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LACTAM ACETALS : PART XXIV
REACTION WITH ACTIVATED HALOALKYL COMPOUNDS WITH AND WITHOUT ZINC [1]

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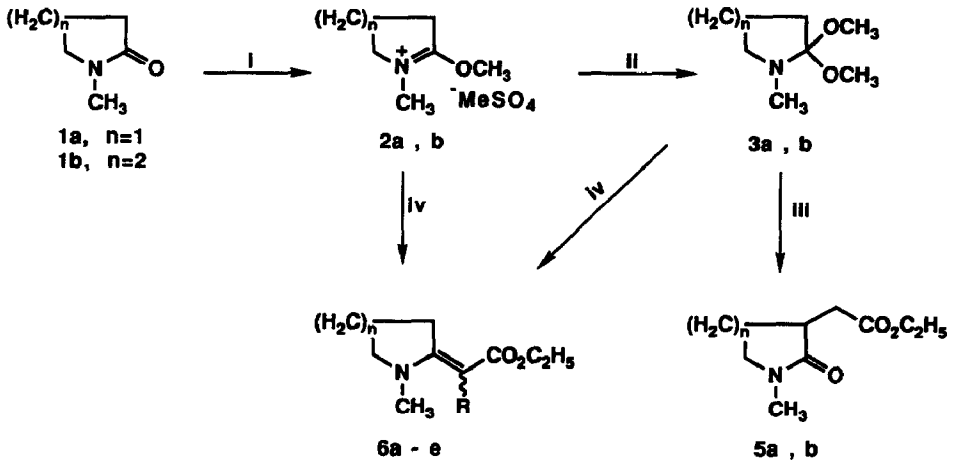
Abstract: *Reaction of 2-alkoxyimmonium methosulfates* **(2)**, *and of lactam acetals* **(3)** *derived therefrom, with α-haloesters in presence of zinc (Reformatsky condition) yielded N-alkyl-2-(α-alkyl-α-alkoxycarbonyl)methylene-1-azacycloalkanes* **(6)**, *while reaction of* **3** *with α-haloesters without zinc gave 3-alkoxycarbonylmethyl-1-azacycloalkane-2-one* **(5)**. *Similar reaction of* **2** *and* **3** *with 4-bromomethylquinolin-2-one* **(4)** *in presence of zinc gave N-alkyl-2-[4-(2-oxoquinolyl)methylene]-1-azacycloalkanes* **(7)**, *a key intermediate for the synthesis of antimalarial quinoline-4-methanols.*

Pyrrolidinyl and piperidinyl-acetic acids are important synthons commonly needed in organic synthesis[2-4]. If a carboxyalkyl residue could be conveniently grafted onto a pyrrolidinyl or piperidinyl substrate by a short path synthesis, these intermediates could become readily available. Pyrrolidone and piperidone acetals[5] (or their immonium intermediates) can react as electrophile at C-2 and as nucleophile at C-3. While α-haloesters similarly act as C-α-electrophiles when used as such or as C-α-nucleophile under Reformatsky conditions[6]. The condensation of pyrrolidone and piperidone acetals (or immonium intermediates thereof) seemed to offer the possibility of direct obtention of the corresponding 2- or 3-carboxyalkyl derivatives depending upon the reaction conditions used. Similarly reaction of 4-bromomethylquinolin-2-one with lactam acetals under conditions where side chain methyl would be electrophilic (as under Reformatsky conditions) seemed to offer a convenient route to the synthesis of 4-[2-(1-azacycloalkyl)methyl]quinolinones, which are useful intermediates for synthesis of quinolinemethanol antimalarials[7] related to quinine and mefloquine. The successful execution of these reactions is reported in this communication.

Condensation of ethyl bromoacetate [35 mmol] with lactam acetals **3a and b** [20 mmol] in a sealed tube at 120° gave 3-carbethoxymethyl-1-

methyl-2-pyrrolidone/piperidone **(5a and b)**[8] in excellent yields **(Scheme 1, Table 1)**. On the other hand, when lactam acetals **3a and b** [12 mmol] were reacted with ethyl 2-bromoacetate/propionate/butyrate [10 mmol] in presence of freshly activated zinc dust [12 mmol] in Reformatsky reaction condition, the corresponding 2-(α-alkyl-α-ethoxycarbonyl)methylene-1-methylpyrrolidines/piperidines **(6a-e)**[9] were obtained in 27-38% yield **(Scheme 1, Table 1)**. With a view to further reduce the number of steps, the Reformatsky reaction was carried out on methoxyimmonium methosulfates **2a and b**, which are intermediates in the preparation of lactam acetals, when 2-(α-alkyl- α-ethoxycarbonyl)methylene-1-methylpyrrolidines/piperidines **(6a-d)** were obtained even more conveniently and in better yield (46-58%) **(Scheme 1, Table 1)**. **6a and d** have been synthesized earlier by reacting (methylthio)alkylideniminium salt with ethyl acetate[2] or with Meldrum's acid[3] whereas **6b** were prepared by alkylation[4] of **6a**.



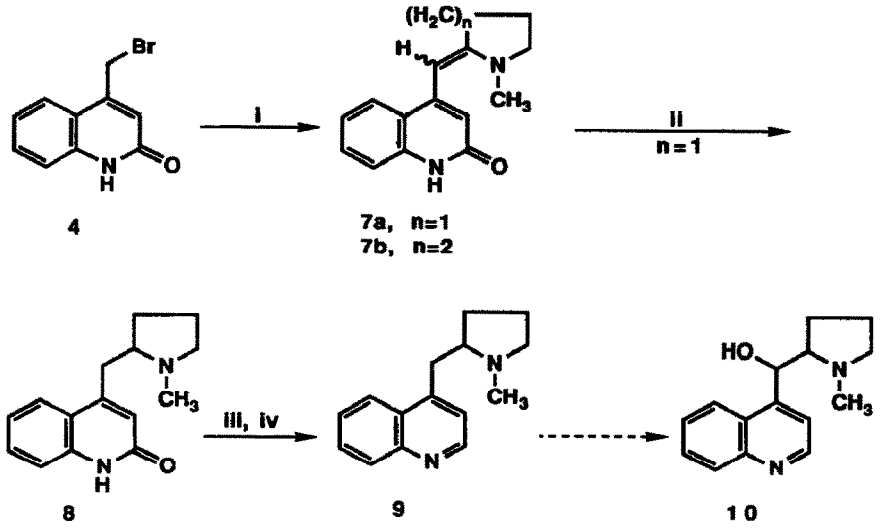
Reagents: I. Me_2SO_4, 80°; II. NaOMe/ MeOH, 50°; III. $BrCH_2CO_2Et$, 120°; IV. Zn, $BrCH(R)CO_2Et$;H^+

SCHEME - 1

The reaction of 4-bromomethyl-1,2-dihydroquinolin-2-one[10] [**4**, 30 mmol] with **2a and b** and/or **3a and b** [36 mmol] and activated zinc dust [39 mmol] in anhydrous THF (50 ml) was next carried out when 4α-(1-methyl-2-pyrrolidinylidene/piperidinylidene)methyl-1,2-dihydroquinolin-2- one **(7a and b)**[11] were obtained **(Scheme 2, Table 1)**. Compound **7a** on catalytic hydrogenation (Pd-C catalyst at 3.5 kg/cm^3 H_2 pressure in a Parr hydrogenator) afforded the 4 α-(1-methyl-2-pyrrolidinyl)methyl-1,2-dihydroquinolin-2-one **(8)**[12] in excellent yield. **8** on $POCl_3$ treatment followed by Pd-C hydrogenation in presence of triethylamine at RTP gave 4α-(1-

methyl-2-pyrrolidinyl)methylquinoline (9)[13] in 77% yield. This easy availability of 4α-(1-methyl-2-pyrrolidinyl)methylquinoline (9) which has earlier been oxygenated to quinolinemethanols 10[7],provides a short and convenient approach to the synthesis of 4α-heterocycloalkyl quinoline-4-methanols.

The Reformatsky reaction of α-haloesters with lactim ethers and lactim thioethers was also studied but proved unsuccessful.



Reagents: I. 2 or 3, Zn, 80°,+H⁺; II. H_2, Pd-C, 45psi; III. $POCl_3$, 80°; iv. H_2, Pd-C, Et_3N, RTP

SCHEME - 2

Table 1 : Physical constants of componds 5-7 #

Entry No.^	n	R	% yield From 2	% yield From 3
5a	1	-	-	89.5
5b	2	-	-	82.1
6a	1	H	58.3	35.5
6b	1	Me	51.7	33.9
6c	1	Et	46.2	27.9
6d	2	H	49.5	36.1
6e	2	Me	46.1	37.3
7a	1	-	63.0	56.5
7b	2	-	42.8	25.6

 # Products were purified by chromatography using Silica gel (230-400 mesh), and chracterised by their IR, NMR, MS data and gave satisfactory elemental analysis.
^ All compounds are oil in nature except 7a (mp. 254°)

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8. Spectral data of **5a**:: IR[Neat,cm^{-1}]: 1740 (ester), 1690 (carbonyl). ^1H NMR[$CDCl_3$, δ ppm]: 1.25 (t, 3H, J=6 Hz, $-CCH_3$), 2.00-2.50 (m, 4H, 4-CH_2 & $-CHC\underline{H}_2$), 2.80-3.10 (m, 4H, $-NCH_3$ & 3-CH), 3.30-3.60 (m, 2H, 5-CH_2), 4.15 (q, 2H, J=6 Hz, $-OCH_2$). MS: m/z 185 (M^+). Analysis calcd for $C_9H_{15}NO_3$: C, 58.35; H, 8.16; N, 7.56. Found: C, 58.79; H, 8.03; N, 7.71%.
9. Spectral data of **6a**:: IR[Neat,cm^{-1}]: 1620 (carbonyl). ^1H NMR[$CDCl_3$, δ ppm]: 1.20 (t, 3H, J=6 Hz, $-CCH_3$), 1.70-2.20 (m, 2H, 4-CH_2), 2.70 (s, 3H, $-NCH_3$), 2.90-3.65 (m, 4H, 3,5-CH_2), 4.05 (q, 2H, J=6 Hz, $-OCH_2$), 4.45 (s, 1H, olefinic-H). MS: m/z 169 (M^+). Analysis calcd for $C_9H_{15}NO_2$: C, 63.87; H, 8.93; N, 8.27. Found: C, 63.90; H, 8.87; N, 8.53%.
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11. Spectral data of **7a**:: IR[KBr,cm^{-1}]: 1625 (carbonyl). ^1H NMR[$CDCl_3$, δ ppm]: 1.70-2.20 (m, 4H, 3' & 4'-CH_2), 2.90 (s, 3H, $-NCH_3$), 3.20-3.50 (m, 2H, 5'-CH_2), 5.22 (s, 1H, =CH), 6.32 (s, 1H, 3-ArH), 7.00-7.90 (m, 4H, ArH). MS: m/z 240 (M^+). Analysis calcd for $C_{15}H_{16}N_2O$: C, 75.00; H, 6.66; N, 11.66. Found; C, 74.77; H, 6.33; N, 11.51%.
12. Spectral data of **8**:: yield 72.0%, IR[KBr,cm^{-1}]: 1620 (carbonyl). ^1H NMR[$CDCl_3$, δ ppm]: 1.51-2.00 (m, 4H, 3' & 4'-CH_2), 2.19-2.91 (m, 5H, $-NCH_3$ & 1'-CH_2), 3.02-3.61 (m, 3H, 5'-CH_2 & 2'-CH), 6.68 (s, 1H, 3-ArH), 7.00-7.92 (m, 4H, ArH). MS: m/z 242 (M^+). Analysis calcd for $C_{15}H_{19}N_2O$: C, 74.38; H, 7.43; N, 11.57. Found: C, 74.11; H, 7.07; N, 11.17%.
13. Spectral data of **9**:: yield 77.0%, IR[Neat, cm^{-1}]: 1600 (aromatic). ^1H NMR[$CDCl_3$, δ ppm]: 1.60-2.10 (m, 4H, 3' & 4'-CH_2), 2.60 (s, 3H, $-NCH_3$), 2.80-3.10 (m, 5H, 1' & 5'-CH_2 & 2'-CH), 7.28-7.35 (m, 1H, 3-ArH), 7.58-8.20 (m, 4H, ArH), 8.80-8.90 (m, 1H, 2-ArH). MS: m/z 226 (M^+). Analysis calcd for $C_{15}H_{18}N_2$: C, 79.64; H, 7.96; N, 12.38. Found: C, 79.42; H, 7.56; N, 12.00%.

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