Tetrahedron Vol. 36, pp 305 to 307
© Pergamon Press Ltd., 1980. Printed in Great Britain

0040-4020/80/0115-0305/$02.0070

MECHANISM OF THE ETHERIFICATION OF 2-ALKYLAMINO-1-PHENYLETHANOL DERIVATIVES

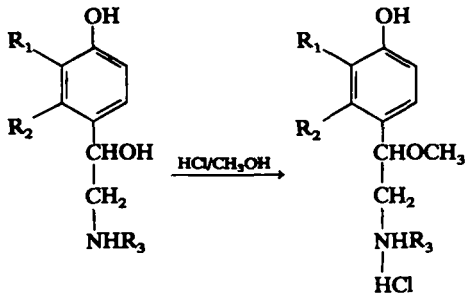
D. P. VENTER* and D. F. GREEFF
Department of Pharamacology, Potchefstroom University for C.H.E., Potchefstroom 2520, Republic of South Africa

(*Received in U.K.* 17 *April* 1979)

Abstract—Derivatives of 2-alkylamino-1-(4-hydroxyphenyl)-1-ethanol have been converted to the β-methylethers in good yield. Etherification of 2-alkylamino-1-(4-methoxyphenyl)-1-ethanol could not be accomplished. Based on this unreactivity, a mechanism is proposed whereby the etherification proceeds via a quinoidal intermediate and not via a carbonium ion intermediate. It is concluded that the acid catalyzed racemization of catecholamines may occur via a quinoidal intermediate.

Studies have shown that compounds such as *p*-hydroxybenzylalcohol and *p*-methoxybenzylalcohol[1] undergoes very rapid etherification in the presence of an acid to give the benzylethers as products. The rate of reaction and the yield of the ether tend to increase sharply as the electron-releasing ability of the *para* substituent of the benzylalcohol increases.[2] It has been predicted by Ingold[2] and found by Baker[3] and Bordwell[4] that the conjugative ability of the electron releasing groups MeO and HO are equal. The accelerative effect of the *para* substituents on the rate of etherification has been attributed to the ability of these groups to stabilize the positive charge, in the carbonium ion transition state, by delocalization. This phenomenon of aryl-stabilized carbonium ion intermediates are well documented.[5]

In this paper we wish to present evidence that the onium group, in phenethanolamine structures, will profoundly affect reactions that usually proceed through aryl-stabilized carbonium ions.



1. $R_1 = OH$, $R_2 = H$, $R_3 = CH(CH_3)_2$
2. $R_1 = OH$, $R_2 = H$, $R_3 = CH_3$
3. $R_1 = OH$, $R_2 = H$, $R_3 = H$,
4. $R_1 = OCH_3$, $R_2 = H$, $R_3 = CH(CH_3)_2$
5. $R_1 = H$, $R_2 = H$, $R_3 = H$
6. $R_1 = OH$, $R_2 = Cl$, $R_3 = CH(CH_3)_2$

RESULTS AND DISCUSSION

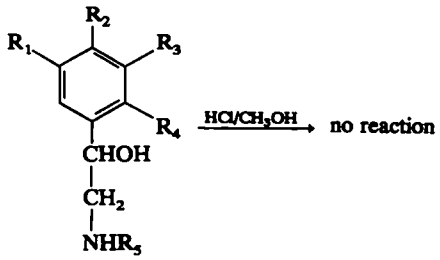
In the etherification of the phenethanolamine compounds **1–2** in acidic media, one would, according to the current theory, expect resonance stabilization of the intermediate carbonium ions, by the conjugative ability of the *p*-MeO and *p*-HO groups. Etherification was performed by allowing the phenethanolamines **1–6** to react in hydrogen chloride saturated methanol for a short period of time. This reaction resulted in the smooth conversion to the β-methylether derivatives (Table 1).

In contrast to the above mentioned reaction, the unreacted phenethanolamines were obtained in quantitative yield when compounds **7–12** were treated with hydrogen chloride saturated methanol.

All attempts, even at elevated temperature and extended reaction time, failed to produce the desired β-methylether derivatives. The starting materials **7–12** were isolated as the sole products. This

Table 1. β-Methylether derivatives prepared from compounds **1–6**

	β-Methylether of compound nr.	Melting point °C	Recrystn. solvent	Analysis	Yield %
1	(N-isopropyl-noradrenaline)	183–185	MeOH—Et_2O	$C_{12}H_{20}ClNO_3$	85
2	(adrenaline)	163–165	MeOH—Et_2O	$C_{10}H_{16}ClNO_3$	98
3	(noradrenaline)	169–171 (lit.[7] 170–171)	MeOH—Et_2O	$C_9H_{14}ClNO_3$	80
4	[8]	128–130	iso-PrOH—Et_2O	$C_{13}H_{22}ClNO_3$	84
5	(Octopamine)	176–177	MeOH—Et_2O	$C_9H_{14}ClNO_2$	90
6	[9]	174–175	iso-PrOH—Et_2O	$C_{12}H_{19}Cl_2NO_3$	93

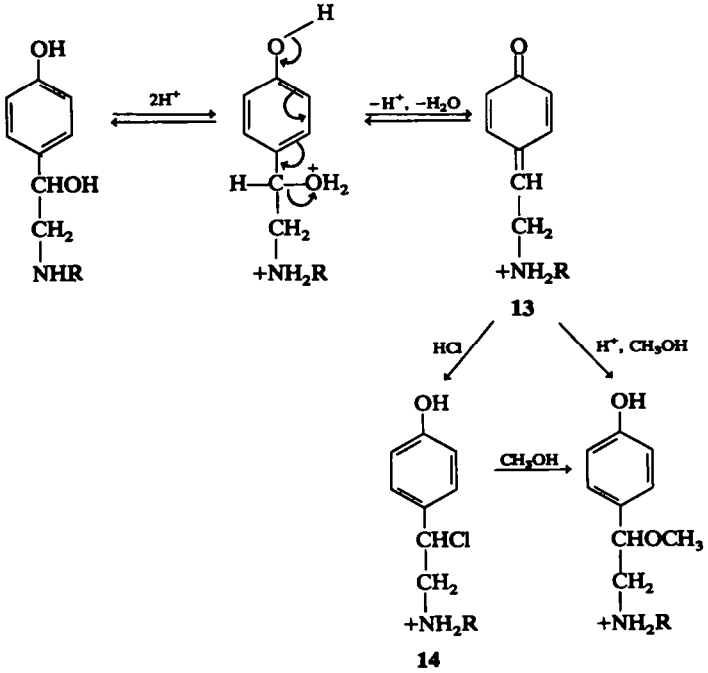


7. $R_1 = H$, $R_2 = OCH_3$, $R_3 = OCH_3$, $R_4 = H$, $R_5 = CH(CH_3)_2$
8. $R_1 = H$, $R_2 = OCH_3$, $R_3 = OH$, $R_4 = H$, $R_5 = CH(CH_3)_2$
9. $R_1 = Cl$, $R_2 = OCH_3$, $R_3 = OCH_3$, $R_4 = H$, $R_5 = CH(CH_3)_2$
10. $R_1 = H$, $R_2 = OCH_3$, $R_3 = OH$, $R_4 = Cl$, $R_5 = CH(CH_3)_2$
11. $R_1 = OCH_3$, $R_2 = H$, $R_3 = OCH_3$, $R_4 = H$, $R_5 = CH(CH_3)_2$
12. $R_1 = OH$, $R_2 = H$, $R_3 = OH$, $R_4 = H$, $R_5 = CH(CH_3)_2$

result was somewhat surprising. Especially confusing was the unreactivity of the benzylic HO group of the *p*-MeO compounds **7–10**. This unreactivity in the presence of a *p*-MeO is remarkable in view of the equal electron-donating ability of MeO and HO groups.[2-4]

Evidently *p*-HO—C_6H_4—CHOH—NHR is activated towards etherification, but substitution of the *p*-HO group with *p*-MeO, as in *p*-MeO—C_6H_4—CHOH—CH_2—NHR, renders this compound unreactive. Since the transition-state stability of the benzylic carbonium ion is of fundamental importance, a possible explanation of these somewhat anomalous results could conceivably lie in a destabilization of the carbonium ion intermediate which is supposed to form. The electron withdrawing-effect of the positive charged onium-group in C_6H_5—CHOH—CH_2—NH_2R, is extensive enough to exert a strong destabilizing effect. This type of destabilization would tend to increase the positive charge of the carbonium ion and it would certainly outweigh the possible stabilization by the electron-donating *p*-MeO group.

The successful conversion of the *p*-HO compounds **1–6** demonstrates that the etherification process in these compounds may proceed without the formation of a carbonium ion intermediate. In view of these results, it would appear that the observed reactions can be explained in terms of the mechanism shown in Scheme 1. In the presence of strong acid, protonation of the benzylic HO group can be expected to occur. Loss of water and subsequent proton abstraction from this protonated intermediate results in the formation of a quinoidal intermediate **13**. This reactive quinoidal intermediate suffers protonation and nucleophilic attack



Scheme I

by halide ion or methanol. Alcoholysis of the chloro intermediate **14** eventuates in the formation of the β-methylether derivatives of the parent compounds **1–6**. Obviously, the quinoidal intermediate **13** is not possible in compounds **7–12**. Thus, according to the proposed reaction mechanism, compounds **7–12** will be totally unreactive towards acid catalyzed etherification.

It is interesting to note that it was proposed that the acid catalyzed racemization of adrenaline (**2**) proceeded through a Snl reaction.[6] It is apparent from the results in the present study that the acid catalyzed racemization of catecholamines will probably not proceed via a Snl reaction. There remains to be established whether a quinoidal intermediate participates in this racemization. A systematic study of this question is now in progress and will be reported at a later date.

EXPERIMENTAL

M.ps were taken in open capillary tubes on a Gallenkamp mp apparatus and are uncorrected. Each analytical sample was homogeneous by tlc and had IR, and NMR spectra compatible with its structure. IR spectra (KBr-disc) were recorded on a Beckman IR-18 spectrophotometer. NMR spectra were recorded on a Varian T60 spectrometer, using TMS as a standard. Elemental analyses were performed on a Hewlett Packard analyser and analytical values are within 0.4% of the calculated values.

Preparation of the β-ether derivatives of compounds **1–6**. Anhyd HCl was passed into a stirred soln of 0.01 mol preparatory material (**1–6**) in 100 ml MeOH until a clear soln was obtained. The soln was allowed to stand at ambient temp for 15 min. The solvent was evaporated *in vacuo*. The residue was crystallized from the indicated solvent (Table 1) to give the corresponding hydrochloride salt.

REFERENCES

[1]E. F. Prat and P. W. Erickson, *J. Am. Chem. Soc.* **78**, 76 (1956).
[2]C. K. Ingold and E. A. Ingold, *J. Chem. Soc.* 1310 (1926); E. K. Holmes and C. K. Ingold, *Ibid.* 1328 (1926).
[3]J. W. Baker, C. F. Barrett and W. T. Tweed, *Ibid.* 2831 (1952).
[4]F. G. Bordwell and P. J. Bouton, *J. Am. Chem. Soc.* **78**, 854 (1956).
[5]*Carbonium ions* (Edited by G. A. Olah and P. von R. Schleyer) Vol 4, pp. 1501–1579. Wiley-Interscience, New York, N.Y. (1973).
[6]L. C. Schroeter and T. Higuchi, *J. Am. Pharm. Assoc.* **47**, 426 (1958).
[7]B. F. Tullar, *J. Am. Chem. Soc.* **70**, 2067 (1948).
[8]P. Pratesi, E. Grava, L. Lilla, A. La Manna and L. Villa, *Farmaco Pavia*, Ed. Sci., **18**, 932 (1963).
[9]For preparation of 6 see: C. Kaiser, D. F. Colella, A. M. Pavloff and J. R. Wardell, Jr., *J. Med. Chem.* **17**, 1071 (1974).