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ACKNOWLEDGMENTS AND ADDRESSES

Received October 17, 1969, from the *Department of Biochemistry, University of Texas Medical Branch, Galveston, TX 77550*

Accepted for publication December 11, 1969.

The authors acknowledge gifts of 3β-hydroxychol-5-enic acid from Dr. M. J. Thompson, U. S. Department of Agriculture, Beltsville, Md., and Dr. H. L. Herzog, Schering Corp., Bloomfield, N. J. Financial support for these studies was by U. S. Public Health Service Research Grant HE-10160.

Paper IX of the series: L. L. Smith and J. E. van Lier, *J. Atheroscler. Res.*, to be published.

New Compounds: Mannich Bases from 1,2-Diphenylindolizine—*N*-Substituted Cyclohexylaminomethyl Derivatives

WILLIAM B. HARRELL*, SHAO-WEN KUANG, and CROSSLEY O'DELL

Abstract □ Seven new Mannich bases, involving *N*-substituted cyclohexylamines and 1,2-diphenylindolizine, have been synthesized as potential biologically active compounds.

Keyphrases □ Mannich bases—synthesis □ *N*-Substituted cyclohexylamines—synthesis from 1,2-diphenylindolizine □ 1,2-Diphenylindolizine—Mannich base synthesis

In previously reported work, it has been shown that certain Mannich bases derived from indolizines exhibited CNS-depressant activity (1–3). As part of a continuing exploration of indolizines with potential biological activity, a series of Mannich bases involving *N*-substituted cyclohexylamines was synthesized from 1,2-diphenylindolizine (4) (Table I).

EXPERIMENTAL[1]

The appropriate secondary amine (0.045 mole) was combined with 30 ml. of 1,4-dioxane and 2.25 ml. of 40% aqueous formaldehyde (0.030 mole). The mixture was placed in the refrigerator and allowed to stand for 48 hr. To the mixture was then added 4.1 g. of 1,2-diphenylindolizine (0.015 mole); the resulting clear solution was stirred at room temperature for 72 hr., during which

[1] Melting points were taken on a Thomas-Hoover melting-point apparatus and are uncorrected. Elemental analyses were obtained from Strauss Microanalytical Laboratories, Oxford, England.

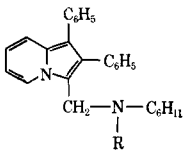
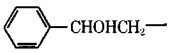


Table I—Mannich Bases

Compound	R	M.p.	Yield, %	Formula	Anal. Calcd.	Anal. Found
I		182–183°	85	$C_{33}H_{38}N_2$	C, 85.67 H, 8.28 N, 6.05	C, 85.72 H, 8.32 N, 6.18
II	CH_3CH_2—	123–124°	90	$C_{29}H_{33}N_2$	C, 85.25 H, 7.89 N, 6.86	C, 85.32 H, 7.92 N, 6.69
III	CH_3—	112–113°	88	$C_{28}H_{30}N_2$	C, 85.24 H, 7.66 N, 7.10	C, 85.36 H, 7.66 N, 7.09
IV	$(CH_3)_2CH$—	127–128°	84	$C_{30}H_{34}N_2$	C, 85.26 H, 8.11 N, 6.63	C, 85.42 H, 8.09 N, 6.42
V	$NCCH_2CH_2$—	152–153°	92	$C_{30}H_{31}N_3$	C, 83.10 H, 7.21 N, 9.69	C, 83.13 H, 7.19 N, 9.48
VI	$HOCH_2CH_2$—	138–139°	74	$C_{29}H_{32}N_2O$	C, 82.04 H, 7.60 N, 6.60	C, 82.11 H, 7.65 N, 6.78
VII		137–138°	84	$C_{35}H_{36}N_2O$	C, 83.96 H, 7.25 N, 5.59	C, 83.92 H, 7.31 N, 5.42

the crystalline product appeared. The product was collected and recrystallized from acetone. Each compound gave a negative color reaction with *p*-dimethylaminobenzaldehyde reagent, indicating that substitution had occurred at the C-3 position (5).

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ACKNOWLEDGMENTS AND ADDRESSES

Received October 2, 1969, from *The School of Pharmacy, Texas Southern University, Houston, TX 77004*

Accepted for publication November 12, 1969.

Supported by a grant from the Robert A. Welch Foundation.

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COMMUNICATIONS

Time Integral of Drug Concentration in the Central (Plasma) Compartment

Keyphrases ☐ Drug concentration time integral—central compartment ☐ Absorption comparison method—different formulations

Sir:

A well-known result in pharmacokinetics is that the time integral of the concentration of a drug in the central (plasma) compartment is equal to the total amount of drug absorbed divided by the product of the volume of distribution for the compartment and the elimination rate constant. The result is of great practical importance in that amounts of drug absorbed from different formulations of a drug can be readily compared by administering the different formulations to the same subject. Standard statistical designs, such as balanced incomplete block designs, can thus be employed. The result has been proved for one-compartment and two-compartment systems under suitable conditions. The usual procedure has been to obtain an expression for the concentration in the central compartment (by solving the appropriate differential equations) and to integrate this expression over time to obtain the stated result. A recent example of this procedure is given in Eqs. 11*a* through 14*a* of Gibaldi *et al.* (1). The purpose of the present note is to show that the result is a direct consequence of two basic assumptions and thus holds under quite general conditions. In fact, the present proof is implicit in the derivation given for nonintravenous routes of administration in Eq. 22*a* of the reference.

The two basic assumptions are:

1. Elimination of the drug takes place only from the central compartment, that is, the compartment over