New Compounds: Oxazolidines and Derived Amino Alcohols

J. HARRISON AGER and EVERETTE L. MAY

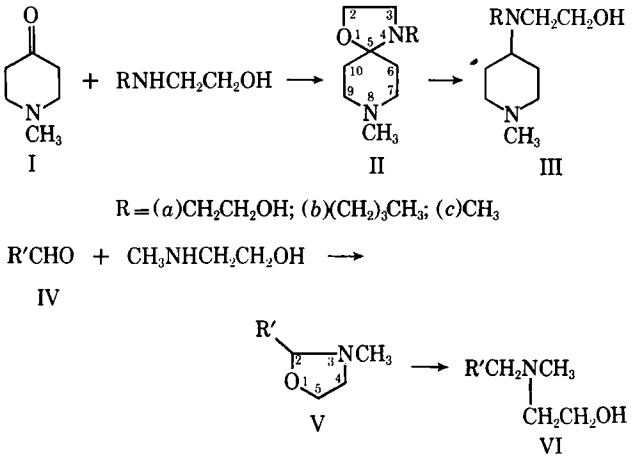
Abstract □ Oxazolidines II and V were prepared from 1-methyl-4-piperidone (I) and from 2-naphthalenecarboxaldehyde or *p*-chlorobenzaldehyde (IV) and appropriate secondary 2-aminoethanols. Platinum-catalyzed hydrogenation of II and V gave amino alcohols III and VI, respectively. These oxazolidines and the corresponding amino alcohols showed no carcinolytic activity in experimental tests. Compound III*a* had marginal antimalarial activity in the mouse, *P. berghei* screen.

Keyphrases □ Oxazolidines, alcohol derivatives—synthesis □ Antimalarial activity—oxazolidines, derivatives □ IR spectrophotometry—structure □ NMR spectroscopy—structure

The synthesis of oxazolidines II and V and their room-temperature, catalytic-hydrogenation products, III and VI, are herein reported. Interest in these compounds was generated principally by reports that 9-[(2-hydroxybutyl)methylaminomethyl]-1,2,3,4-tetrahydrophenanthrene (1) showed carcinolytic activity in mice[1] and that 9-(2-hydroxypentyl)aminomethylphenanthrene (1)[2] was weakly active against *P. gallinaceum* in chicks.

Reaction of 1-methyl-4-piperidone (I) with 2-methylaminoethanol, 2-butylaminoethanol, or 2,2′-iminodiethanol in boiling benzene (2) gave oxazolidines II*c–a*, respectively, which were purified by distillation. Compounds V*a* and V*b* were similarly prepared from 2-methylaminoethanol and 2-naphthalenecarboxaldehyde (IV*a*) or *p*-chlorobenzaldehyde (IV*b*). Hydrogenation of II and V in methanol (room temperature and pressure, platinum oxide) (3)[3] gave amino alcohols III and VI, respectively, which were also purified by distillation and further characterized, in some instances, as hydrochloride salts (see Scheme I). IR and NMR data substantiated the oxazolidine and amino alcohol structures. The latter are complex and are available on request.

Marginal antimalarial activity (mouse, *P. berghei*) was demonstrated with amino alcohol III*a* only.[4] All oxazolidines and amino alcohols reported here were found ineffective as anticancer agents in preliminary tests (tissue-culture, Walker-muscular, L-1210) by the Cancer Chemotherapy National Service Center, NIH (private communication), and as analgesics in the mouse-hot plate method by the pharmacology unit of the Laboratory of Chemistry, NIH.



Scheme I

EXPERIMENTAL

Melting points were determined in capillary tubes (Hershberg apparatus, total immersion thermometers). Distillations were effected with a 60.96-cm. (2-ft.), Nester-Faust, spinning-band column. IR spectra were measured on a spectrometer.[5] Another spectrophotometer[6] ($CDCl_3$, tetramethylsilane) was used for NMR measurements. Microanalyses were done by the Section on Instrumentation, National Institutes of Health.[7]

4-(2-Hydroxyethyl)-8-methyl-1-oxa-4,8-diazaspiro[4.5]decane (II*a*)—2,2′-Iminodiethanol (31.5 g., 0.3 mole), 33.9 g. (0.3 mole) of I, and 100 ml. of benzene were refluxed for 2 hr. with azeotropic distillation of 5.4 ml. of water. Distillation of the benzene, then the residue gave 35.5 g. (60%) of II*a*, b.p. 95° (0.06 mm.), m.p. 56–61°, $\nu_{max.}^{film}$ 3,200 (OH), 1,180, 1,130, 1,080 (N—C—O) cm.$^{-1}$ (4), n_D^{20} 1.5028.

Anal.—Calcd. for $C_{10}H_{20}N_2O_2$: C, 60.0; H, 10.1; N, 14.0. Found: C, 59.8; H, 9.99; N, 13.9.

4-Butyl-8-methyl-1-oxa-4,8-diazaspiro[4.5]decane (II*b*)—Compound II*b*, prepared in 90% yield from 11.3 g. of I and 11.7 g. of 2-butylaminoethanol as described above, had b.p. 99–100° (0.05 mm.), n_D^{20} 1.4739, $\nu_{max.}^{film}$ 1,140, 1,085, 1,062 (N—C—O) cm.$^{-1}$.

Anal.—Calcd. for $C_{12}H_{24}N_2O$: C, 67.9; H, 11.4; N, 13.2. Found: C, 67.8; H, 11.2; N, 13.0.

4,8-Dimethyl-1-oxa-4,8-diazaspiro[4.5]decane (II*c*)—This compound was prepared from I and 2-methylaminoethanol as described for II*a* and II*b*; b.p. 64.5° (0.05 mm.), n_D^{20} 1.4786.

Anal.—Calcd. for $C_9H_{18}N_2O$: C, 63.5; H, 10.7; N, 16.5. Found: C, 63.5; H, 10.6; N, 16.2.

The monopicrate of II*c* (from acetone) melted at 150–151°.

Anal.—Calcd. for $C_{15}H_{21}N_5O_8$: C, 45.1; H, 5.2; N, 17.5. Found: C, 45.3; H, 5.3; N, 17.2.

3-Methyl-2-(2-naphthyl)oxazolidine (V*a*)—2-Methylaminoethanol (9.8 g.), 21 g. of IV*a*, and 100 ml. of benzene, refluxed for 0.75 hr. with collection of 2.3 ml. of water, gave 24 g. (83%) of V*a*, b.p. 155° (0.05 mm.), m.p. 59–61.5° (from ether-ligroin, b.p. 30–60°).

[1] Private communication from the Cancer Chemotherapy National Service Center.

[2] This compound was designated SN 5845 by G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, Public Health Monograph No. 9, Federal Security Agency, Public Health Service.

[3] Hitherto (3), palladium on charcoal and hydrogen pressure of four atmospheres were used.

[4] Private communication from Dr. David Jacobus, Walter Reed Army Institute of Research, Washington, D. C.

[5] Perkin-Elmer model 421.

[6] Varian Associates model A-60.

[7] Dr. William C. Alford.

Anal.—Calcd. for $C_{14}H_{15}NO$: C, 78.8; H, 7.1; N, 6.6. Found: C, 78.9; H, 7.4; N, 6.3.

2-(p-Chlorophenyl)-3-methyloxazolidine (Vb)—As described for V*a*, this compound was prepared from IV*b* in a yield of 80%[8]; b.p. 92–94° (0.1 mm.), n_D^{20} 1.5394.

Anal.—Calcd. for $C_{10}H_{12}ClNO$: C, 60.8; H, 6.1; Cl, 17.9; N, 7.1. Found: C, 60.9; H, 6.3; Cl, 18.0; N, 6.9.

4-(Butyl-2-hydroxyethyl)amino-1-methylpiperidine (IIIb)—Compound II*b* (10 g.), 1 g. of platinum oxide and 80 ml. of methanol absorbed one molar equivalent of hydrogen during 6 hr. giving 9.6 g. of III*b*, b.p. 86° (0.05 mm.), $\nu_{max.}^{film}$ 3,250 cm.$^{-1}$.

Anal.—Calcd. for $C_{12}H_{26}N_2O$: C, 67.2; H, 12.2; N, 13.1. Found: C, 67.0; H, 12.4; N, 13.0.

Similarly prepared (quantitative yield) were III*a* (*Anal.*—Calcd. for $C_{10}H_{22}N_2O_2$: C, 59.4; H, 11.0; N, 13.9. Found: C, 59.3; H, 10.7; N, 13.9) and III*c*, b.p. 43° (0.15 mm.) (*Anal.*—Calcd. for $C_9H_{20}N_2O$: C, 62.7; H, 11.7; N, 16.3. Found: C, 62.6; H, 11.7; N, 15.8) from II*a* and II*c*, respectively.

2-[Methyl(2-naphthylmethyl)]aminoethanol (VIa)—Hydrogenation of 9 g. of V*a* in methanol (1 g. of platinum oxide) required 1.5 hr. and gave a 90% yield of VI*a* after short-pass distillation at 150° (0.1 mm.); $\nu_{max.}^{film}$ 3,250 cm.$^{-1}$.

[8] Also isolated in 10% yield was the 2-methylaminoethanol salt of *p*-chlorobenzoic acid, m.p. 95–97° alone or in mixture with authentic material. This must have resulted from a Cannizzaro reaction on IV*b*.

Anal.—Calcd. for $C_{14}H_{17}NO$: C, 78.1; H, 8.0; N, 6.5. Found: C, 78.2; H, 8.2; N, 6.7.

The hydrochloride of VI*a* (from acetone) melted at 114–115°.

Anal.—Calcd. for $C_{14}H_{18}ClNO$: C, 66.8; H, 7.2; Cl, 14.1; N, 5.6. Found: C, 66.6; H, 7.1; Cl, 14.2; N, 5.5.

Similarly V*b* gave VI*b*; hydrochloride salt, m.p. 126–127° (from methanol); $\nu_{max.}^{CHCl_3}$ 3,400, cm.$^{-1}$ yield 99%.

Anal.—Calcd. for $C_{10}H_{15}Cl_2NO$: C, 50.9; H, 6.4; Cl, 30.0; N, 5.9. Found: C, 50.8; H, 6.4; Cl, 29.7; N, 5.8.

REFERENCES

(1) E. L. May, *J. Org. Chem.*, **11**, 353(1946).

(2) M. Senkus, *J. Am. Chem. Soc.*, **67**, 1515(1945).

(3) E. Gil-Av, *ibid.*, **74**, 1346(1952).

(4) E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. Trav. Chim.*, **71**, 168(1952); I. C. Nordin, *J. Heterocyclic Chem.*, **3**, 351(1966).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 27, 1968, from the *Laboratory of Chemistry, National Institutes of Health, Bethesda, MD 20014*

Accepted for publication December 6, 1968.

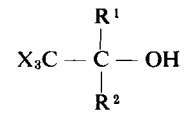
New Compounds: Preparation of Some Esters of Trihalogenated Alcohols

JOSEPH SAM AND A. J. BEJ*

Abstract □ The syntheses of a number of esters of trihalogenated monohydroxy alcohols are described. The results of preliminary pharmacological tests are reported.

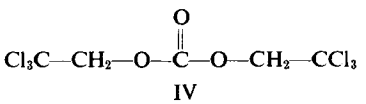
Keyphrases □ Trihalogenated monohydroxy alcohol esters—synthesis □ Analgesic activity—trihalogenated monohydroxy alcohol esters

The useful depressant properties of trihalogenated monohydroxy alcohols such as 2,2,2-trichloroethanol (I), 2,2,2-tribromoethanol (II), and 1,1,1-tribromo-2-methyl-2-propanol (III) are well-known (1). A number of esters of the alcohols above also have been evaluated for hypnotic activity (1). Recently, Swintosky *et al.* (2)



I, X = Cl, $R^1 = R^2 = H$
II, X = Br, $R^1 = R^2 = H$
III, X = Br, $R^1 = R^2 = CH_3$

reported on the sedative properties of bistrichloroethyl carbonate (IV). The presence of the 3,4,5-trimethoxybenzoyl and 3,4,5-trimethoxycinnamoyl group in the rauwolfia alkaloids (3) and other artifacts possessing CNS activities prompted the preparation of 3,4,5-trimethoxybenzoates and 3,4,5-trimethoxycinnamates of some of the same trihalogenated monohydroxy alcohols.



IV

The esterifications of alcohols substituted in the β-position by halogens are difficult because of their acidic nature arising from the inductive effect of the halogens. Such alcohols as 2,2,2-trichloroethanol and 2,2,2-tribromoethanol are not easily esterified by an acid. With an acid halide, esterification has been accomplished by heating the alcohol and acyl halide at temperatures up to 130° without a solvent medium (4–7). Hill reported (8, 9) that acidic alcohols were easily esterified with acyl halides under mild conditions using catalytic amounts of aluminum chloride or aluminum bromide. The results of the preparations of esters of representative acid chlorides utilizing the procedure of Hill (8, 9) are summarized in Table I.

Preliminary pharmacological studies[1] in mice were carried out with Compounds 3, 4, 5, 6, and 7 of Table I.

[1] The authors are grateful to Dr. H. Leo Dickison, Bristol Laboratories, Syracuse, N. Y. for the pharmacological data.