FACILE SYNTHESIS OF STYRYLQUINUCLIDINES

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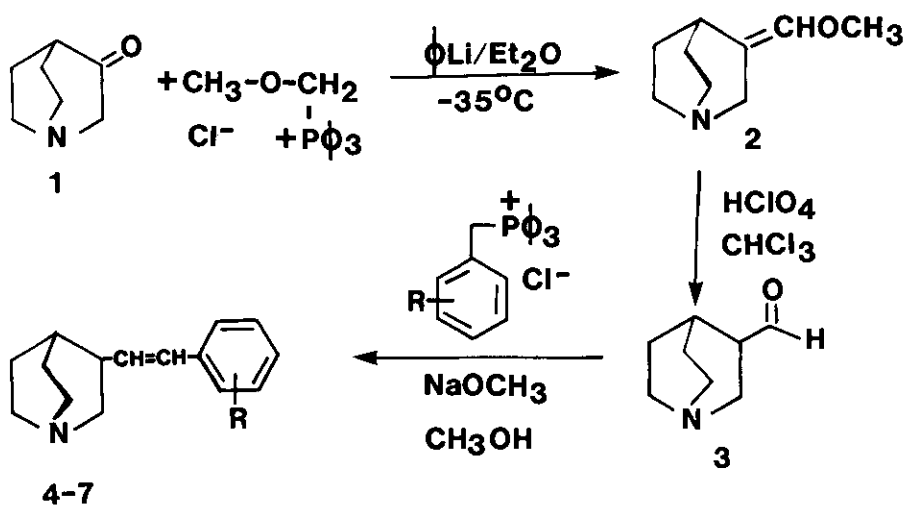
Abstract - 3- and 2-Quinuclidinecarboxaldehydes, 3 and 12, were prepared by Wittig reaction and DIBAH reduction respectively. These aldehydes were used to prepare the corresponding 3 - and 2-styrylquinuclidines, 4-7 and 13-16, via Wittig reactions.

In the course of our investigation of centrally active inhibitors of acetylcholine synthesis, it was necessary to prepare several 3- and 2-styryl-substituted quinuclidines. Preparation of these derivatives was accomplished via the corresponding 3- and 2-quinuclidinecarboxaldehydes 3 and 12. Difficulty with the synthesis of 3 and 12 has restricted their use in the literature[1-3]. Convenient syntheses of these key intermediates were carried out in our laboratory.

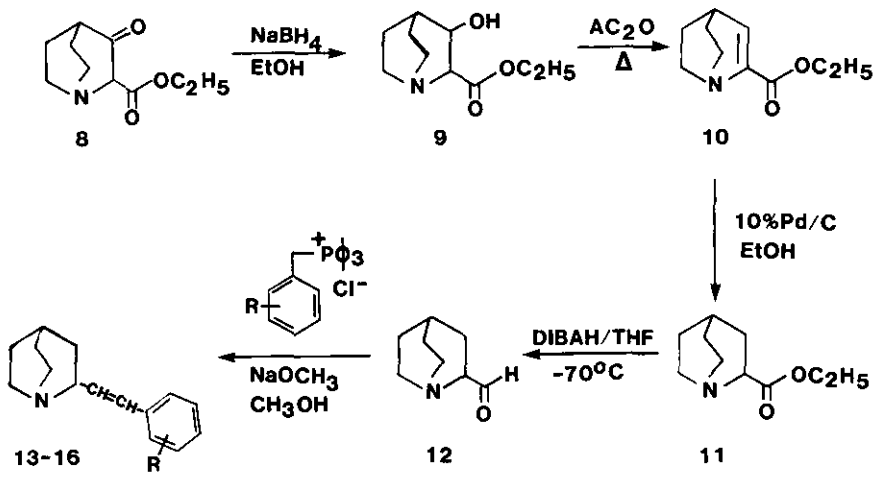
The reaction of methoxymethyltriphenylphosphonium chloride with 3-quinuclidinone 1 and phenyl lithium provides a convenient and stable precursor to 3 (Scheme I). We encountered considerable difficulty and very low yields with the hydrolysis of the methyl enol ether 2 in several acids (acetic, hydrochloric, sulfuric, boron trifluoride). Furthermore, while dilute HCl effects complete hydrolysis, this method leads to a very impure product. Perchloric acid in chloroform, however, was found to effect quantitative hydrolysis. Attempts to further derivatize the aldehyde resulted in significant loss of product, thus 3 was best stored as the enol ether 2. After hydrolysis and workup it was possible to use the aldehyde without further purification. Subsequent Wittig reactions of 3 with the appropriately substituted benzylphosphonium salt were easily carried out with sodium methoxide in methanol to give the 3-styryl-quinuclidines 4-7.



Scheme I

In the preparation of quinuclidine-2-carboxyaldehyde 12, 3-keto-2-carboethoxyquinuclidine 8 was used as the precursor as shown in Scheme II. Reduction of the ketone 8 has been reported utilizing Raney nickel[3], however, the increased difficulty of large scale reactions, as was our need, led us to the more facile and convenient use of sodium borohydride. Attempts to improve the yield of dehydration of the resultant alcohol 9 using stronger dehydrating agents resulted in lower yields in all cases. Conversion of the ester 11 to the aldehyde,[4,5] was effected using DIBAH (Diisobutyl Aluminum Hydride) in tetrahydrofuran at -70°C. Compound 12 was produced in good yield and with sufficient purity to be used directly in the ensuing reactions. Wittig reactions of 12 provided the desired 2-substituted quinuclidines 13-16 without difficulty. Purification of final products 4 to 7 and 13 to 16 was best carried out by column chromatography of either

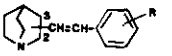
the free bases or the corresponding hydrochloride salts on silica gel. Several of the styryl quinuclidines inhibited cholineacetyl-transferase in vitro with Ki values in the range of 10^{-5}M/L.



Scheme II

EXPERIMENTAL

Synthesis of 3-Quinuclidinyl Aldehyde 3 via the Methyl Enol Ether 2:
This reaction was carried out under nitrogen using previously dried glassware, syringes, needles and spatulas. Methoxymethyltriphenylphosphonium chloride (29.6 gms, 0.0865 M) and 150 ml of dry ether were added to a 500 ml 3-necked flask equipped with a magnetic stirrer, dropping funnel, nitrogen inlet and a septum. Thirty two ml of a 2.7 M solution of phenyl lithium in ether (0.0865 M) was added dropwise, via syringe through the septum covered inlet, at room temperature with stirring. As the ylid formed, the contents of tne reaction flask developed a reddish-orange color. After complete addition of the phenyl lithium, the mixture was stirred for an additional 15 min and then cooled to -35°C (acetone/dry ice). The quinuclidinone (0.0865 M) in dry ether was added slowly in a dropwise fashion via the dropping funnel, at a rate that maintained the bath temperature at -35°C.

Table 1. Styrylquinuclidines 

Cpd. #[a]	R	mp[b] °C	Molecular Formula[c]	^{1}H-NMR ($CDCl_3$/TMS_{int}) ppm	Mass m/z
4	H	237-238°	$C_{15}H_{18}N$ (212.30)	1.02-2.12 (m,5H), 2.30-3.42 (m,7H), 5.88 (t,1H), 6.57 (d,1H), 7.37 (s,5H)	213
5	p-Cl	188-189	$C_{15}H_{17}NCl$ (246.76)	1.00-1.97 (m,5H), 2.30-3.27 (m,7H), 5.98 (t,1H), 6.57 (d,1H), 7.40 (q,4H)	247
6	m-Cl	176-178	$C_{15}H_{17}NCl$ (246.76)	1.08-2.23 (m,5H), 2.35-3.27 (m,7H), 5.97 (t,1H), 5.52 (d,1H), 7.05-7.60 (m,4H)	247
7	3,4-Cl_2	108-109	$C_{15}H_{16}NCl_2$ (281.20)	1.17-2.03 (m,5H), 2.50-3.23 (m,7H), 5.93 (t,1H), 6.43 (d,1H), 6.93-7.65 (m,3H)	281
13	H	107-108	$C_{15}H_{18}N$ (212.30)	1.1-2.1 (m,7H), 2.5-3.3 (m,4H), 3.3-3.8 (m,1H), 5.55-6.25 (m,1H), 6.3-6.65 (m,1H), 7.2-7.7 (m,5H)	213
14	p-Cl	205-206	$C_{15}H_{17}NCl$ (246.76)	1.1-2.0 (m,7H), 2.6-3.2 (m,4H), 3.2-3.45 (m,1H), 5.90 (d,1H), 6.48 (d,1H), 7.0-7.4 (m,4H)	247
15	m-Cl	173-175	$C_{15}H_{17}NCl$ (246.76)	1.0-2.1 (m,7H), 2.6-3.2 (m,4H), 3.3-3.9 (m,1H), 5.6-6.1 (m,1H), 6.3-6.8 (m,1H), 7.2-7.65 (m,4H)	247
16	3,4-Cl_2	169-170	$C_{15}H_{16}NCl_2$ (281.20)	1.0-2.1 (m,7H), 2.4-3.2 (m,4H), 3.2-3.8 (m,1H), 5.6-6.7 (m,2H), 6.8-7.6 (m,3H)	281

a. Products 4-7 are substituted at the 3-position of quinuclidine; Products 13-16 are substituted at the 2-position of quinuclidine.
b. Melting points of the corresponding hydrochloride salt.
c. Satisfactory microanalyses were obtained.

The mixture was allowed to come to room temperature slowly and thereafter stirred overnight under nitrogen. The reaction mixture was then filtered through Celite-545 using a sintered glass funnel, the filtrate cooled to precipitate triphenylphosphine oxide and lithium chloride and refiltered. The solvent was removed under vacuum and the residue distilled to give the enol ether (yield: 61%) as a clear, colorless oil boiling at 57-58°C (2.5 mm Hg). NMR ($CDCl_3$): δ = 5.83 (s,1H); 3.60 and 3.55 (2s,3H); 3.42 (s,2H); 2.67-3.19 (t,5H); 1.37-1.93 (m,4H).

The enol ether in chloroform was treated with concentrated perchloric acid (8 drops per 100 mg of enol ether) added dropwise over 10 min at room temperature. The mixture was stirred for an additional 15 min, placed in an ice bath and basified with saturated sodium carbonate solution. The phases were separated, the aqueous layer extracted with fresh chloroform, the organic layers combined and dried over sodium sulfate, filtered, and the solvent removed under vacuum to yield the aldehyde 3 as a yellow oil which was immediately used in the next reaction. NMR ($CDCl_3$): δ = 9.83 (s,1H); 2.38-3.13 (m,6H); 2.32 (m,1H); 1.23-1.90 (m,5H).

Preparation of 2-Carboethoxy-3-hydroxyquinuclidine, 9:

2-Carboethoxy-3-ketoquinuclidine, 8, was prepared according to literature methods.[3] A solution of this ketoester (20 mM) in anhydrous ethanol (25 ml) was cooled to 5°C in an ice bath. A solution of sodium borohydride (5.5 mM) in 25 ml of ethanol was then added dropwise with stirring over a period of 30 min. The reaction was allowed to warm to room temperature and stir for an additional 2 h. The solution was then cooled to 0°C and neutralized with concentrated hydrochloric acid. The ethanol was removed under reduced pressure and saturated aqueous potassium carbonate (5 ml) was added to the residue. The mixture was extracted with chloroform, the organic layer dried over sodium sulfate, filtered, and removed under reduced pressure to affort 9 as a solid in 78% yield. As a mixture of two diastereomers, evidenced as two distinct spots on TLC, the product has a broad melting range up to 148°C in agreement with literature values[3]. NMR ($CDCl_3$): δ = 1.20 (t,3H); 1.0-2.2

(m,6H); 2.23 (s,1H,D_2O exchangeable); 2.5-3.4 (m,4H); 4.29 (q,2H); 4.20 (br s, 1H).

Preparation of 2-Quinuclidinecarboxaldehyde, 12:

A mixture of cis and trans-2-carboethoxy-3-hydroxyquinuclidine 9 in acetic anhydride was refluxed for 6 h. Workup afforded 2-carboethoxy-2-dehydroquinuclidine 10 which was then hydrogenated over 10% palladium on activated carbon in ethanol for 1 h to give 2-carboethoxy-2-quinuclidine 11 in 72% overall yield[3]. A solution of the aforementioned ester (2.14 mM) in 20 ml of tetrahydrofuran under nitrogen was cooled to -70°C. Diisobutyl aluminum hydride (4.28 mM) in 4.28 ml of tetrahydrofuran was added dropwise over a period of 15 min and the mixture was allowed to stir at -70°C for 3 h. The reaction was quenched with the addition of dry methanol (3 ml) followed by 3 ml of methanol saturated with hydrogen chloride gas. The solution was warmed to 15°C and the solvent removed under reduced pressure at this temperature. Aqueous potassium carbonate (20%, 10 ml) was added and stirring continued until effervescence ceased. Ether (25 ml) was added and the mixture filtered. The layers were then separated and the solid was washed with several portions of hot ether. These washings were used to extract the aqueous layer. The combined ether fractions were dried over sodium sulfate and evaporated to dryness to afford the aldehyde 12 as an oil in 66% yield. The aldehyde was used immediately in the next reaction to form the various 2-styrylquinuclidines. NMR ($CDCl_3$): δ = 1.0-2.4 (m,7H); 2.5-4.2 (m,5H); 9.86 (s,1H).

Synthesis of Styrylquinuclidines (4-7; 13-16):

Sodium (230 mg; 10 mM) was dissolved in 25 ml of dry methanol in a 100 ml round bottom flask. The appropriate Wittig salt (8.2 mM) was then added to the solution of sodium methoxide to give a yellow suspension which was stirred an additional 10 min in an ice bath. The suspension of the ylid was added to a solution of 8.2 mM of quinuclidinyl aldehyde in 10 ml of dry methanol and the mixture stirred at room temperature, under nitrogen, overnight.

The reaction mixture was acidified to pH 2 with 4 N hydrochloric acid in an ice bath, and the methanol removed under vacuum. Water was then added to the residue and the mixture extracted with three 20 ml portions of benzene. The aqueous layer was basified to pH 12 with 40% sodium hydroxide in an ice bath and re-extracted with chloroform. The chloroform layer was dried over sodium sulfate, filtered, and the solvent removed under vacuum to give a yellow oil. The 2-styrylquinuclidine free bases, 4-7, were isolated via chromatography on silica gel using chloroform:methanol (3:2) with 1% ammonium hydroxide. The eluate was stripped of solvent under vacuum and evaporated to give the product as an oil (yield: 60-70%).

The 3-styrylquinuclidine free bases, 13-16, were isolated via chromatography on silica gel using chloroform:methanol (3:2) with 1% ammonium hydroxide; the oil thus derived was then converted to the hydrochloride salt and rechromatographed on silica gel using chloroform:methanol (1:1) with 0.5% HCl. The eluate was stripped of solvent under vacuum and the residue treated with saturated sodium carbonate solution. The aqueous solution was then extracted with chloroform, the organic layer dried over sodium sulfate, filtered, and evaporated to give the product as an oil (yield: 80-85%).

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