**Acknowledgment.**—We wish to thank Drs. C. I. Judd and J. H. Biel for especially helpful discussions and encouragement. Mr. E. Kluchesky is also thanked for his capable direction of the analytical services. We are indebted to Mr. D. Gauger of the Pharmacology Department for his technical work.

# Behavioral Stimulants. 4-Oxazolidinones

JOHN B. BICKING, SARA F. KWONG, MICHAEL H. FISHER, AND WILLIAM H. NICHOLSON

*Merck Sharp and Dohme Research Laboratories, Division of Merck and Company, Inc., West Point, Pennsylvania*

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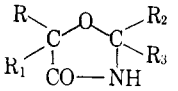
4-Oxazolidinones were synthesized by the acid-catalyzed condensation of α-hydroxyamides with acetone and other low molecular weight ketones. A number were found to have stimulant activity in animal operant behavior tests. One of the most active compounds, 2,2-dimethyl-5-styryl-4-oxazolidinone, has undergone extensive pharmacological and clinical testing.

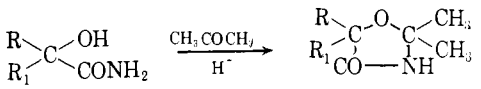
Although central nervous system (CNS) depressant activity is ordinarily associated with compounds which may be classed as cyclic amides (barbiturates, hydantoins, oxazolidinediones), stimulant and convulsant activity have been found in a number of compounds of this class.[1] 2-Imino-5-phenyl-4-oxazolidinone has recently been introduced into therapy as a CNS stimulant.[2]

Certain 4-oxazolidinones of the type I were found in these laboratories to possess stimulant properties of a magnitude and type that prompted us to prepare a series of these compounds for study.



I

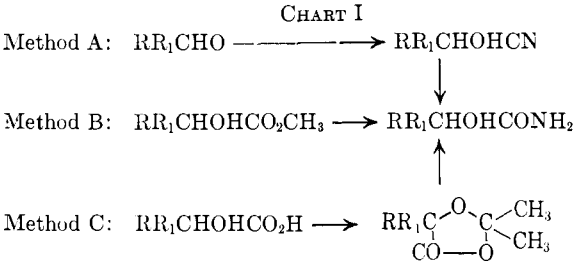
In Table I are listed 2,2-dimethyl-4-oxazolidinones prepared by the acid-catalyzed condensation of α-hydroxyamides with acetone, following the method described by Fischer, *et al.*[3] Chemical[3,4] and infrared[4,5] spectral evidence for the cyclic (oxazolidinone) struc-



ture of the condensation products of ketones and aldehydes with α-hydroxyamides has been presented.

The three methods used for the preparation of the required α-hydroxyamides are outlined in Chart I. Method A consisted of the preparation of aldehyde cyanohydrins by either of two methods and the hydrolysis of these, directly, without purification, to the α-hydroxyamides which are listed in Table II. Method B involved the ammonolysis of methyl esters of α-hydroxy acids. In method C, α-hydroxy acids were condensed with acetone to give 2,2-dimethyl-1,3-dioxolan-4-ones which were converted by ammonolysis to the α-hydroxyamides.

CHART I



When 2,2-dimethyl-5-styryl-4-oxazolidinone (IIb) was found to have outstanding stimulant activity, the condensation of the intermediate 2-hydroxy-4-phenyl-3-butenamide (IIa)[6,7] with ketones other than acetone and with benzaldehyde was studied. The resulting 4-oxazolidinones are listed in Table III. Ethyl methyl ketone was not markedly less reactive than acetone. Only one of the two possible racemates was obtained crystalline from the reaction mixture. Diethyl ketone reacted sluggishly to give the oxazolidinone in low yield. Fractional crystallization of the product from the condensation of IIa with acetylacetone gave the two racemic forms of 2-acetonyl-2-methyl-5-styryl-4-oxazolidinone.

The 4-oxazolidinones are colorless, crystalline compounds with a high degree of thermal stability, several having been purified by vacuum distillation. Their infrared spectra exhibit the characteristic[5] carbonyl absorption band in the range 1708–1722 cm.$^{-1}$ (KBr pellet). The oxazolidinones in contact with hot dilute mineral acids are rapidly hydrolyzed to the component α-hydroxyamides.

The expected derivatives of IIb were obtained by hydrogenation and bromination of the double bond. The N-methyl derivative, 2,2,3-trimethyl-5-styryl-4-oxazolidinone, was obtained by reaction of the sodio derivative of IIb with methyl iodide and was readily characterized by its infrared carbonyl absorption band at 1710 cm.$^{-1}$. The low-melting O-methyl derivative, obtained by the reaction of IIb with methyl iodide in the presence of silver oxide, was unstable and an entirely satisfactory analysis could not be obtained.

(1) P. K. Knoefel [*J. Pharmacol. Exptl. Therap.*, **84**, 26 (1945)] has reviewed the stimulant and convulsant barbituric acids.

(2) (a) L. Schmidt, *Arzneimittel-Forsch.*, **6**, 423 (1956); (b) G. A. Lienart and W. Janke, *ibid.*, **7**, 436 (1957).

(3) H. O. L. Fischer, G. Dangschat, and H. Stettiner, *Ber.*, **65**, 1032 (1932).

(4) W. Davies, T. H. Ramsay, and E. R. Stone, *J. Chem. Soc.*, 2633 (1949).

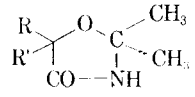
(5) K. Eichenberger, E. Ganz, and J. Druey, *Helv. Chim. Acta*, **38**, 284 (1955).

(6) R. Fittig and M. Ginsburg, *Ann.*, **299**, 23 (1898).

(7) Each α-hydroxyamide is designated by a Roman numeral followed by the letter a; the derived 2,2-dimethyl-4-oxazolidinone is designated by the same numeral followed by b.

Table I

4-Oxazolidinones by Condensation of α-Hydroxyamides with Acetone



| Compd. | R | R' | % yield[a] | Recrystn. solvent[b] | M.p.,[c] °C. | Formula | Carbon, %—Calcd. | Carbon, %—Found | Hydrogen, %—Calcd. | Hydrogen, %—Found | Nitrogen, %—Calcd. | Nitrogen, %—Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IIb | $C_6H_5CH=CH-$ | H | 80 | A | 147.5–149.0 | $C_{13}H_{15}NO_2$ | 71.86 | 71.95 | 6.90 | 7.10 | 6.45 | 6.39 |
| IIIb | $m$-$ClC_6H_4CH=CH-$ | H | 40 | B | 107.5–109.5 | $C_{13}H_{14}ClNO_2$ | 62.03 | 62.22 | 5.60 | 5.64 | 5.57 | 5.58 |
| IVb | $p$-$ClC_6H_4CH=CH-$ | H | 71 | C | 164.0–165.0 | $C_{13}H_{14}ClNO_2$ | 62.03 | 61.83 | 5.60 | 5.71 | 5.57 | 5.52 |
| Vb | $o$-$ClC_6H_4CH=CH-$ | H | 34 | C | 120.0–121.0 | $C_{13}H_{14}ClNO_2$ | 62.03 | 61.88 | 5.60 | 5.50 | 5.57 | 5.51 |
| VIb | $p$-$CH_3C_6H_4CH=CH-$ | H | 76 | A | 144.5–145.5 | $C_{14}H_{17}NO_2$ | 72.70 | 72.39 | 7.41 | 7.30 | 6.06 | 6.03 |
| VIIb | $C_6H_5CH=CH-$ | $CH_3$ | 59 | D | 142.0–143.0 | $C_{14}H_{17}NO_2$ | 72.70 | 72.59 | 7.41 | 7.38 | 6.06 | 6.01 |
| VIIIb | $C_6H_5CH=C(CH_3)-$ | H | 58 | C | 140.5–142.5 | $C_{14}H_{17}NO_2$ | 72.70 | 72.25 | 7.41 | 7.30 | 6.06 | 5.99 |
| IXb | $C_6H_5C(CH_3)=CH-$ | H | 62 | A | 132.0–133.0 | $C_{14}H_{17}NO_2$ | 72.70 | 72.49 | 7.41 | 7.20 | 6.06 | 6.10 |
| Xb | $p$-$CH_3OC_6H_4CH_2CH-$ | H | 50 | F | 79.5–81.5 | $C_{14}H_{19}NO_3$ | 67.44 | 67.51 | 7.68 | 7.56 | 5.62 | 5.58 |
| XIb | $\beta$-$C_{10}H_7$–[d] | H | 37 | C | 190.5–192.0 | $C_{16}H_{15}NO_2$ | 74.66 | 74.68 | 6.27 | 6.28 | 5.81 | 5.78 |
| XIIb | $C_6H_5OCH_2-$ | H | 71 | E | 109.0–110.0 | $C_{12}H_{15}NO_3$ | 65.13 | 64.98 | 6.83 | 6.69 | 6.33 | 6.43 |
| XIIIb | $C_6H_5CH_2-$ | H | 84 | E | 111.0–112.0 | $C_{12}H_{15}NO_2$ | 70.21 | 70.25 | 7.37 | 7.26 | 6.82 | 6.89 |
| XIVb | $C_6H_5SCH_2-$ | H | 79 | E | 102.0–103.0 | $C_{12}H_{15}NO_2S$ | 60.74 | 60.52 | 6.37 | 6.41 | 5.90 | 5.97 |
| XVb | $C_6H_5CH_2SCH_2-$ | H | 48 | B | 106.0–107.5 | $C_{13}H_{17}NO_2S$ | 62.12 | 62.31 | 6.82 | 6.79 | 5.57 | 5.51 |
| XVIb | $C_6H_5CH=CHCH_2-$ | H | 81 | E | 115.0–116.0 | $C_{14}H_{17}NO_2$ | 72.69 | 72.98 | 7.41 | 7.49 | 6.06 | 5.84 |
| XVIIb | $C_6H_5(CH_2)_3CH_2-$ | H | 47 | E | 94.5–96.0 | $C_{14}H_{19}NO_2$ | 72.07 | 71.99 | 8.21 | 8.07 | 6.00 | 5.96 |
| XVIIIb | $p$-$CH_3O(C_6H_4(CH_2)_3-$ | H | 72 | E | 74.0–75.0 | $C_{15}H_{21}NO_3$ | 68.23 | 68.39 | 8.04 | 8.09 | 5.32 | 5.31 |
| XIXb | $C_6H_5CH=CH-CH=CH-CH_2-$ | H | 53 | C | 153.0 | $C_{15}H_{17}NO_2$ | 74.66 | 73.91 | 7.05 | 7.00 | 5.76 | 5.60 |
| XXb | $C_6H_5(CH_2)_4-$ | H | 51 | H | 64.5–66.5 | $C_{15}H_{21}NO_2$ | 72.84 | 72.95 | 8.56 | 8.51 | 5.66 | 5.63 |
| XXIb | Cyclo-$C_6H_{11}CH_2CH_2-$ | H | 54 | G | 79.5–81.5 | $C_{13}H_{23}NO_2$ | 69.29 | 69.38 | 10.29 | 10.30 | 6.22 | 6.19 |
| XXII | $CH_3(CH_2)_4-$ | H | 55 | [e] | 119–123 (0.55 mm.) | $C_9H_{19}NO_2$ | 64.83 | 64.50 | 10.34 | 10.30 | 7.56 | 7.45 |

[a] Yield of product with melting point indicated. [b] A = 1-PrOH, B = 1-PrOH and $H_2O$, C = EtOH, D = MeOH and $H_2O$, E = EtOH and $H_2O$, F = benzene and petroleum ether, G = EtOAc, H = petroleum ether, J = benzene. [c] All melting points are corrected. [d] The required 2-hydroxy-2-(β-naphthyl)acetamide was prepared by the method of R. Schweitzer [*Ber.*, **24**, 547 (1891)]. [e] Uncorrected boiling range.

TABLE II

α-HYDROXYAMIDES FROM ALDEHYDE CYANOHYDRINS

RCHO → [RCHOHCN] → RCHOHCONH$_2$

| Compd. | R | Method[a] | % yield[b] | Recrystn. solvent[c] | M.p., °C.[d] | Formula | —Carbon, %— Calcd. | Found | —Hydrogen, %— Calcd. | Found | —Nitrogen, %— Calcd. | Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | $C_6H_5CH=CH-$ | A-1 | 39 | C | 141.5–142.5[e] | $C_{10}H_{11}NO_2$ | | | | | 7.91 | 7.92 |
| IIIa | $m$-$ClC_6H_4CH=CH-$ | A-1 | 47 | G | 126.5–128.0 | $C_{10}H_{10}ClNO_2$ | | | | | 6.62 | 6.62 |
| IVa | $p$-$ClC_6H_4CH=CH-$ | A-1 | 22 | B | 158.0–159.0 | $C_{10}H_{10}ClNO_2$ | 56.75 | 56.60 | 4.76 | 5.06 | 6.62 | 6.54 |
| Va | $o$-$ClC_6H_4CH=CH-$ | A-1 | 47 | G | 117.0–118.0 | $C_{10}H_{10}ClNO_2$ | | | | | 6.62 | 6.58 |
| VIa | $p$-$CH_3C_6H_4CH=CH-$ | A-1 | 40 | A | 168.0–169.0 | $C_{11}H_{13}NO_2$ | | | | | 7.33 | 7.29 |
| VIIIa | $C_6H_5CH=C(CH_3)-$ | A-1 | 39 | C | 164.0–167.0 | $C_{11}H_{13}NO_2$ | 69.09 | 68.72 | 6.85 | 6.67 | 7.33 | 7.30 |
| IXa | $C_6H_5C(CH_3)=CH-$ | A-1 | 21 | G | 133.0–135.0 | $C_{11}H_{13}NO_2$ | | | | | 7.33 | 7.28 |
| XIIIa | $C_6H_5CH_2-$ | A-2 | 40 | B | 111.0–112.0[f] | | | | | | | |
| XIIa | $C_6H_4OCH_3-$ | A-2 | 33 | C | 149.0–150.0[g] | $C_9H_{11}NO_3$ | 59.65 | 59.17 | 6.12 | 6.03 | 7.73 | 7.87 |
| XIVa | $C_6H_5SCH_2-$ | A-2 | 51 | C | 113.0–114.0 | $C_9H_{11}NO_2S$ | 54.78 | 54.50 | 5.62 | 5.60 | 7.10 | 7.20 |
| XVa | $C_6H_5CH_2S(CH_2)_2-$ | A-2 | 61[h] | G | 98.5–99.5 | $C_{10}H_{13}NO_2S$ | | | | | 6.63 | 6.62 |
| XVIa | $C_6H_5CH=CH-CH_2$ | A-2 | 45 | J | 114.0–115.0 | $C_{11}H_{13}NO_2$ | 69.11 | 69.18 | 6.86 | 6.90 | 7.33 | 6.91 |
| XVIIa | $C_6H_5(CH_2)_3-$ | A-2 | 35 | G | 105.5–108.0 | $C_{11}H_{15}NO_2$ | | | | | 7.25 | 7.22 |
| XVIIIa | $p$-$CH_3OC_6H_4(CH_2)_3-$ | A-2 | 69 | C | 138.0–139.0 | $C_{12}H_{17}NO_3$ | 64.55 | 64.64 | 7.67 | 7.22 | 6.27 | 6.25 |
| XXIa | Cyclo-$C_6H_{11}CH_2CH_2-$ | A-2 | 49 | G | 115.0–116.0 | $C_{10}H_{19}NO_2$ | | | | | 7.56 | 7.51 |
| XXIIa | $CH_3(CH_2)_4CH_2-$ | A-1 | 15 | C | 147.5–149.5 | $C_7H_{15}NO_2$ | | | | | 9.65 | 9.62 |

[a] See Experimental section. [b] Yields, except in one case, are over-all from the aldehydes. [c] See code in footnote *b* of Table I. [d] All melting points are corrected. [e] Lit.[6] m.p. 141.5°. [f] A. McKenzie, G. Martin, and H. G. Rule [*J. Chem. Soc.*, 1588 (1914)] report m.p. 111–112°. [g] C. F. Koelsch [*J. Am. Chem. Soc.*, **52**, 2430 (1930)] reports m.p. 149–150°. [h] This is the yield of hydrolysis of the intermediate cyanohydrin, 3-benzylthiolacetonitrile, reported by O. Gawron and A. J. Glaid [*ibid.*, **71**, 3232 (1949)].

A number of unsuccessful attempts were made to prepare 4-oxazolidinones unsubstituted at the 2-position by the condensation of formaldehyde or formaldehyde reagents with α-hydroxyamides. The amides reacted readily with formalin to give gums from which no crystalline product could be isolated. Campbell and Jones[8] reported the preparation of 5-trichloromethyl-4-oxazolidinone, m.p. 229–231° dec., by the reaction of 3,3,3-trichloro-2-hydroxypropionamide with either chloromethyl methyl ether, or diethoxymethane in cyclohexane with *p*-toluenesulfonic acid. The only crystalline product obtained from the reaction of IIa with chloromethyl methyl ether was N,N′-methylenebis(2-hydroxy-4-phenyl-3-butenamide) (XXX). When IIa was treated with diethoxymethane in the manner of Campbell and Jones, a mixture of XXX and N-ethoxymethyl-2-hydroxy-4-phenyl-3-butenamide (XXXI) was obtained.




2-Hydroxy-5-phenylvaleramide reacted similarly to give open-chain compounds analogous to XXX and XXXI. The work of Campbell and Jones was then repeated. In our hands, 3,3,3-trichloro-2-hydroxypropionamide gave with chloromethyl methyl ether an uncrystallizable gum, and with diethoxymethane a compound indicated by analysis and infrared spectrum to be N,N′-methylenebis(2-hydroxy-3,3,3-trichloropropionamide), m.p. 238–239° dec.

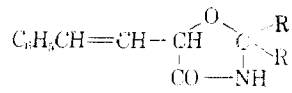
**Pharmacology.**—The evaluation of the stimulant activity of the 4-oxazolidinones was carried out mainly by operant conditioning techniques.[9] The compounds were administered to rats, squirrel monkeys, and rhesus monkeys trained on a variety of behavioral schedules. Changes in the number and distribution of lever presses after dosage were the dependent variables. The 4-oxazolidinones were found to possess behavioral activity similar to that of 2-imino-5-phenyl-4-oxazolidinone and sympathomimetic amines such as *d*-amphetamine inasmuch as they increase the rate of lever pressing in rats and monkeys trained to lever press to avoid electric shock (Sidman avoidance schedule RS 40-SS5) and in animals rewarded with food (VI 1 and FI 5). The 4-oxazolidinones possess certain other activities in common with 2-imino-5-phenyl-4-oxazolidinone and barbiturate-like agents: at appropriate doses they decrease lever pressing on all schedules, do not produce increased random activity measured by the photocell apparatus, do not decrease food intake, and make animals apparently oblivious to punishment when lever responses are both rewarded and punished on a so-called conflict schedule (mult: $s^{\Delta}$, VI 1, concurrent FR 10, VR 15 punishment). None of these compounds produce disruption of temporally controlled behavior (FI 5) comparable to that produced by 2-imino-5-phenyl-4-oxazolidinone and barbiturates. The most active oxazolidinones produce significantly increased lever pressing over a dose range of 16–64

(8) A. Campbell and W. A. Jones, U. S. Patent 2,915,527 (Dec. 1, 1959).

(9) C. B. Ferster and B. F Skinner, "Schedules of Reinforcement," Appleton-Century-Crofts, New York, N. Y., 1957.

Table III

4-Oxazolidinones by Condensation of 2-Hydroxy-4-phenyl-3-butenamide (IIa) with Carbonyl Compounds

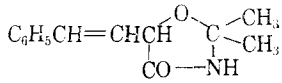


| Compd. | R | R' | M.p., °C. | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| XXIII | $C_2H_5$ | $CH_3$ | 103.0–105.0 | $C_{14}H_{17}NO_2$ | 72.70 | 72.74 | 7.41 | 7.38 | 6.05 | 6.03 |
| XXIV | $C_2H_5$ | $C_2H_5$ | 70.5–73.0 | $C_{15}H_{19}NO_2$ | 73.44 | 73.74 | 7.81 | 7.87 | 5.71 | 5.64 |
| XXV | $-(CH_2)_4-$ | | 126.0–128.0 | $C_{15}H_{15}NO_2$ | 74.05 | 73.74 | 7.04 | 7.12 | 5.76 | 5.69 |
| XXVI | $-(CH_2)_5-$ | | 168.0–169.0 | $C_{16}H_{19}NO_2$ | 74.68 | 74.55 | 7.44 | 7.47 | 5.44 | 5.41 |
| XXVII[a] | $CH_3COCH_2-$ | $CH_3$ | 138.0–139.0 | $C_{15}H_{17}NO_3$ | 69.49 | 69.28 | 6.61 | 6.58 | 5.40 | 5.53 |
| XXVIII[a] | $CH_3-$ | $CH_3COCH_2-$ | 174.0–175.0 | $C_{15}H_{17}NO_3$ | 69.49 | 69.49 | 6.61 | 6.54 | 5.40 | 5.28 |
| XXIX | $C_6H_5$ | H | 174.0–175.0 | $C_{17}H_{15}NO_2$ | 76.96 | 77.04 | 5.70 | 5.80 | 5.28 | 5.28 |

[a] One of the pair of racemates from IIa and acetylacetone.

mg./kg. At higher doses the decreased levels of lever pressing mentioned above are observed.

Structure–activity relationships will be discussed by noting the effects of structural changes on the stimulant activity (production of increased rate of lever pressing) of 2,2-dimethyl-5-styryl-4-oxazolidinone (IIb), a highly active and the most extensively studied member of this series.



IIb

Compounds comparable to IIb in stimulant activity were obtained on methylation of the nitrogen atom of IIb and on hydrogenation of the double bond to give 2,2-dimethyl-5-phenethyl-4-oxazolidinone (XXXII). Certain variations in the hydrocarbon chain joining the phenyl and oxazolidinone rings in XXXII gave active compounds. Compound XVIIb (Table I) in which the chain is lengthened by one methylene unit is slightly more active than IIb. Addition of yet another methylene unit (XXb) or shortening the chain to obtain XIIIb reduces stimulant activity. The known 2,2-dimethyl-5-phenyl-4-oxazolidinone[3] is inactive. Compound XIVb in which a sulfur atom replaces a methylene group of XXXII is as active as IIb; the higher homolog is less active.

Replacement of the 5-hydrogen atom (VIIb) or of either of the vinyl hydrogens (VIIIb or IXb) of IIb by a methyl group reduced activity. Increasing the size of the 2-position substituents was detrimental; of the compounds in Table III, only the 2-ethyl-2-methyl compound (XXIII) retained the strong stimulant activity of IIb. Aromatic ring substitution gave compounds with reduced stimulant activity with the exceptions of the *p*-methyl derivative of IIb and the *p*-methoxy derivative of XXXII.

The activity and low toxicity (i.p. $LD_{50}$ = 818 mg./kg.; *p.o.* $LD_{50}$ = 1630 mg./kg. in mice) of IIb led to its selection for clinical trial; however, it was found to have insufficient stimulant activity in man to be clinically useful.

## Experimental[10,11]

The aldehydes, acids, and esters required for the synthesis of the α-hydroxyanides were prepared by the literature procedures when known.

***m*-Chlorocinnamaldehyde.**—A solution of 17.6 g. (0.4 mole) of acetaldehyde in 40 ml. of water was added dropwise during 1 hr. to a well-stirred mixture of 46 g. (0.33 mole) of *m*-chlorobenzaldehyde, 1.2 g. of NaOH, 75 ml. of water, and 30 ml. of ethanol. The mixture was stirred 2 hr. more and acidified with acetic acid. The oil layer was taken up in ether, washed with sodium bicarbonate solution and water, and dried ($Na_2SO_4$). Distillation gave 23 g. (42%) of product, b.p. 162–166° (20 mm.). A small sample redistilled for analysis [b.p. 160–162° (19 mm.)] crystallized in the receiver and melted at 38.5–39.5° after crystallization from cyclohexane.

*Anal.* Calcd. for $C_9H_7ClO$: C, 64.88; H, 4.24. Found: C, 64.56; H, 4.34.

**Phenylmercaptoacetaldehyde** was obtained by hydrolysis (1% sulfuric acid–acetic acid, 1.5-hr. reflux) of phenylmercaptoacetaldehyde[12] diethylacetal. The aldehyde was extracted with ether and used without purification.

**4-*p*-Methoxyphenylbutyraldehyde** was prepared from 3-*p*-methoxyphenylpropyl bromide by the method described by Kumler, *et al.*,[13] for the preparation of 4-phenylbutyraldehyde and was used directly without purification.

**Methyl 2-Hydroxy-2-methyl-4-phenyl-3-butenoate.**—A solution of methylmagnesium iodide in 150 ml. of ether was prepared from 35.5 g. (0.25 mole) of methyl iodide and 6.1 g. (0.25 g.-atom) of magnesium, and was added dropwise during 45 min. to a solution of 41.5 g. (0.22 mole) of methyl benzylidenepyruvate in 450 ml. of ether with cooling in an ice–salt bath. The mixture was then stirred 0.5 hr. in the cooling bath, and 0.5 hr. without cooling. It was poured into a mixture of ice and dilute HCl. The ether layer was separated, washed with sodium bicarbonate solution, dried ($Na_2SO_4$), and distilled to yield 23.3 g. (56%) of hydroxy ester, b.p. 110–114° (0.5 mm.), $n^{23}D$ 1.5455.

*Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.67; H, 6.99.

**2,2-Dimethyl-5-(4-phenyl-1,3-butadien-1-yl)-1,3-dioxolan-4-one.**—Concentrated sulfuric acid (9.6 g.) was added dropwise to a stirred slurry of 19 g. (0.093 mole) of 2-hydroxy-6-phenyl-3,5-hexadienoic[14] acid in 100 ml. of acetone. The temperature was maintained at −15 to −10° during the addition and was allowed to rise to 0° following removal of the cooling bath. The mixture was then poured into an ice-cold solution of 19.5 g. of sodium carbonate in 175 ml. of water. The precipitated material which contained sodium carbonate was dried and extracted with hot ethanol. The extract was diluted with water to cause the dioxolanone to crystallize. There was obtained 10 g. of crystals, m.p. 77–78°.

*Anal.* Calcd. for $C_{15}H_{14}O_3$: C, 73.72; H, 6.60. Found: C, 73.53; H, 6.58.

**2-Hydroxy-4-*p*-tolyl-3-butenamide (VIa) (Method A-1, Table II).**—Concentrated HCl was added dropwise to a stirred mixture of 48 g. (0.33 mole) of *p*-methylcinnamaldehyde, 350 ml. of ether, and 42.9 g. (0.66 mole) of potassium cyanide at 5° until the mixture was brought approximately to pH 7. The mixture was stirred 4 hr. at 0–5°, and then let stand 2 days at 5°. The ether

(10) All melting points are corrected and were taken in a Thomas Hoover capillary melting point apparatus. Molecular weights were determined by the Rast method in camphor.

(11) We are indebted to Mr. K. B. Streeter and his staff for the analytical data.

(12) B. D. Vilsmaier, *Pharm. Industrie Anal. Sci.*, **32A**, 390 (1950).

(13) W. D. Kumler, L. A. Strait, and E. L. Allen, *J. Am. Chem. Soc.*, **72**, 1463 (1950).

(14) E. Erlenmeyer, *Ber.*, **37**, 1315 (1904).

layer, containing the cyanohydrin, was made up to a volume of 500 ml. by the addition of fresh ether, and mixed with an ice-cold solution of 200 ml. of concentrated HCl and 200 ml. of concentrated sulfuric acid. After standing 4 hr. at 5°, the solution was diluted with ice water to precipitate the product which was recrystallized from isopropyl alcohol. Yields and properties of VIa and similarly prepared compounds are found in Table II.

**3-Phenoxylactamide (XIIa) (Method A-2, Table II).**—Phenoxyacetaldehyde (48 g., 0.35 mole) was added dropwise to a stirred solution of 96 g. of sodium bisulfite in 192 ml. of water. The precipitated bisulfite addition compound (65 g.) was stirred at 5° with a mixture of 100 ml. of water and 100 ml. of ether while a solution of 17.2 g. (0.35 mole) of sodium cyanide in 35 ml. of water was added. After 2 hr., the ether layer was separated, dried over sodium sulfate, and evaporated, leaving as a residue 45.5 g. of the crude oily cyanohydrin. The cyanohydrin was dissolved in 280 ml. of ether, the solution was chilled to 5° and mixed with an ice-cold solution of 200 ml. of concentrated HCl and 200 ml. of concentrated sulfuric acid. After a 16-hr. period at 5°, 400 ml. of ice water was added to precipitate 3-phenoxylacetamide which was purified by recrystallization from ethanol. Yields and properties of this and similarly prepared compounds are found in Table II.

**2-Hydroxy-2-methyl-4-phenyl-3-butenamide (VIIa).**—Methyl 2-hydroxy-2-methyl-4-phenyl-3-butenoate (18.6 g., 0.09 mole) was added to 75 ml. of ethanol which had been saturated with ammonia at 5°, and the solution was heated 120 hr. at 70° in an autoclave. Volatile materials were then evaporated *in vacuo*, and the residue was stirred with petroleum ether to cause crystallization. There was obtained 14.5 g. of amide, m.p. 116–118°. Recrystallization from aqueous isopropyl alcohol gave a sample with a constant m.p. 116.5–118.5°.

*Anal.* Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.22.

Shapiro, Rose, Roskin, and Freedman[15] have prepared VIIa from the cyanohydrin of 4-phenyl-3-buten-2-one and report m.p. 97–99°.

**2-Hydroxy-4-*p*-methoxyphenylbutyramide (Xa).**—A solution of 70 g. (0.33 mole) of 2-hydroxy-4-*p*-methoxyphenylbutyric acid,[16] and 80 ml. of concentrated sulfuric acid in 825 ml. of methanol was refluxed 6 hr. Most of the methanol was evaporated *in vacuo*, and the residue was poured into a saturated solution of sodium bicarbonate. The oily methyl ester was separated and shaken with 250 ml. of concentrated ammonium hydroxide solution. The amide quickly formed and solidified. Recrystallization from ethanol gave 46.5 g. of the amide, m.p. 158.5–160.5°.

*Anal.* Calcd. for $C_{11}H_{15}NO_3$: N, 6.69. Found: N, 6.68.

**2-Hydroxy-6-phenylhexanamide (XXa)** was prepared in the same manner from 2-hydroxy-6-phenylhexanoic acid through the methyl ester. It melts at 123.5–125.5°.

*Anal.* Calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.77; H, 8.08; N, 6.75.

**2-Hydroxy-6-phenyl-3,5-hexadienamide (XIXa).**—2,2-Dimethyl-5-(4-phenyl-1,3-butadien-1-yl)-1,3-dioxolan-4-one (20 g., 0.082 mole) was added to 250 ml. of liquid ammonia, and the mixture was allowed to stand overnight in a Dewar flask, and then to evaporate. The residue was extracted with water, and the solid product was recrystallized from ethanol to yield 6.2 g. of amide, m.p. 175–176°. An analytical sample had m.p. 176–177°.

*Anal.* Calcd. for $C_{12}H_{13}NO_2$: C, 70.94; H, 6.45; N, 6.90. Found: C, 71.21; H, 6.51; N, 7.17.

**Condensation of Acetone with α-Hydroxyamides. General Procedure for Table I.**—The α-hydroxyamide was dissolved in a large excess of acetone (approx. 10 ml./g.) in which was dissolved either 1 g. of HCl/100 ml., or 2 g. of concentrated sulfuric acid/100 ml. The solution was allowed to stand 16 hr. at room temperature, neutralized by the addition of saturated sodium bicarbonate solution, concentrated to about one-third volume by vacuum distillation, and diluted with water to precipitate the 4-oxazolidinone. The 4-oxazolidinones were purified by recrystallization from the solvents indicated in Table I.

**Condensations of 2-Hydroxy-4-phenyl-3-butenamide (IIa) with Carbonyl Compounds (Table III). A. 2-Ethyl-2-methyl-5-styryl-4-oxazolidinone (XXIII).**—A solution of 17.7 g. (0.1 mole) of IIa and 2.0 g. of HCl in 200 ml. of 2-butanone was allowed to stand 22 hr. at room temperature. The solution was neutralized by the addition of saturated sodium bicarbonate solution, and the excess ketone was removed by vacuum distillation. The oily product was taken up in ether, dried over sodium sulfate, and distilled; yield, 15 g. of a viscous oil, b.p. 193–195° (1.3 mm.). When the oil was dissolved in benzene and the solution was diluted with petroleum ether, the 4-oxazolidinone crystallized. Repeated recrystallization from aqueous isopropyl alcohol gave 6.0 g. of XXIII. Melting points and analytical data are collected in Table III for this and the following compounds prepared from IIa.

**B. 2,2-Diethyl-5-styryl-4-oxazolidinone (XXIV).**—A solution of 21.2 g. (0.12 mole) of IIa, and 1.5 ml. of concentrated sulfuric acid in 250 ml. of diethyl ketone was heated at 65° for 6 hr. and then worked up as above. The oil obtained by distillation [18.8 g., b.p. 190–198° (0.8 mm.)] was dissolved in petroleum ether, and the solution was chilled to cause the 4-oxazolidinone to crystallize. Repeated recrystallization from aqueous isopropyl alcohol gave 4.0 g. of XXIV.

**C. 2,2-Tetramethylene-5-styryl-4-oxazolidinone (XXV).**—A solution of 10.6 g. (0.06 mole) of IIa and 0.7 ml. of concentrated sulfuric acid in 60 ml. of cyclopentanone was allowed to stand 3 days at room temperature, and was then neutralized by the addition of saturated sodium bicarbonate solution. The organic layer was separated and evaporated *in vacuo*. The solid residue recrystallized from ethanol gave 2.5 g. of XXV.

**D. 2,2-Pentamethylene-5-styryl-4-oxazolidinone (XXVI).**—A solution of 5.3 g. (0.03 mole) of IIa and 1.0 g. of hydrogen chloride in 30 ml. of cyclohexanone was allowed to stand 2 hr. at room temperature and was then chilled to precipitate the oxazolidinone. Recrystallization from ethanol gave 3.6 g. of XXVI.

**E. 2-Acetonyl-2-methyl-5-styryl-4-oxazolidinone.**—A solution of 20 g. (0.114 mole) of IIa and 2 ml. of concentrated sulfuric acid in 200 ml. of acetylacetone stood 18 hr. at room temperature, was neutralized with saturated sodium bicarbonate, and concentrated to dryness *in vacuo*. The residue was slurried with water, and the insoluble material was collected and recrystallized from methanol; 5.6 g. of a mixture of the two racemic modifications, m.p. 140–170°, was obtained. Recrystallization from 150 ml. of methanol gave 3.4 g. of the higher melting racemate, m.p. 174–175° (XXVIII). Evaporation of the mother liquor from this last recrystallization, and recrystallization of the residue from methanol gave 1.8 g. of the lower melting racemate, m.p. 138–139° (XXVII). The infrared spectra of the racemates are essentially similar with amide carbonyl bands at 1710 cm.$^{-1}$ and ketone carbonyl bands at 1720 cm.$^{-1}$.

**F. 2-Phenyl-5-styryl-4-oxazolidinone (XXIX).**—A solution of 5.3 g. (0.03 mole) of IIa, 3.5 g. (0.033 mole) of benzaldehyde, and 0.2 g. of *p*-toluenesulfonic acid in 85 ml. of benzene was refluxed 16 hr. under a constant water separator. The dark solution was cooled, and the precipitated product was recrystallized from isopropyl alcohol; yield, 1.7 g. of XXIX.

**Derivatives of 2,2-Dimethyl-5-styryl-4-oxazolidinone (IIb). A. 2,2,3-Trimethyl-5-styryl-4-oxazolidinone.**—A solution of 10.8 g. (0.05 mole) of IIb in 100 ml. of dry benzene was added during 15 min. to a vigorously stirred slurry of 1.3 g. (0.055 mole) of sodium hydride in 50 ml. of benzene. Methyl iodide (9.2 g., 0.065 mole) was then added, and the solution was refluxed for 2 hr. The mixture was cooled and shaken with water, and the organic layer was separated, dried ($Na_2SO_4$), and evaporated to dryness *in vacuo*. The residue was recrystallized from isopropyl alcohol to obtain 6.0 g. (52%) of product, m.p. 86–88°.

*Anal.* Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.41; H, 7.37; N, 6.02.

**B. 2,2-Dimethyl-5-phenethyl-4-oxazolidinone (XXXII).**—Hydrogenation at room temperature and 1 atm. of 4.4 g. (0.02 mole) of IIb in 80 ml. of ethanol using 1 g. of a 5% platinum-on-charcoal catalyst proceeded rapidly with the uptake of 0.02 mole of hydrogen. Removal of the catalyst, evaporation of the solvent, and recrystallization of the residue from aqueous isopropyl alcohol gave 2.3 g. of product, m.p. 91–93°.

*Anal.* Calcd. for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.16; H, 7.93; N, 6.38.

This compound was also prepared in 83% yield by the condensation of acetone with 2-hydroxy-4-phenylbutyramide[17] using the general procedure of Table I.

(15) S. L. Shapiro, I. M. Rose, E. Roskin, and L. Freedman, *J. Am. Chem. Soc.*, **81**, 386 (1959).

(16) P. Cordier, *Bull. soc. chim. France*, 564 (1956).

(17) F. Nerdel and H. Rachel, *Chem. Ber.*, **89**, 671 (1956).

**C. 2,2-Dimethyl-5-(1,2-dibromophenylethyl)-4-oxazolidinone.**—Bromine (3.7 g., 0.023 mole) in 10 ml. of chloroform was added to a solution of 5 g. (0.023 mole) of IIb in 25 ml. of chloroform. The solvent was evaporated and the residue was triturated with ethanol and recrystallized from aqueous ethanol to yield 4.5 g. (52%) of the dibromide, m.p. 182–183° dec.

*Anal.* Calcd. for $C_{13}H_{15}Br_2NO_2$: Br, 42.39. Found: Br, 42.47.

**D. 4-Acetoxy-2,2-dimethyl-5-styryl-3-oxazoline.**—Acetic anhydride (10 ml.) and 1 g. (0.0046 mole) of IIb were refluxed 1 hr. and held at room temperature for 18 hr. Excess acetic anhydride was evaporated *in vacuo*. The residue stirred with cold ethanol yielded 1 g. of crystalline product, m.p. 68–69°. Recrystallization from aqueous ethanol did not raise the melting point. The infrared spectrum corroborated the structure given, having absorption bands at 1320 (-C-O-C-), 1757 (C=O), and 1710 cm.$^{-1}$ (C=N).

*Anal.* Calcd. for $C_{15}H_{17}NO_3$: C, 69.49; H, 6.61; N, 5.40. Found: C, 69.47; H, 6.61; N, 5.44.

**2,2-Dimethyl-5-phenylsulfonylmethyl-4-oxazolidinone.**—A solution of 1 g. (0.004 mole) of 2,2-dimethyl-5-phenylmercaptomethyl-4-oxazolidinone (XIVb) and 2 ml. of 30% aqueous hydrogen peroxide in 5 ml. of acetic acid was heated 1 hr. at 80°. Dilution with 25 ml. of water gave 0.7 g. of product, m.p. 152–153°. Recrystallization from water raised the m.p. to 153–154°.

*Anal.* Calcd. for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.91. Found: C, 53.65; H, 5.52; N, 5.28; S, 12.17.

**N,N′-Methylenebis(2-hydroxy-4-phenyl-3-butenamide) (XXX).**—A mixture of 10 g. (0.057 mole) of IIa and 100 ml. of chloromethyl methyl ether was refluxed 4 hr. The excess ether was evaporated, and the residue stirred with cold methanol to obtain 1.4 g. of crystalline product, m.p. 216–217°. Two recrystallizations from 2-ethoxyethanol gave small white prisms, m.p. 220–221°.

*Anal.* Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65; mol. wt., 366.4. Found: C, 68.93; H, 6.08; N, 7.70; mol. wt., 392.

**N,N′-Methylenebis(2-hydroxy-5-phenylvaleramide)** was prepared similarly from 2-hydroxy-5-phenylvaleramide (XVIIa) and chloromethyl methyl ether; m.p. 147–148° (from ethanol).

*Anal.* Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.33; H, 7.59; N, 7.03; mol. wt., 398. Found: C, 69.68; H, 7.56; N, 7.08; mol. wt., 384.

**N-Ethoxymethyl-2-hydroxy-4-phenyl-3-butenamide (XXXI).**—A solution of 17.7 g. (0.1 mole) of IIa, 13 g. (0.125 mole) of diethoxymethane, and 0.5 g. of *p*-toluenesulfonic acid in 50 ml. of toluene and 50 ml. of cyclohexane was refluxed 3 hr. with continuous removal of the cyclohexane–ethanol azeotrope as it distilled. The reaction mixture was cooled and the precipitated N,N′-methylenebis(2-hydroxy-4-phenyl-3-butenamide), m.p. 220–221° (3 g.), was filtered off. The filtrate on standing deposited 5 g. of crystals, m.p. 84–85°. Three recrystallizations from benzene–cyclohexane raised the m.p. to 93–94°.

*Anal.* Calcd. for $C_{13}H_{17}NO_3$: C, 66.34; H, 7.28; N, 5.95; mol. wt., 235. Found: C, 65.91; H, 7.08; N, 6.18; mol. wt., 240.

**N-Ethoxymethyl-2-hydroxy-5-phenylvaleramide.**—A solution of 19.3 g. (0.1 mole) of 2-hydroxy-5-phenylvaleramide (XVII), 13 g. (0.125 mole) of diethoxymethane, and 0.16 g. of *p*-toluenesulfonic acid, in 45 ml. of toluene and 50 ml. of cyclohexane was refluxed 4 hr. with continuous removal of the cyclohexane–ethanol azeotrope. The solution was cooled, filtered, and diluted with an equal volume of petroleum ether to precipitate 7 g. of white crystals, m.p. 62–63°. Recrystallization from cyclohexane did not change the melting point.

*Anal.* Calcd. for $C_{13}H_{21}NO_3$: C, 66.91; H, 8.43; N, 5.58; mol. wt., 251. Found: C, 66.95; H, 8.36; N, 5.77; mol. wt., 255.

**N,N′-Methylenebis(2-hydroxy-3,3,3-trichloropropionamide).**—A solution of 14 g. (0.073 mole) of 2-hydroxy-3,3,3-trichloropropionamide, 11.7 ml. of diethoxymethane, and 0.12 g. of *p*-toluenesulfonic acid, in 35 ml. of toluene and 37 ml. of cyclohexane was refluxed 45 min., with continuous removal of the cyclohexane–ethanol azeotrope. The mixture was cooled, and the crystalline product (4.6 g., m.p. 232–233° dec.) was recrystallized from methanol to obtain 2.5 g. of white needles, m.p. 238–239° dec.

*Anal.* Calcd. for $C_7H_8Cl_6N_2O_4$: C, 21.48; H, 2.03; Cl, 53.60; N, 7.06; mol. wt., 397. Found: C, 21.24; H, 2.05; Cl, 53.46; N, 7.21; mol. wt., 396.

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# Behavioral and Neuropharmacological Actions of N-Aralkylhydroxylamines and Their O-Methyl Ethers

F. BENINGTON, R. D. MORIN, AND L. C. CLARK, JR.

*University of Alabama Medical Center, Birmingham, Alabama*

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The syntheses of a number of ring-substituted 1-aryl-2-hydroxyamino- and 1-aryl-2-methoxyaminopropanes are described. These compounds are compared pharmacologically with the corresponding 1-aryl-2-aminopropanes. The hydroxyamino compounds are, in general, central stimulants, and O-methylation diminishes this activity. Two compounds within this series were found to be monamine oxidase inhibitors.

In a continuation of our studies of compounds related to the physiologically active β-phenethylamines,[1] we have synthesized and examined the pharmacology of a number of 4-substituted 1-aryl-2-hydroxyamino- and 1-aryl-2-methoxyaminopropanes (Table I). Substituents which have been examined include methoxy, chloro, methyl, and hydrogen; a few compounds such as 1-(3-indolyl)-2-hydroxyaminopropane and β-1,2,3,4-tetrahydronaphthylhydroxylamine were prepared in order to examine the hydroxyamino analogs of α-methyltryptamine, a monamine oxidase inhibitor, and 1,2,3,4-tetrahydro-β-naphthylamine, a pyretogenic compound which produces rage in the cat.

Considerable literature is available on the synthesis and pharmacology of O-substituted aralkylhydroxylamines and related substances.[2] Relatively little work has been reported of the corresponding N-substituted compounds. Major[3] has published a synthesis of 1-

(1) (a) F. Benington, R. D. Morin, L. C. Clark, Jr., and R. P. Fox, *J. Org. Chem.*, **23**, 1979 (1958); (b) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Am. Chem. Soc.*, **76**, 5555 (1954); (c) *J. Org. Chem.*, **23**, 2034 (1958); (d) *ibid.*, **22**, 332 (1957).

(2) See references in the beginning of E. L. Schumann, R. V. Heinzelman, M. E. Greig, and W. Veldkamp, *J. Med. Chem.*, **7**, 329 (1964).

(3) R. T. Major and K. W. Ohly, *ibid.*, **4**, 51 (1961).