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REACTIONS OF N-METHYL-4,7-DIACETHOXY-6-METHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE WITH AMINES OR THIOLS

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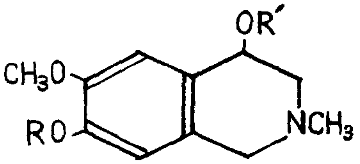
In a preceding paper (1), treatment of N-methyl-4,7-diacetoxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (I) with a variety of alcohols in the presence of KOH has been found to give the corresponding 4-alkoxy compounds (II) in moderate yields.

From the above fact, attack of other nucleophiles on 4-position of I was reasonably anticipated and the present paper is concerning successful reaction of I with amines or thiols.

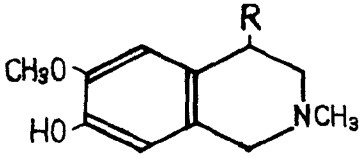
Some experimental details were as follows.

In the presence of KOH (i) A solution of I (200 mg) in 30% CH_3NH_2 (40 ml) containing KOH (200 mg) was stirred at room temperature for 15 min. The solution turned reddish brown. After the excess of CH_3NH_2 was removed under reduced pressure, the resultant solution was carefully acidified with 10% HCl and then made basic with K_2CO_3 (powder). Usual work-up of the $CHCl_3$ layer obtained on extraction of the product with $CHCl_3$ gave an oil (89 mg) yielding colorless prisms (III, R=$NHCH_3$) [76 mg (50.3%), mp 142-143^o (decomp.) (*n*-hexane)] (2).

The structure of III (R=$NHCH_3$) was assumed to be N-methyl-4-methylamino-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline from its elemental analysis, NMR spectral measurement (3) [τ : 7.60, 7.50 (each 3H, S., -NH$\underline{CH_3}$ and =N$\underline{CH_3}$), 6.8, 6.37 (each 1H, AB quartet, C_1-gem. protons, J_{AB}=15 cps),



I R=R'=$COCH_3$
II R=H, R'=ALKYL



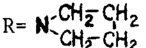
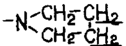
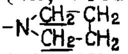
III

TABLE 1

Solvents	Catalyst	Reaction Times (min.)	Products mg (%)	Mps. of 4-Substituted Compounds (°C)
28% NH_4OH	---	15	78(55.0)	mp 142-143.5° (n-hexane)
30% CH_3NH_2	KOH	15	76(50.3)	mp 142-143° (decomp.) (n-hexane)
30% CH_3NH_2	---	15	88(57.8)	
70% $CH_3CH_2NH_2$	KOH	15	110(68.0)	mp 92-93° (decomp.) (n-hexane)
50% $C_6H_5CH_2NH_2$	---	15	140(70.0)	mp 95-96° (n-hexane)
50% $C_6H_5CH_2CH_2NH_2$	---	15	178(84.0)	mp 145-146° (CH_3OH-H_2O)
$C_6H_5NH_2$-dioxane-H_2O	KOH	30	106(66.0)	mp 166-167° (CH_3CH_2OH-H_2O)
50% $(CH_3)_2CHNH_2$	---	15	110(71.0)	mp 141.5-142.5° (decomp.) (n-hexane)
30% $(CH_3)_2NH$	---	15	112(70.0)	mp 118-120° (C_6H_6-n-hexane)
50% pyrrolidine	---	15	123(69.0)	mp 111-112.5° (n-hexane)
50% morpholine	---	15	104(55.0)	mp 139-140° (n-hexane)
50% piperidine	---	15	104(55.0)	mp 134-136° (n-hexane)
$NH_2CONHNH_2.HCl$-H_2O	K_2CO_3	420	113(62.0)	mp 132-133.5° (CH_3OH-H_2O)
$NH_2CSNHNH_2$-H_2O	K_2CO_3	120	80(41.0)	mp 200-202° (CH_3OH)
20% CH_3SNa	---	30	142(85.0)	mp 134-135° (n-hexane)
50% CH_3CH_2SH	K_2CO_3	600	132(76.0)	mp 106.5-107° (n-hexane)
$C_6H_5CH_2SH$-H_2O	KOH	15	182(85.0)	mp 117-118° (n-hexane)
C_6H_5SH-H_2O	KOH	1050	125(65.0)	mp 137-139° (n-hexane)

6.46 (1H, complex t., C_4-H), 3.51, 3.18 (each 1H, S., aromatic ring protons)] and by analogy with the introduction of alkoxy groups in I.

(ii) A solution of I (200 mg) and thiobenzylalcohol (425 mg) in H_2O (4 ml) containing KOH (210 mg) was stirred at room temperature for 15 min. Then the reaction mixture was acidified with 10% HCl and the acidic solution was washed with ether. The aqueous layer was basified with K_2CO_3 (powder) and the product was taken up in $CHCl_3$. Usual treatment of $CHCl_3$ layer gave an oil (220 mg) yielding colorless prisms (III, R=$SCH_2\ C_6H_5$) [182 mg (85%), mp 117-118° (n-hexane)]. NMR τ: 7.56 (3H, S., $=N\underline{CH_3}$), 6.20 (2H, S., $-S\underline{CH_2}Ar$), 6.19 (3H, S., $O\underline{CH_3}$), 5.90 (1H, defused t, C_4-H), 3.48, 3.13 (each 1H, S., aromatic ring protons), 2.19 (5H, S., aromatic ring protons).

In the absence of KOH A solution of I (200 mg) in 50% pyrrolidine (4 ml) was stirred at room temperature for 15 min. Then the same treatment of the reaction mixture as described in (ii) gave an oil (193 mg) yielding colorless prisms (III, R= ) [123 mg (69%), mp 111-112.5° (n-hexane)]. NMR τ : 8.26 (4H, broad S.,- ), 7.60 (3H, S., $=N\underline{CH_3}$), 7.32, 7.28 (each 2H, broad S.,- ), 6.69, 6.48 (each 1H, AB quartet, C_1-gem. protons, J_{AB}=15 cps), 6.16 (3H, S., $O\underline{CH_3}$), 6.09 (1H, defused t., C_4-H), 3.50, 3.02 (each 1H, S., aromatic ring protons).

Similar reactions of I with other amines or thiols were carried out to afford the result shown in Table 1.

From the above result, 4-acetoxy group in I was found to be replaced more easily with amines or thiols than alcohols as expected. However the reaction of I with 50% $(CH_3CH_2)_2NH$ failed to give the corresponding 4-diethylamino compound. When compared with cyclic secondary amines, such as piperidine or morpholine, this fact seemed instructive as to sterical limitation.

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References

1) B. Umezawa, O. Hoshino and Y. Yamanashi, Tetrahedron Letters.

2) All melting points were uncorrected using a Yanagimoto micro melting points measuring apparatus.
Satisfactory elemental analyses for all compounds whose melting points were described in this paper were obtained.

3) NMR spectra were taken with a JNM-4H-100 (at 100 Mc) spectrometer in $CDCl_3$ (5 - 10% solution) using Me_4Si as internal standard.