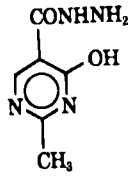
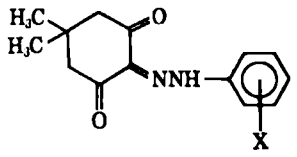


V



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

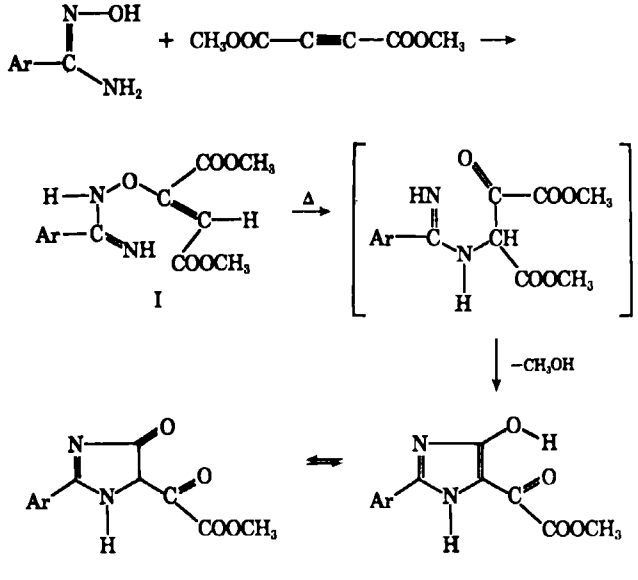
NED D. HEINDEL▲ and MARIA C. CHUN*

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

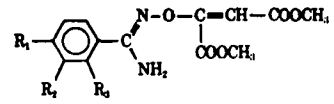


Table I—Amide Oxime–Dimethyl Acetylenedicarboxylate Adducts

Compound	R_1	R_2	R_3	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
Ia	H	H	H	61	78–79°	$C_{12}H_{14}N_2O_5$	C 56.11	56.04
							H 5.07	5.22
							N 10.07	10.22
Ib	Cl	H	H	64	57–58°	$C_{12}H_{13}ClN_2O_5$	C 49.91	49.63
							H 4.19	4.04
							N 8.96	8.72
Ic	CH_3	H	H	59	69–70°	$C_{14}H_{16}N_2O_5$	C 57.52	57.25
							H 5.52	5.62
							N 9.59	9.55
Id	H	H	CH_3	58[a]	—	—	Compound not isolated	—
								—
								—
Ie	OCH_3	OCH_3	H	64	82–84°	$C_{15}H_{18}N_2O_5$	C 58.81	59.01
							H 5.92	6.02
							N 9.15	9.32
If	CH_3	CH_3	H	62[a]	—	—	Compound not isolated	—
								—
								—

[a] Not obtained in crystalline form; viscous oils used directly for cyclization step.

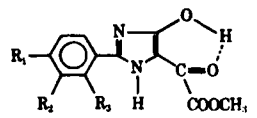


Table II—Imidazolinone Glyoxylates

Compound	R_1	R_2	R_3	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
IIa	H	H	H	68	240–242°	$C_{12}H_{10}N_2O_4$	C 58.53	58.63
							H 4.09	4.25
							N 11.38	11.20
IIb	Cl	H	H	63	256–257°	$C_{12}H_9ClN_2O_4$	C 51.35	51.49
							H 3.20	3.49
							N 9.98	10.02
IIc	CH_3	H	H	41	256–258°	$C_{13}H_{12}N_2O_4$	C 59.99	60.26
							H 4.64	4.86
							N 10.77	11.01
IId	H	H	CH_3	59	222–224°	$C_{13}H_{12}N_2O_4$	C 59.99	60.12
							H 4.64	4.50
							N 10.77	10.63
IIe	OCH_3	OCH_3	H	52	268–269°	$C_{14}H_{14}N_2O_6$	C 54.89	54.66
							H 4.61	4.63
							N 9.14	9.12
IIf	CH_3	CH_3	H	48	260–264°	$C_{14}H_{14}N_2O_4$	C 61.31	61.27
							H 5.15	5.13
							N 10.22	10.24

Simple ketoximes readily add to such acetylene esters (8). When these adducts (I) are heated to 250°, a thermal rearrangement ensues and the imidazolinones result. Several such Claisen-like transformations were reported recently (2, 8, 9).

BIOLOGICAL ACTIVITY

Compounds II*a–f* were administered as a single intraperitoneal injection in water–methylcellulose solution or suspension to each of four mice. The compounds were nontoxic at doses up to 300 mg./kg., and at that level all but II*f* effected marked depression and reduction of spontaneous motor activity. With the exception of the inactive II*f*, all of the compounds induced some writhing and an abnormal gait in the test animals. With II*a* at 300 mg./kg., there was also a loss of righting reflex. The most active member of the class appeared to be II*b*, since physiological signs (depression, lacrimation, body drop, loss of spontaneous activity, and Staub tail phenomenon) were most rapid in onset (6 min. *versus* a minimum of 15 min. for the other analogs at the 300-mg./kg. level). Furthermore, with II*b*, activity persisted down to 30 mg./kg., while no other test agent was active below 100 mg./kg. Moderate hypothermia (approximately 2.5°) was evident at 300 mg./kg. with II*b*, II*c*, and II*e*. None of the compounds was deemed sufficiently active to merit further study.

EXPERIMENTAL[1]

Preparation of the Amide Oximes—Benzamidoxime (10), *p*-chlorobenzamidoxime (11), *p*-methylbenzamidoxime (10), *o*-methylbenzamidoxime (10), and 3,4-dimethylbenzamidoxime (12) were prepared by the Method A_1 described by Eloy and Lenaers (10) and had physical properties in agreement with those reported. The yet unreported 3,4-dimethoxybenzamidoxime was synthesized by Method A_1 in 73% yield, m.p. 163–164° (from methanol).

Anal.—Calc. for $C_9H_{12}N_2O_3$: C, 55.24; H, 6.17. Found: C, 55.22; H, 6.19.

General Procedure for Preparation of Amide Oxime–Dimethyl Acetylenedicarboxylate Adducts (I*a–f*)—Equimolar quantities (0.1

[1] Melting points were obtained between cover glasses on a Fisher-Johns block and are uncorrected. Elemental analyses were provided by Dr. George I. Robertson, Microanalytical Laboratory, Florham Park, N. J.

mole) of the aromatic amide oxime and dimethyl acetylenedicarboxylate were dissolved in 100 ml. of anhydrous methanol. The mixing of the reactants was often mildly exothermic, but the solution was heated at reflux for 3 hr. to complete the reaction. The methanol was removed *in vacuo*, and the resulting oil was induced to crystallize by chilling and scratching (two exceptions as noted in Table I). These low melting solids were purified by repeated recrystallization from methanol to analytical purity.

General Procedure for Thermal Rearrangement to Imidazolinones (IIa–f)—A mixture of approximately 2.0 g. of the amide oxime–dimethyl acetylenedicarboxylate adduct and 25 ml. of diphenyl ether was heated at reflux for 2 hr. The solution was cooled to room temperature and diluted with *n*-hexane, and the precipitated solid was collected. The crude product was recrystallized from methanol with the aid of decolorizing carbon. Yields and melting points are reported in Table II.

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Differential Thermal Analysis and X-Ray Diffraction Studies of Griseofulvin–Succinic Acid Solid Dispersions

WIN LOUNG CHIOU▲ and SARFARAZ NIAZI

Abstract □ Differential thermal analysis and X-ray diffraction techniques were employed to study the phase diagrams of griseofulvin–succinic acid systems. The complications of the formation of a thermally decomposed product of succinic acid, succinic anhydride, on the thermograms were discussed. The appearance of typical eutectic peaks and X-ray diffraction peaks of griseofulvin in the resolidified preparations containing 10% or less of griseofulvin indicates that the binary system is a simple eutectic mixture with negligible mutual solid solubilities. This result is partly different from that obtained previously by the microthermal microscope technique, which showed the existence of an extensive solid solution of griseofulvin in succinic acid. The formation of a solid solution was previously concluded to be primarily responsible for the enhanced dissolution of griseofulvin.

Keyphrases □ Griseofulvin–succinic acid solid dispserions—phase diagrams, differential thermal analysis and X-ray diffraction, results compared to microthermal microscope technique □ Succinic acid–griseofulvin solid dispersions—phase diagrams, differential thermal analysis and X-ray diffraction, results compared to microthermal microscope technique □ Differential thermal analysis—phase diagrams of griseofulvin–succinic acid solid dispersions □ X-ray diffraction—phase diagrams of griseofulvin–succinic acid solid dispersions

The classification and pharmaceutical applications of solid dispersion systems were recently reviewed by Chiou and Riegelman (1). A knowledge of the physicochemical properties of a solid dispersion is very important toward an understanding of its applications. Chloramphenicol dispersed in urea was shown to result in faster dissolution and absorption rates (2, 3). The enhancement was thought primarily due to the formation of a solid solution of the drug in the carrier, urea (3). Recently, Chiou (4) used differential thermal analysis and X-ray diffraction methods to reexamine this system, and he concluded that the system is a simple eutectic mixture with negligible mutual solid solubility.

The observed enhancement in both dissolution and absorption rates must, therefore, be mainly due to the reduction of the chloramphenicol crystalline size fol-