SYNTHESIS OF 1-ACYL-1,2-DIHYDRO-1-BENZAZOCINE DERIVATIVES

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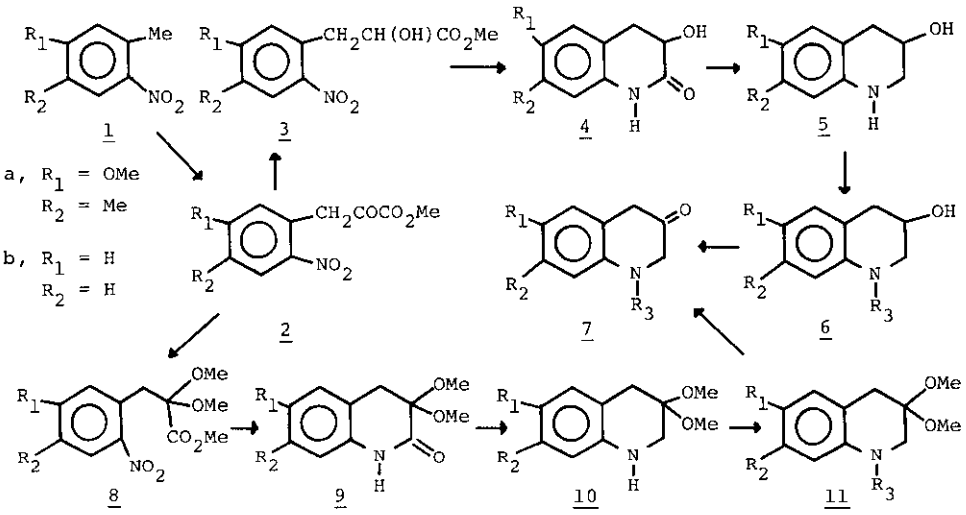
Abstract - Substituted 1,2,3,4-tetrahydroquinolin-3-one (7) was synthesized from nitrobenzene derivatives (1) in several steps. The compound (7a) was converted the pyrrolidine enamine, and then treated with dimethyl acetylenedicarboxylate (DMAD) to give a ring expanded heterocyclic product ; dimethyl 1-acetyl-1,2-dihydro-3-hydroxy-8-methoxy-9-methyl-1-benzazocine-4,5-dicarboxylate (13a).

As a part of our programme of studies on heterocyclic compounds, we reported a synthetic approach to mitomycin derivatives using a transannular cyclization of 8-membered ring compounds.[1] Now, we have designed the preparation of substituted 1,2,3,4-tetrahydroquinolin-3-one which might be expected to be useful for the syntheses of benzazocine derivatives and others. In our initial approach shown in scheme 1, methyl 5-methoxy-4-methyl-2-nitrophenylpyruvate (2a) was reduced with $NaBH_4$ followed by esterification to methyl 5-methoxy-4-methyl-2-nitrophenyllactate (3a, mp 125-126°, 87%). Catalytic hydrogenation of the nitro group with hydrogen over palladium at atmospheric pressure directly afforded the ring closed product 3-hydroxy-6-methoxy-7-methyl-1,2,3,4-tetrahydroquinolin-2-one (4a, mp 189-191°, 89%). Whereas the amide group of 4a was easily reduced with sodium bis-(2-methoxyethoxy)aluminium hydride in dry benzene at 60-70° for 1 hr to give the amine (5a, mp 97-98°, 43.8%), subsequent direct oxidation of the hydroxy function proved difficult.

Therefore, the transformation of the amino alcohol (5b) into the 3-keto compounds (7b) was examined. While various N-blocked alcohols (6b, R_3 = $COCH_3$, Ms, Ts, $COCF_3$, COOEt), prepared from 5b, stoutly resisted oxidation to 7b under various conditions, the oxidation of 6b (R_3 = $COCH_3$) with CrO_3-AcOH-c.H_2SO_4[2] at low



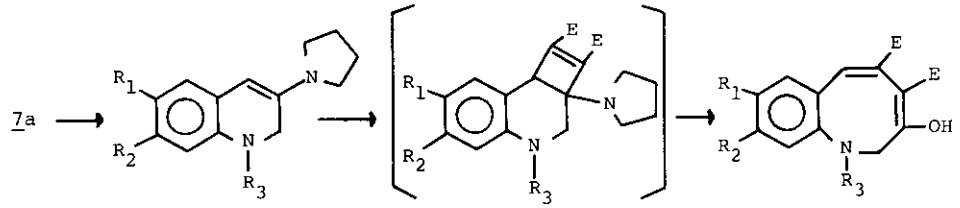
sheme 1

temperature gave the desired product (7b, $R_3 = COCH_3$) as an oil contaminated with 6b in poor yield. Evidence in support of structure 7b ($R_3 = COCH_3$) rested on the ^1H nmr ($CDCl_3$) spectrum which showed three singlets at δ 2.23 (3H, $COCH_3$), 3.54 (2H, $-CH_2-$) and 4.34 (2H, $-CH_2-$), and aromatic protons at δ 7.09, 7.21 (4H, broad), but various attempted purification of 7b ($R_3 = COCH_3$) failed.

After preparation of 7 was tried by several alternate routes, a satisfactory method was found. Treatment of pyruvic acid ester (2a) with a large excess of trimethy orthoformate in refluxing MeOH for long time in the presence of boron trifluoride-diethyl ether afforded the acetal (8a, mp 99-101°, 58%). Formation of the ring closed compound (9a, mp 231-232°) from 8a proceeded smoothly by catalytic hydrogenation over Pd-C in 95.6% yield. Subsequent reduction with sodium bis-(2-methoxyethoxy)aluminium hydride in dry benzene afforded the secondary amino compound (10a, mp 121-123°, 56.6%). Compound (10a) was acetylated quantitatively with Ac_2O in dry ether to give 11a ($R_3 = COCH_3$, mp 113-114°). The deacetallization of 11a could be accomplished by brief warming in 85%aq.AcOH or stirring with dil.HCl in CH_2Cl_2 at r.t. to give 7a in 75-85% yield; 7a [$R_3 = COCH_3$, mp 149-151°, $C_{13}H_{15}NO_3$, m/e 233 (M^+), ^1H nmr ($CDCl_3$) δ 2.23 (s, 6H, C-CH_3 and $COCH_3$), 3.56 (s, 2H, $-CH_2-$), 3.84 (s, 3H, OCH_3), 4.35 (s, 2H, $-CH_2-$), 6.64 (s, 1H, aromatic), 7.04 (br.s, 1H, aromatic), In the ^{13}C nmr ($CDCl_3$) spectrum eleven signals were

observed.].[3)]

Thus, the desired 1,2,3,4-tetrahydroquinolin-3-one (7a) was obtained in fairly good yield. Treatment of 7a with pyrrolidine gave a labile oily product [12a, R_3 = $COCH_3$, ^{1}H nmr ($CDCl_3$) δ 1.90 (m, 4H, $-CH_2CH_2-$), 2.19 (s, 6H, C-CH_3 and $COCH_3$), 3.29 (m, 4H, $-CH_2NCH_2-$), 3.81 (s, 3H, OCH_3), 4.55 (s, 2H, $-CH_2-$), 5.03 (s, 1H, vinylic), 6.44 (s, 1H, aromatic), 6.77 (br.s, 1H, aromatic)], which was



12 13

E = CO_2Me

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not purified and treated with DMAD in acetonitrile at room temperature. The addition product (13a, R_3 = $COCH_3$) was isolated by preparative TLC (Wakogel 13-5F) as a crystalline solid in 61% yield; 13a [mp = 98-101°, $C_{19}H_{21}NO_7$, m/e 375 (M^+), ^{1}H nmr ($CDCl_3$) δ 1.59 (s, 3H, $COCH_3$), 2.23 (s, 3H, C-CH_3), 3.68 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.71 (d, 1H, J = 18Hz, C_2-H), 6.75 (s, 1H, aromatic), 7.02 (s, 1H, aromatic), 7.63 (s, 1H, vinylic), 13.00 (s, 1H, OH), The ^{13}C nmr ($CDCl_3$) showed eighteen signals.].

Further investigations relating to these tetrahydroquinolone derivatives (7) are in progress.

Acknowledgements and References

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1 a J. W. Lown and T. Itoh, Canad. J. Chem. Soc., 1975, 53, 960.

b T. Itoh, T. Hata and J. W. Lown, Heterocycles., 1976, 4, 47.

2 S. S. Chatterjee and A. Shoeb, Synthesis., 1973, 153.

3 The structure assignments of the products are based on the satisfactory elemental analyses and spectral data.

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