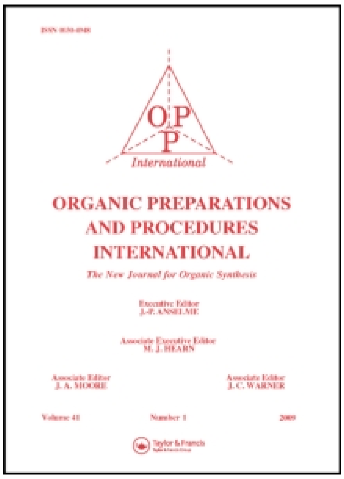

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A NEW SYNTHESIS OF N-BENZYL-2,3-DIHYDRO-4(1H)-ISOQUINOLONE

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A NEW SYNTHESIS OF N-BENZYL-2,3-DIHYDRO-4(1H)-ISOQUINOLONE

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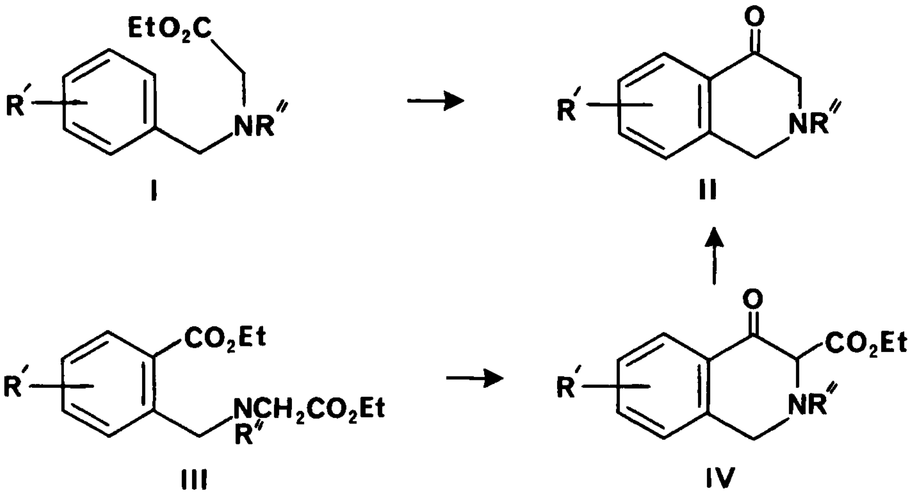
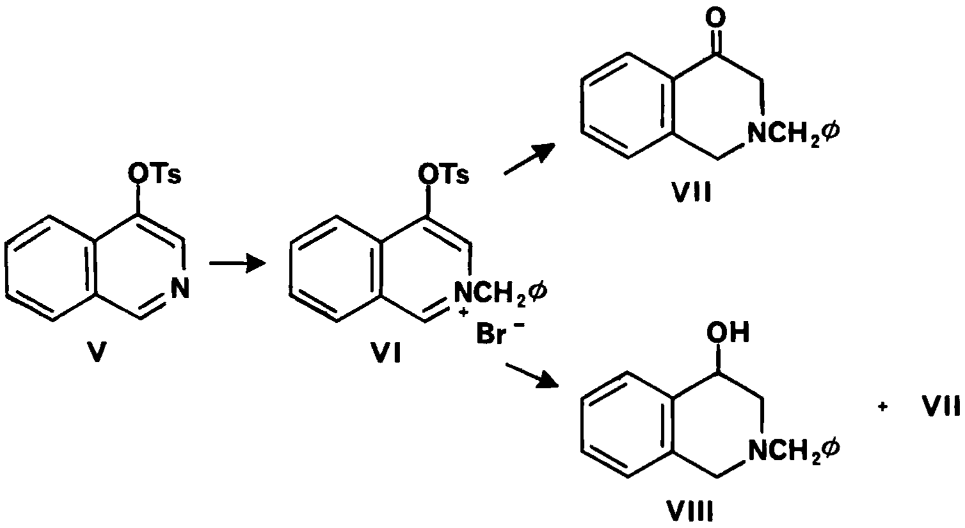
The 2,3-dihydro-4(1H)-isoquinolone (II) ring system has previously been synthesized by acid-catalyzed cyclization of appropriately substituted N-benzylglycine derivatives (I),[1a] and by the Dieckmann cyclization of a diester (III) followed by hydrolysis and decarboxylation of the intermediate β-keto ester (IV).[1b]



The former method suffers from the drawbacks that the aromatic ring must be activated in some manner in order for cyclization to occur since labile groups at R' will not withstand the strong acidic conditions required for cyclization, and the group at R" must be introduced relatively early in the synthetic scheme. When R' is H or an electron-withdrawing substituent, the latter method must be employed and requires various substituted o-toluic esters which are often difficult to synthesize; problems with the separation of isomers also exist.[1b]

We wanted a synthetic scheme which would be mild enough to allow a variety of substituents at R', allow introduction of R" at a relatively late stage in the process and could be carried out on a large scale. Our approach utilizes the rearrangement of isoquinoline-N-oxide with p-toluenesulfonyl chloride to give 4-tosyloxyisoquinoline (V) as described by Ochiai.[2] The quaternization of V with benzyl bromide gave VI in good yield.



Treatment of VI with $NaBH_4$ in pyridine[3,4] gave a 1:1 mixture (determined by nmr and mass spec) of VII and VIII. Apparently VII underwent further reduction with excess $NaBH_4$ to give VIII. Reaction of VI with $NaBH_3CN$ in pyridine at 65° for 45 min gave a 65% yield of VII identical in all respects to an authentic sample of VII prepared by the Dieckmann cyclization method.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR8 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60 spectrometer with d_6-DMSO as solvent and TMS as internal standard. Chemical shifts are reported in δ values in parts per million (ppm) downfield from the TMS signal. Mass spectra were determined on a Hitachi-Perkin-Elmer RMU-6H mass spectrometer. Elemental analyses were obtained on a Perkin-Elmer model 240 C,H,N analyzer.

4-[(4-Methylphenyl)sulfonyl]oxy-2-phenylmethylisoquinolinium bromide (VI). - A solution of 3.0 g (0.010 mole) of 4-tosyloxyisoquinoline[2] in 60 ml of THF was treated with 2.2 g (0.013 mole) of benzyl bromide and the mixture was heated at reflux for 5 hr. The solution was concentrated *in vacuo* and addition of diethyl ether to the residue caused a white solid to precipitate. The solid was collected by filtration and dried to yield 3.2 g (66%) of VI, mp.170-173°, in analytical purity. IR (KBr) cm^{-1} 2940, 1590, 1385, 1165, 725. ^1H nmr (d_6-DMSO): δ 2.46 (S,3H,$\underline{CH_3}$), 6.17 (S,2H,$\overset{+}{N}$-$\underline{CH_2}$-C_6H_5), 7.30-8.90 (m,13H,aromatic), 8.98 (S,1H,3-$\underline{H}$), 10.72 (S,1H,1-$\underline{H}$).

Anal. Calcd. for $C_{23}H_{20}BrNO_3S$: C, 58.73; H, 4.29; N, 2.98

Found: C, 58.74; H, 4.34; N, 2.96

2-Benzyl-2,3-dihydro-4(1H)-isoquinolone hydrochloride (VII).- To a stirred solution of 75 g (1.2 mole) of $NaBH_3CN$ in 500 ml of pyridine at 50° was added 150 g (0.3 mole) of VI over a 5-min period. The temperature rose to 90° during addition and was maintained at 65° for 40 min. The reaction mixture was poured into 2 l. of a cold 2% NaOH solution, NaCl was added, and the solution extracted several times with diethyl ether. The combined extracts were washed with H_2O, dried over Na_2SO_4, and treated with HCl gas. The solid which precipitated was collected by filtration and recrystallized from ethanol-isopropyl ether to yield 56 g (65%) of VII as an off-white powder, mp 199-200°. IR (KBr) cm^{-1} 1880, 1415, 1280, 770, 695. ^1H nmr (d_6-DMSO): δ 4.18 (S,2H,CO-CH_2-N), 4.54 (S,2H,N-CH_2-C_6H_5), 4.60 (S,2H,ring CH_2), 7.35-8.15 (m,9H,aromatic).

Anal. Calcd. for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12

Found: C, 70.33; H, 5.93; N, 5.21

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