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ALCOHOLYSIS OF N-METHYL-4,7-DIACETOXY-6-METHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE

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In a previous communication (I), a facile acetoxy group rearrangement of a quinolacetate (II) derived from corypalline (I) with $Pb(OAc)_4$ has been shown to give N-methyl-4,7-diacetoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (III) under Thiele's condition (Ac_2O-conc.H_2SO_4, at room temperature).

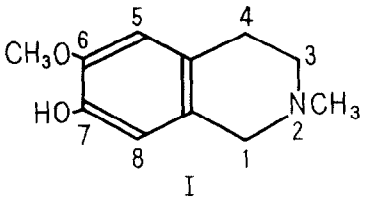
We now wish to report a novel alcoholysis, introduction of alkoxy groups into 4-position of III, when III was treated in a variety of alcohols in the presence of KOH.

A typical experiment of methanolysis of III was as follows. A solution of III (200 mg) in 5% methanolic KOH (3.0 ml) was stirred for 45 min. at room temperature. After removal of the solvent under reduced pressure, water was added to the residue and the resultant solution was acidified with 10% HCl under ice-cooling. The acidic solution was carefully basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. Usual treatment of the $CHCl_3$ layer gave an oil (112 mg), which was purified by column chromatography (silicic acid, Mallinckrodt). Elution with $CHCl_3$-MeOH (100:2)-(100:4) afforded colorless prisms (IV) (2) [70 mg (46.0%), mp 101-104° (n-hexane)].

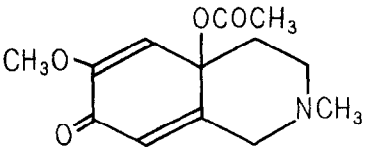
Structure of IV was supposed to be N-methyl-4,6-dimethoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline from its NMR spectrum (3) [τ : 7.56 (3H, S., =N-$\underline{CH_3}$), 6.54 (3H, S., aliphatic O$\underline{CH_3}$), 6.15 (3H, S., aromatic O$\underline{CH_3}$), 5.66 (1H, complex t., C_4-H), 3.45, 3.15 (each 1H, S., aromatic ring protons)] and the fact that hydrolysis of III in 5% aq. KOH gave the corresponding 4,7-dihydroxy compound (V) (1) only. Further, methylation of IV with diazomethane in MeOH furnished the corresponding 4,6,7-trimethoxy compound (VI) [oil, picrate, mp 126-129°(CH_3OH)].

Validity of the structure of IV was undoubtedly confirmed by an alternate synthesis.

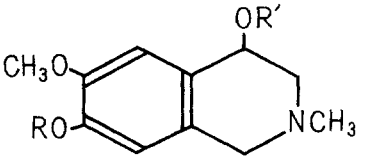
Cyclization of N-formyl-N-veratrylglycine (VII) with PPA gave 4-keto compound (VIII) (1), which was reduced with $NaBH_4$ to give 4-hydroxy compound (IX) [45.7%, mp 90-91° (CCl_4)]. Heating of a methanolic solution of IX with CH_3I in the presence of Ag_2O afforded the corresponding 4,6,7-trimethoxy compound (X) [54.5%, mp 122-124° (benzene)], $LiAlH_4$ reduction (in ab. Et_2O-ab.THF, under reflux) of which gave N-methyl-4,6,7-trimethoxy compound [oil, picrate, mp 124-126° (iso-PrOH)].



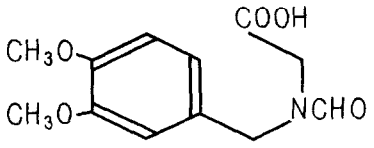
I



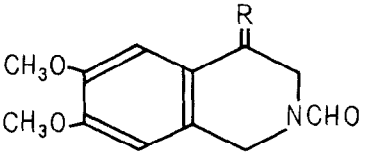
II



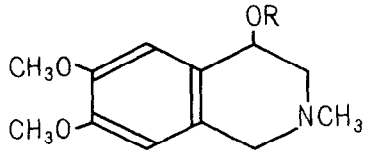
III R = R′ = $COCH_3$
IV R = H , R′ = CH_3
V R = R′ = H
VI R = R′ = CH_3



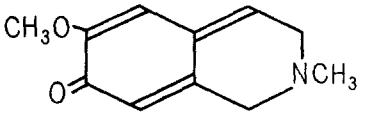
VII



VIII R = O
IX R = <OH H
X R = <OCH_3 H



XI R = $COCH_3$
XII R = H



XIII

Identity of VI from IV with the above authentic N-methyl-4,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline was secured by comparison of their GLC retention times (4) (1.5% SE-30, 170°) and their IR spectra (5) (KBr, picrate) and by a mixed fusion of each picrate, respectively.

Analogous reactions of III with other alcohols were carried out to give the result shown in Table 1.

TABLE 1

Solvents	Reaction Times (min.)	Products: 4-Alkoxy mg (%)	Products: 4-Hydroxy mg (%)	Mps. of 4-Alkoxy Compounds or Their Derivatives (°C)
CH_3OH [a]	45	70 (46.0)	-----	mp 101-104° (n-hexane), picrate, mp 165-166.5° (iso-PrOH)
50% CH_3OH [a]	90	63 (41.4)	-----	
CH_3CH_2OH [a]	40	82 (51.0)	-----	picrate, mp 163-164.5° (iso-PrOH)
$CH_2=CHCH_2OH$ [a]	30	90 (52.9)	-----	picrate, mp 134-135° (iso-PrOH)
$CH_3CH_2CH_2OH$ [a]	30	43 (25.2)	-----	mp 77-80° (n-hexane)
$PhCH_2OH$ [a]	120	48 (24.0)	-----	picrate, mp 153-154° (iso-PrOH)
$(CH_3)_2CHOH$ [a]	35	25 (14.6)	8 (4.9)	mp 92-94° (n-hexane)
$C_6H_{11}OH$ [a]	150	25 (12.5)	9 (5.5)	mp 116-118° (n-hexane)
50%$(CH_3)_3CCH_2OH$ [b]	180	-----	23 (16.0)	-----
$(CH_3)_3COH$ [b]	720	-----	45 (16.0)	-----

a) Diacetate (III) (200 mg) in each alcohol was subjected to the same reaction as in CH_3OH and reaction times were checked by TLC.
b) Diacetate (III) (400 mg) was used.

Therefore, these experiments showed the fact that 4-acetoxy group could be easily replaced by a number of alkoxy groups. In this substitution reaction, the length or branching of alkoxy chain was responsible to the product ratio, 4-alkoxy compound vs. 4-hydroxy showing that steric factor was governing as expected.

Further, the presence of 7-acetoxy group in III was a necessary requirement for the novel alcoholysis, since treatment of 6,7-dimethoxy-4-

acetoxy compound (XI) [mp 90-91.5° (n-hexane)] with 5% methanolic KOH gave only the normal hydrolyzed product, 4-hydroxy compound (XII) (1) (mp 126-128°).

Thus, p-quinoid structure (XIII) appeared to be a hypothetical intermediate until now.

Acknowledgment

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References

1) B. Umezawa, O. Hoshino and Y. Terayama, Chem. Pharm. Bull. (Tokyo), 16, 180 (1968).
2) All melting points were uncorrected using a Yanagimoto micro melting points measuring apparatus. Satisfactory elemental analyses for all compounds whose melting points are described in this paper were obtained.
3) NMR spectrum was measured at 60 Mc by a JNR-C60S spectrometer in $CDCl_3$ (5 - 10% solution) using Me_4Si as internal standard.
4) Gas liquid chromatography (GLC) was taken with a Shimadzu GC-1C gas chromatograph equipped with a hydrogen flame ionization detector.
5) IR spectrum was obtained with a Hitachi infrared spectrometer Model EPI-S_2.