Preparation of Some 5-Hydroxyimidazolidin-2-ones, 4-Imidazolin-2-ones, and Hydantoins from 3,4-Diphenyl-4-oxazolin-2-one

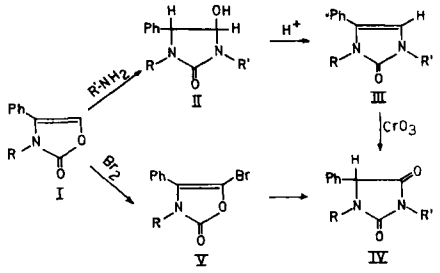
By M. F. SAETTONE and V. NUTI

A series of 1,3,4-trisubstituted 5-hydroxyimidazolidin-2-ones (II) was prepared by reaction of 3,4-diphenyl-4-oxazolin-2-one with primary amines. Compounds II were dehydrated to 4-imidazolin-2-ones (III). The action of bromine on the latter compounds, leading to 1,3,5-trisubstituted hydantoins (IV), was investigated. Compounds IV were also prepared from 5-bromo-3,4-diphenyl-4-oxazolin-2-one and primary amines. The results of some preliminary pharmacological studies are reported.

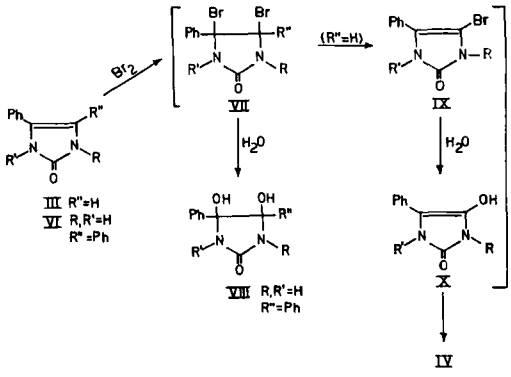
It was reported in a previous paper (1) that 5-unsubstituted 4-oxazolin 2-ones (I, Scheme I) can be converted into 5-hydroxyimidazolidin-2-ones (II) by reaction with primary amines. As a part of the structural proof, Compounds II were dehydrated to the corresponding 4-imidazolin-2-ones (III), and these were in turn oxidized to hydantoins (IV). The preparation of 1,3,5-trisubstituted hydantoins *via* a different route, involving bromination of compounds of Type I at the 5-position and reaction of the bromo derivative (V) with primary amines, was also described.

The recent discovery (2) of the potent central nervous system depressant activity shown by some 1-aminoalkyl-3-aryl derivatives of imidazolidin-2-one, prompted the authors to prepare by their method a number of 5-hydroxyimidazolidin-2-ones (II and Table I) in order to test their biological properties. It also appeared interesting to prepare the Δ^4-unsaturated (III and Table II), and 5-oxo (IV and Table III) analogs of Compounds II, in an endeavor to establish structure-activity relationships between the three related series.

All 1,3,5-trisubstituted 5-hydroxyimidazolidin-2-ones prepared in the present study were obtained by reaction of 3,4-diphenyl-4-oxazolin-2-one (I, R = Ph) with primary amines, in satisfactory yields. The dehydration of the hydroxy derivatives II to 4-imidazolin-2-ones (III), and the conversion of Compounds III into hydantoins (IV), were thoroughly reinvestigated. Best results were obtained (60–95% yields) when the dehydration was carried out with dilute sulfuric acid at room temperature, rather than with boiling acetic acid as described before (1). Chromic acid oxidation proved to be a poor method for conversion of 4-imidazolinones to hydantoins, particularly when applied to compounds bearing a 2-aminoalkyl side chain. However, it was found that bromination of Compounds III followed by crystallization of the resulting unstable bromo-derivatives from aqueous ethanol resulted in smooth conversion into hydantoins. 4-Imidazolinones bearing basic side-chains were transformed by this procedure directly into hydantoin hydrobromides. The reaction (Scheme II) probably involves addition of bromine to the double bond of Compounds III to give the dibromo derivatives VII (R″ = H), elimination of hydrogen bromide from VII to give the unstable 5-bromo derivatives IX, substitution of the bromine atom by an OH group and tautomerization of the resulting 5-hydroxy-4-imidazolinone X to the hydantoin. 4,5-Disubstituted 4-imidazolin-2-ones (such as VI) have been reported (3) to undergo a similar addition of bromine. However, substitution at the 4 and 5 position prevents elimination of hydrogen bromide, and treatment of the unstable adduct VII (R″ = Ph) with water results in formation of a 4,5-dihydroxyimidazolidin-2-one (VIII).



Scheme I



Scheme II

The hydantoins were also prepared by reaction of 5-bromo-4,5-diphenyl-4-imidazolin-2-one (V, R = Ph) with primary amines: this method gave in general higher yields, and in one case (3-allyl-1,5-diphenyl-hydantoin, Compound *25*) was the only possible route for the preparation of the desired compound. Indeed, treatment of the 1-allylimidazolone *14* with bromine gave the dibromohydantoin XI, also prepared by bromination of the hydantoin *25*.

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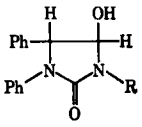
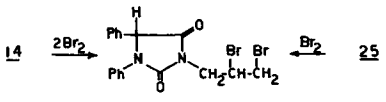
TABLE I—5-HYDROXYIMIDAZOLIDIN-2-ONES



No.	R	Recrystn. Solvent[a]	Yield, %	M.p., °C.[b]	Molecular Formula	Anal., % Calcd.	Found
1	Ethyl	E	84	163–165	$C_{17}H_{18}N_2O_2$	C, 73.32 H, 6.43 N, 9.92	C, 73.10 H, 6.52 N, 10.00
2	*n*-Propyl	E	94	121–123	$C_{18}H_{20}N_2O_2$	C, 72.92 H, 6.80 N, 9.45	C, 73.20 H, 6.83 N, 9.24
3	Allyl	E	78	160–162	$C_{18}H_{18}N_2O_2$	C, 73.45 H, 6.16 N, 9.52	C, 73.38 H, 6.22 N, 9.43
4	*n*-Butyl	B–PE	64	120–122	$C_{19}H_{22}N_2O_2$	C, 73.52 H, 7.14 N, 9.03	C, 73.72 H, 7.29 N, 9.05
5	Isobutyl	E	95	137–139	$C_{19}H_{22}N_2O_2$	C, 73.52 H, 7.14 N, 9.03	C, 73.31 H, 7.17 N, 9.15
6	Cyclohexyl	E	80	151–153	$C_{21}H_{24}N_2O_2$	C, 74.97 H, 7.19 N, 8.33	C, 75.20 H, 7.20 N, 8.35
7	Cyclopentyl	E	59	145–147	$C_{20}H_{22}N_2O_2$	C, 74.51 H, 6.88 N, 8.69	C, 74.42 H, 6.89 N, 8.64
8	2-Dimethylaminoethyl	E	58	164–166	$C_{19}H_{23}N_3O_2$	C, 70.13 H, 7.12 N, 12.91	C, 69.96 H, 7.21 N, 12.77
9	2-Diethylaminoethyl	E	57	108–110	$C_{21}H_{27}N_3O_2$	C, 71.36 H, 7.70 N, 11.89	C, 71.27 H, 7.72 N, 11.81
10	2-(1-Pyrrolidino)ethyl	E	70	166–168	$C_{21}H_{25}N_3O_2$	C, 71.77 H, 7.17 N, 11.96	C, 71.62 H, 7.40 N, 12.02
11	2-(4-Morpholino)ethyl	E	78	169–171	$C_{21}H_{25}N_3O_3$	C, 68.84 H, 6.86 N, 11.44	C, 68.70 H, 7.10 N, 11.37

[a] E, 95% ethanol; B, benzene; PE, petroleum ether, boiling range 60–80°. [b] Uncorrected.



XI

Pharmacological Results[1]—All compounds were submitted to a primary screening, aimed at detecting CNS and other activities. Compound *11* demonstrated antidepressant activity at oral doses of 300 mg./kg., when tested for the reserpine-induced depression and ptosis in mice (4). However, the degree of reversal was slight. Compounds *19*, *20*, and *21* demonstrated smooth muscle relaxant activity, when tested on the isolated guinea pig ileum (5) at the respective concentrations of 10, 10, and 1 mcg./ml. In addition, Compound *20* exhibited local anesthetic activity at a concentration of 2%, when tested against the abolition of the corneal reflex of the rabbit. All levels of activity were considered not sufficient to warrant further investigation. Interestingly, Compound *22* (Δ^4 unsaturated analog of Compound *11*) and all hydantoins were devoid of any activity.

EXPERIMENTAL[2]

1-Substituted 3,4-Diphenyl-5-hydroxyimidazolidin-2-ones (Table I)—Mixtures containing 2.37 g. (0.01 mole) of 3,4-diphenyl-4-oxazolin-2-one (I, R = Ph) (1) and 0.015 mole of a low-boiling amine (*n*-propyl, allyl, *n*-butyl, isobutyl, or cyclopentylamine) were heated 14 hr. under reflux. Similar mixtures containing higher boiling amines were heated 10–12 hr. at 120°. The mixtures were then poured into water; the product which separated was washed with water, triturated with 50% aqueous ethanol, and collected. A crystallization from 95% ethanol (or from benzene–petroleum ether) gave the pure product.

Compound *1* (R = ethyl) was prepared as follows: a suspension of the finely powdered oxazolone (5 g.) in 33% aqueous ethylamine (50 ml.) was allowed to stand 18 days at room temperature, with occasional swirling. After a few days, a clear solution was obtained from which Compound *1* slowly separated. After addition of water (100 ml.) the product was collected and purified as described before.

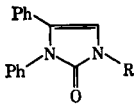
IR spectra: all compounds exhibited a carbonyl absorption band in the 5.98–6.00 μ region.

1-Substituted 3,4-Diphenyl-4-imidazolin-2-ones (Table II)—Solutions of the 5-hydroxyimidazolidinones in 95% ethanol (5 g. in 50 ml.), heated at 50°, were treated with 0.5 ml. of concentrated sulfuric acid, then were allowed to stand 2 hr. at room temperature. The solutions were then concentrated to one-third the original volume (rotary evaporator), and poured into excess water (or excess 10% sodium carbonate in the case of the basic compounds *19*, *20*, *21*, and *22*). The product which separated was collected, washed with water, and crystallized from benzene–petroleum ether.

[1] The authors are grateful to Bristol Laboratories, Syracuse, NY 13201, for the pharmacological data.

[2] All melting points were taken on a Kofler hot stage, and are uncorrected. IR spectra were recorded on Nujol mulls. All microanalyses were performed in the Microanalytical Laboratory of this Institute.

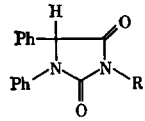
TABLE II—4-IMIDAZOLIN-2-ONES



No.	R	Recrystn. Solvent[a]	Yield, %	M.p., °C.[b]	Molecular Formula	Anal., % Calcd.	Found
12	Ethyl	B-PE	90	115–117	$C_{17}H_{16}N_2O$	C, 77.25 H, 6.10 N, 10.60	C, 77.00 H, 6.33 N, 10.72
13	*n*-Propyl	B-PE	85	121–123	$C_{18}H_{18}N_2O$	C, 77.67 H, 6.52 N, 10.07	C, 77.46 H, 6.79 N, 9.99
14	Allyl	B-PE	85	79–81	$C_{18}H_{16}N_2O$	C, 78.23 H, 5.84 N, 10.14	C, 78.03 H, 6.09 N, 9.92
15	*n*-Butyl	B-PE	95	86–88	$C_{19}H_{20}N_2O$	C, 78.05 H, 6.90 N, 9.58	C, 77.81 H, 7.12 N, 9.72
16	Isobutyl	B-PE	81	106–108	$C_{19}H_{20}N_2O$	C, 78.05 H, 6.90 N, 9.58	C, 77.92 H, 7.16 N, 9.71
17	Cyclohexyl	B-PE	77	125–127	$C_{21}H_{22}N_2O$	C, 79.21 H, 6.96 N, 8.80	C, 79.42 H, 7.20 N, 8.56
18	Cyclopentyl	B-PE	85	129–131	$C_{20}H_{20}N_2O$	C, 78.92 H, 6.62 N, 9.20	C, 78.69 H, 6.83 N, 9.28
19	2-Dimethylaminoethyl	B-PE	60	90–92	$C_{19}H_{21}N_3O$	C, 74.24 H, 6.89 N, 13.67	C, 74.18 H, 7.12 N, 13.71
20	2-Diethylaminoethyl HCl[c]	E-ET	85	218–210	$C_{21}H_{26}ClN_3O$	C, 67.81 H, 7.04 N, 11.32	C, 67.61 H, 6.89 N, 11.32
21	2-(1-Pyrrolidino)ethyl	B-PE	89	110–112	$C_{21}H_{23}N_3O$	C, 75.64 H, 6.95 N, 12.60	C, 75.52 H, 6.97 N, 12.40
22	2-(4-Morpholino)ethyl	B-PE	76	123–125	$C_{21}H_{23}N_3O_2$	C, 72.18 H, 6.63 N, 12.03	C, 72.40 H, 6.88 N, 15.80

[a] B, benzene; PE, petroleum ether, boiling range 60–80°; E, 99.5% ethanol; ET, ethyl ether. [b] Uncorrected. [c] The free base was a viscous oil which could not be induced to crystallize.

TABLE III—HYDANTOINS



No.	R	Recrystn. Solvent[a]	Yield, %[b]	M.p., °C.[c]	Molecular Formula	Anal., % Calcd.	Found
23	Ethyl	E	75 (90)	131–133	$C_{17}H_{16}N_2O_2$	C, 72.84 H, 5.75 N, 9.99	C, 72.84 H, 5.85 N, 9.95
24	*n*-Propyl	E	38 (70)	92–93	$C_{18}H_{18}N_2O_2$	C, 73.45 H, 6.16 N, 9.52	C, 73.24 H, 6.09 N, 9.50
25	Allyl	E	(76)	89–91	$C_{18}H_{16}N_2O_2$	C, 73.95 H, 5.52 N, 9.58	C, 73.80 H, 5.74 N, 9.68
26	*n*-Butyl	E	38 (97)	90–91	$C_{19}H_{20}N_2O_2$	C, 74.00 H, 6.54 N, 9.09	C, 73.84 H, 6.78 N, 9.15
27	Isobutyl	E	47 (89)	119–121	$C_{19}H_{20}N_2O_2$	C, 74.00 H, 6.54 N, 9.09	C, 73.73 H, 6.62 N, 8.91
28	Cyclohexyl	E	55 (45)	130–132	$C_{21}H_{22}N_2O_2$	C, 75.42 H, 6.63 N, 8.38	C, 75.23 H, 6.67 N, 8.46
29	Cyclopentyl	E	24 (69)	113–114	$C_{20}H_{20}N_2O_2$	C, 74.97 H, 6.29 N, 8.74	C, 74.70 H, 6.33 N, 8.87
30	2-Dimethylaminoethyl	E	79 (81)	98–99	$C_{19}H_{21}N_3O_2$	C, 70.56 H, 6.55 N, 13.00	C, 70.38 H, 6.65 N, 12.92
31	2-Diethylaminoethyl	E	65 (90)	107–108	$C_{21}H_{25}N_3O_2$	C, 71.77 H, 7.17 N, 11.96	C, 71.63 H, 7.45 N, 11.99
32	2-(1-Pyrrolidino)ethyl	E	57 (63)	120–122	$C_{21}H_{23}N_3O_2$	C, 72.18 H, 6.63 N, 12.03	C, 71.92 H, 6.81 N, 12.02
33	2-(4-Morpholino)ethyl	E	65 (63)	131–133	$C_{21}H_{23}N_3O_3$	C, 69.02 H, 6.34 N, 11.50	C, 68.64 H, 6.38 N, 11.71

[a] E, 95% ethanol. [b] The yields between parentheses refer to the preparation from 5-bromo-3,4-diphenyl-4-oxazolin-2-one and primary amines. [c] Uncorrected.

Compound *20* separated as an oil, which resisted all attempts at crystallization. It was therefore taken up in ether and characterized as the hydrochloride, m.p. 208–210.°

IR spectra: all compounds exhibited a carbonyl absorption band in the 5.92–5.95 μ region.

3-Substituted 1,5-Diphenylhydantoins (Table III) —*A: Bromination of the 4-Imidazolin-2-ones*—To a solution of the appropriate 4-imidazolinone (0.01 mole) in chloroform (50 ml.) was slowly added, at room temperature, a solution of bromine (1.9 g., 0.012 mole) in chloroform (10 ml.). The solvent was then distilled (evolution of hydrogen bromide) and the oily residue was crystallized from 95% ethanol to afford the hydantoin.

Compound *14* (R = allyl) absorbed two molar equivalents of bromine to afford in 45% yield 3-(2,3-dibromo-1-propyl)1,5-diphenylhydantoin (XI), m.p. 131–133° after crystallization from benzene–petroleum ether. The same compound was obtained on treatment of the allylhydantoin *25* with one molar equivalent of bromine, in 65% yield.

Anal.—Calcd. for $C_{18}H_{16}Br_2N_2O_2$: C, 47.81; H, 3.56; N, 6.19. Found: C, 47.83; H, 3.73; N, 6.00.

Treatment of the 4-imidazolinones *19*, *20* (as the oily base), *21*, and *22* with bromine, followed by crystallization of the oily reaction product from ethanol, afforded the hydrobromides of the hydantoins *30* (m.p. 224–226°; N% Calcd. 10.39. Found: 10.30.); *31* (m.p. 189–191°; N% Calcd. 9.72. Found: 9.56.); *32* (m.p. 258–261° dec.; N% Calcd. 9.72. Found: 9.61)., and *33* (m.p. 287–288° dec.; N% Calcd. 9.41. Found: 9.38.). The salts were converted into the free bases by treatment with 10% sodium carbonate.

B: Treatment of 5-Bromo-3,4-diphenyl-4-oxazolin-2-one (V, R = Ph) with Amines—Mixtures containing 3.16 g. (0.01 mole) of the bromooxazolone (1) and 0.015 mole of the appropriate amine were heated 6 hr. at 100°. Mixtures containing low-boiling amines (*n*-propyl, *n*-butyl, isobutyl, and allylamine) were heated at the reflux temperature of the amine for 8–10 hr. The excess amine was then distilled off at reduced pressure and the crude product was crystallized from 95% ethanol.

IR spectra: all compounds exhibited a typical hydantoin carbonyl absorption (6) (two bands in the regions 5.68–5.69 μ and 5.87–5.89 μ).

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Keyphrases

3, 4 - Diphenyl - 4 - oxazolin - 2 - one derivatives—synthesis
Pharmacological screening—3,4-diphenyl-4-oxazolin-2-one derivatives
IR spectrophotometry—structure

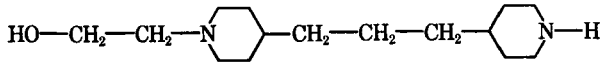
Antibacterial and Antifungal Activity of Certain β-Aminoketones

By RAJENDRA S. VARMA* and W. LEWIS NOBLES

Preliminary biological evaluation for 17 compounds is provided. Eleven compounds in this study exhibited some degree of activity.

UNDER THE CONDITIONS of the Mannich reaction, a series of β-aminoketones dihydrochlorides was synthesized utilizing 1-(*N*-β-hydroxyethyl-4-piperidyl)-3-(4-piperidyl)-propane (I) and several aromatic ketones (1). In this report, preliminary screening results for antibacterial and antifungal activities are described.

Several techniques are available to test for antimicrobial activity. Among the *in vitro* methods are dilution or agar diffusion techniques. The former methods are suitable for assay procedures, but the methods are time consuming for screening of a large number of compounds, and many of them are not satisfactory to determine antifungal activity when filamentous fungi are used as test organisms. This is particularly true if partial inhibition is studied because it is difficult to determine the amount of growth of these fungi (2). Diffusion methods such as those represented by the use of filter paper disks on an agar plate were chosen because of their suitability for water-soluble compounds and their simplicity of operation.



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* Current address: Department of Chemistry, Georgia State College, Atlanta, GA 30302