give samples of analytical purity. Recrystallizations from hot polar solvents invariably led to partial or total isomerization to the trans isomer. Uv spectra on all three compounds were as expected.

Potential Antidiabetics. VI. 3-Methyl-4-arylhydrazono-2-isoxazolin-5-ones and 3-Methyl-4-arylazo-5-(methyl/phenyl)isoxazoles

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In view of the weak hypoglycemic[1–5] and chemotherapeutic[6] properties of some pyrazoles, the synthesis of 3-methyl-4-arylhydrazono-2-isoxazolin-5-ones (I), 3,5-dimethyl-4-arylazoisoxazoles (IIa), and 3-methyl-5-phenyl-4-arylazoisoxazoles (IIb) containing both isoxazolyl and either arylhydrazono or arylazo grouping was undertaken.

Oral administration at various doses (12.5 to 100 mg/kg) in fasted male guinea pigs for 18 hr prior to and during testing, of 3-methyl-4-arylhydrazono-2-isoxazolin-5-ones (I) and 3,5-dimethyl-4-arylazoisoxazoles

(1) Part V, W. U. Malik, H. G. Garg, P. P. Singh, Veena Arora, *J. Med. Chem.*, **13**, 780 (1970).

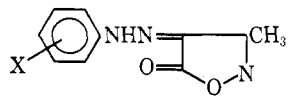
(2) H. G. Garg and P. P. Singh, *ibid.*, **11**, 1103 (1968).

(3) H. G. Garg and P. P. Singh, *ibid.*, **11**, 1104 (1968), and ref cited therein.

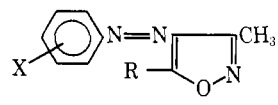
(4) H. G. Garg, D.Sc. Thesis, Agra University, Agra, India, 1969, unpublished.

(5) W. E. Dulin and G. C. Gerritsen, *Proc. Soc. Exp. Biol. Med.*, **113** 683 (1963).

(6) R. G. Micetich, *J. Med. Chem.*, **12**, 611 (1969).



I



IIa, R = CH_3
b, R = C_6H_5

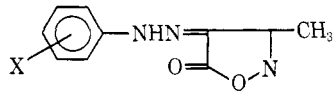
(IIa) produced essentially no hypoglycemic activity as compared to chloropropamide. After a predetermined time of peak effect the blood was analyzed for glucose with the aid of a Technician auto-analyzing unit using the modified method of Hoffman.[7]

Experimental Section

Melting points were taken with a Kofler hot-stage apparatus and are uncorrected.

Arylhydrazono Derivatives. General Procedure.—These were obtained by adapting the route of Garg, *et al.*[1-3]

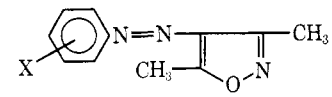
TABLE I
CHARACTERISTICS OF
3-METHYL-4-ARYLHYDRAZONO-2-ISOXAZOLIN-5-ONES



No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	H	70	186	YF	$C_{10}H_9N_3O_2$	N
2	2-NO_2	65	158	YN	$C_{10}H_8N_4O_4$	N
3	3-NO_2	60	192	PeYN	$C_{10}H_8N_4O_4$	N
4	4-NO_2	70	210	OY	$C_{10}H_8N_4O_4$	N
5	2-Me	65	155	YN	$C_{11}H_{11}N_3O_2$	N
6	3-Me	60	150	PeY	$C_{11}H_{11}N_3O_2$	N
7	4-Me	50	189–191	PeYN	$C_{11}H_{11}N_3O_2$	N
8	2-MeO	45	163	ON	$C_{11}H_{11}N_3O_3$	N
9	3-MeO	50	167–169	YN	$C_{11}H_{11}N_3O_3$	N
10	4-MeO	55	180–181	YON	$C_{11}H_{11}N_3O_3$	N
11	2-EtO	50	130	ON	$C_{12}H_{13}N_3O_3$	N
12	4-EtO	60	141	YON	$C_{12}H_{13}N_3O_3$	N
13	2,4-Me_2	50	110	ON	$C_{12}H_{13}N_3O_2$	N
14	2,5-Me_2	55	149–150	DR	$C_{12}H_{13}N_3O_4$	N
15	2,5-Cl_2	70	180	OYN	$C_{10}H_7Cl_2N_3O_2$	Cl

[a] B, brown; D, dark; F, fibres; G, golden; N, needles; O, orange; P, plates; Pe, pale; R, red; V, violet; Y, yellow.

TABLE II
CHARACTERISTICS OF 3,5-DIMETHYL-4-ARYLAZOISOXAZOLES



No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	H	60	46	PeYN	$C_{11}H_{11}N_3O$	N
2	2-NO_2	65	150–152	ON	$C_{11}H_{10}N_4O_3$	N
3	3-NO_2	60	147	GYN	$C_{11}H_{10}N_4O_3$	N
4	2-MeO	55	120	OYN	$C_{12}H_{13}N_3O_2$	N
5	3-MeO	55	58	YP	$C_{12}H_{13}N_3O_2$	N
6	4-MeO	65	100–101	PeY	$C_{12}H_{13}N_3O_2$	N
7	2-EtO	50	98	OYN	$C_{13}H_{15}N_3O_2$	N
8	4-EtO	60	76	PeYN	$C_{13}H_{15}N_3O_2$	N
9	2,4-Me_2	65	104	YN	$C_{13}H_{15}N_3O$	N
10	2,5-Me_2	60	64	YN	$C_{13}H_{15}N_3O$	N
11	2,6-Me_2	60	66	YON	$C_{13}H_{15}N_3O$	N
12	2,5-Cl_2	70	130–132	YN	$C_{11}H_9Cl_2N_3O$	Cl
13	2,5-$(MeO)_2$	55	104–105	BRN	$C_{13}H_{15}N_3O_3$	N
14	2-Cl-6-Me	65	102	ON	$C_{12}H_{12}ClN_3O$	Cl

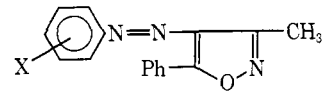
[a] See footnote *a* of Table I.

(7) W. S. Hoffman, *J. Biochem.*, **120**, 51 (1937).

3-Methyl-4-arylhydrazono-2-isoxazolin-5-ones (I).—$NH_2OH \cdot HCl$ (0.005 mole) in H_2O (5 ml) and NaOAc (1.0 g) was added to an appropriate ethyl 2,3-dioxobutyrate 2-phenylhydrazone (0.005 mole) in EtOH (20 ml). It was refluxed for 2 hr. On cooling shining crystals separated and was recrystallized from EtOH (Table I).

3,5-Dimethyl-3-methyl-5-phenyl-4-arylazoisoxazoles were prepared from 3-arylhydrazono derivatives of 1,3-diketones and $NH_2OH \cdot HCl$ as described for I analogs (see Tables II and III).

TABLE III
CHARACTERISTICS OF 3-METHYL-5-PHENYL-4-ARYLAZOISOXAZOLES



No.	X	Yield, %	Mp, °C	Color[a]	Formula	Analyses
1	H	60	97	YN	$C_{16}H_{13}N_3O$	N
2	2-NO_2	50	166–168	YF	$C_{16}H_{12}N_4O_2$	N
3	3-NO_2	60	132	OYN	$C_{16}H_{12}N_4O_3$	N
4	2-Me	55	90–91	OYN	$C_{17}H_{15}N_3O$	N
5	2-MeO	45	117	OYN	$C_{17}H_{15}N_3O_2$	N
6	3-MeO	50	88	BYN	$C_{17}H_{15}N_3O_2$	N
7	4-EtO	55	107–108	YN	$C_{18}H_{17}N_3O_2$	N
8	2,4-Me_2	65	104–105	YN	$C_{18}H_{17}N_3O$	N
9	2,5-Me_2	60	100	OYN	$C_{18}H_{17}N_3O$	N
10	2,5-Cl_2	70	174	OYN	$C_{16}H_{11}Cl_2N_3O$	Cl
11	2,6-Cl_2	65	121	OY	$C_{16}H_{11}Cl_2N_3O$	Cl
12	2,5-$(MeO)_2$	55	122–124	B	$C_{18}H_{17}N_3O_3$	N

[a] See footnote *a* of Table I.

Acknowledgment.—We thank Dr. Maxwell Gordon, Smith Kline and French Laboratories, Philadelphia, Pa., for the supply of some rare chemicals, Professor W. U. Malik, Head of this Department, for the facilities for work, and the C.S.I.R., New Delhi, for a junior Research Fellowship (to P. P. S.).

Pyrolysis of 1-Adamantyl Azidomethyl Ketone

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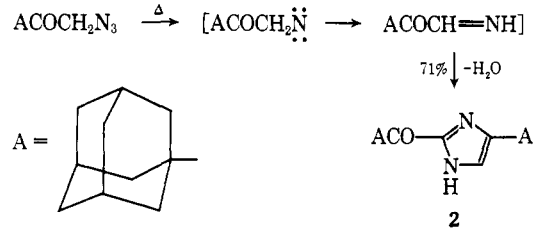
Our search for new structures in the adamantane series for testing as medicinals[1] led us to investigate the pyrolysis of the title compound **1**. A good yield



of the imidazole **2** was obtained. The mode of formation of **2** undoubtedly parallels that of the pyrolysis of phenacyl azides.[2]

* To whom correspondence should be addressed.

(1) See for instance: (a) W. L. Davies, R. R. Grunert, R. F. Haff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. C. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffmann, *Science*, **144**, 862 (1964); (b) K. Gerzon, D. J. Tobias, Sr., R. E. Holmes, R. E. Rathbun, and R. W. Kattau, *J. Med. Chem.*, **10**, 603 (1967).

(2) J. H. Boyer and D. Straw, *J. Amer. Chem. Soc.*, **74**, 4506 (1952).