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Cyclization of Secondary Aromatic Amines with Formaldehyde and Cyclopentanone

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Abstract — Secondary aliphatic–aromatic and aromatic amines react with formaldehyde and cyclopentanone in the presence of perchloric acid to form cyclopenta[*c*]quinolinium salts in good yields. The yields of the cyclization conditions as a function of reagent ratio and reaction time and temperature were studied, and procedures for isolation and purification of the target compounds were developed.
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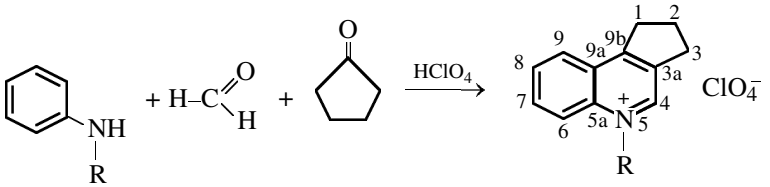
Condensed heterocyclic compounds containing, along with the pyridine ring, saturated five- and six-membered rings exhibit a broad-spectrum biological activity. Such molecular fragments (pharmacophores) enter in the composition of alkaloids and medicines [1].

It was previously shown that secondary aromatic amines in the presence of mineral acids react with formaldehyde and acetone to form *N*-alkyl- and *N*-aryl-substituted lepidinium salts [2]. Depending on reaction conditions and reagent structure, both phenanthridium [3] and acridinium derivatives can form [4].

Of particular interest is to synthesize quinolinium derivatives condensed with the cyclopentane ring, since such compounds have exhibited anticarcinogenic activity [5]. The formation of cyclopenta[*c*]quinolinium derivatives would be expected on condensation of aromatic amines with cyclopentanone and formaldehyde [6, 7]. Actually, we found that the cyclocondensation of secondary aromatic amines with formaldehyde and cyclopentanone in a mixture of 1-butanol and nitrobenzene in an acidic medium (HCl, HBr, $HClO_4$) readily occurs in one stage and gives rise to cyclopenta[*c*]quinolinium salts. The reaction can also be accomplished with aliphatic–aromatic (*N*-methyl-, *N*-ethyl-, and *N*-benzylanilines), secondary aromatic [diphenylamine, (2-naphthyl)phenylamine], and heterocyclic (tetrahydroquinoline) amines. Such a wide range of amines allows one to widely vary substituents at the nitrogen atom in the target reaction products.

The cyclization was performed by heating amine with excess cyclopentanone in a 1-butanol–nitrobenzene solvent. Therewith, nitrobenzene functions as a mild oxidative agent. The use of perchloric acid is preferred, since the resulting salts are readily crystallized. The solvents are removed by steam distillation. Crystals of salts form and are filtered off and recrystallized from a corresponding solvent.

The reactions of *N*-methyl-, *N*-ethyl-, and *N*-benzylanilines with formaldehyde and cyclopentanone can take two pathways to form linear or angular products. However, our reaction occurs regioselectively and gives a single product that contains the cyclopentane ring in position [*c*] of the quinoline nucleus (compounds **I**–**IV**) (see table).



I–IV

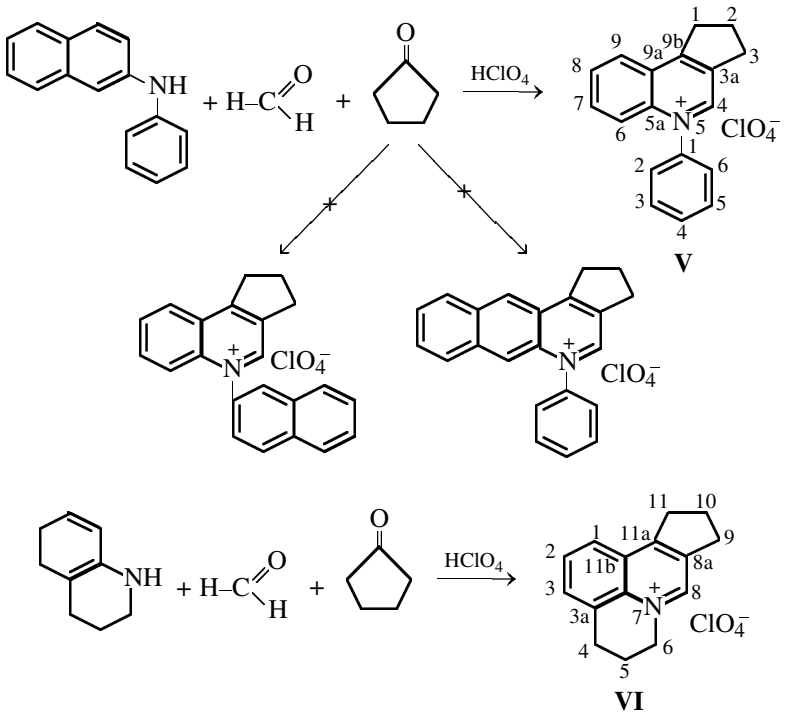
R = CH_3 (**I**), C_2H_5 (**II**), $CH_2C_6H_5$ (**III**), C_6H_5 (**IV**).

Yields, melting points, IR, UV, and ^{1}H NMR spectra, and elemental analyses of salts **I**–**VI**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	IR spectrum, cm^{-1}			UV spectrum, λ, nm (log ε)	^{1}H NMR spectrum, δ, ppm	Found N, %	Formula	Calculated N, %
			aromatic	aliphatic	ClO_4^-					
I	30	215–216 (*i*-PrOH)	708 s, 900 arom	1456 m, 1364 s (CH_3), 736 m (CH_2)	2979 1090 s	212 (2.89), 228 (3.06), 280 (2.15)	7.80–8.06 (4H, Ph), 9.12 (1H, 4-CH), 3.57 (2H, 1-CH_2), 2.50 (2H, 2-CH_2), 3.34 (2H, 3-CH_2), 2.41 (3H, NCH_3)	4.85	$C_{13}H_{14}ClNO_4$	4.94
II	32	203–205 (EtOH)	708 s, 900 m	1456 m, 1464 s (CH_3), 736 m (CH_2)	2972 s, 1090 s	212 (3.22), 240 (3.40), 315 (2.61)	8.0–8.52 (4H, Ph), 9.36 (1H, 2-CH), 3.41 (2H, 1-CH_2), 2.50 (2H, 2-CH_2), 3.05 (2H, 3-CH_2), 5.05 (2H, N-CH_2), 1.88 (3H, CH_3 in 5-Et)	4.65	$C_{14}H_{16}ClNO_4$	4.70
III	43	180–182 (EtOH)	748 s, 768 s, 904 m	1452 s (CH_2), 704 s (CH_2)	2850 s, 1100 s	212 (2.82), 239 (2.90), 329 (2.05)	7.39–7.96 (5H, Ph), 8.09–8.48 (4H, Ph), 9.69 (1H, 2-CH), 3.65 (2H, 1-CH_2) 2.47 (2H, 2-CH_2), 3.42 (2H, 3-CH_2), 6.31 (3H, CH_3)	4.15	$C_{19}H_{18}ClNO_4$	4.05
IV	51	204–205 (*i*-PrOH)	750 s, 770 s, 910 m	1450 s (CH_2)	2840 s, 1100 s	210 (3.46), 240 (3.40), 330 (2.65)	7.60–7.80 (5H, NPh), 8.05–8.49 (4H, Ph), 9.42 (1H, 2-CH), 3.74 (2H, 1-CH_2), 2.50 (2H, 2-CH_2), 3.44 (2H, 3-CH_2)	3.85	$C_{18}H_{16}ClNO_4$	3.89
V	15	220–222 (*i*-PrOH)	804 s, 980 m (CH_2)	1452 s, 690 s	28900 s, 18000 s	230 (3.53), 245 (3.49), 286 (3.11)	7.50–7.80 (5H, Ph), 7.96–8.96 (5H, benzo-[*f*]), 9.5 (1H, 2-CH), 4.17 (2H, 1-CH_2), 2.50 (2H, 2-CH_2), 3.44 (2H, 3-CH_2)	3.5	$C_{22}H_{16}ClNO_4$	3.56
VI	30	159–161 (EtOH)	775 s, 800 s, 920 s	1468 v.s, 1462 (CH_2)	2800 v.s, 1050 v.s	210 (3.88), 245 (4.6), 333 (3.11)	7.89–8.10 (3H, Ph), 9.30 (1H, 8-CH), 3.15 (2H, 4-CH_2), 2.41 (2H, 5-CH_2), 4.93 (2H, 6-CH_2), 3.33 (2H, 9-CH_2), 2.41 (2H, 10-CH_2), 3.59 (2H, 11-CH_2)	4.45	$C_{15}H_{16}ClNO_4$	4.52

With (2-naphthyl)phenylamine, the cyclization can occur both into the *ortho* position of the benzene ring and into the α and β positions of the naphthalene ring, but, here, too, the reaction is regioselective. Analysis of the ^{1}H NMR spectrum of an isolated salt **V** led us to conclude that the cyclization involves the α position of the naphthalene ring (see table).

A cyclic amine, tetrahydroquinoline, gives rise to compound **VI** that has a similar structure.



The composition and structure of salts **I**–**VII** were proved by elemental analysis and ^{1}H, UV, and IR spectroscopy (see table). The UV spectra of the products display three absorption maxima: one in the near UV region (205–212 nm) and two at 240–500 nm, which is characteristic of conjugated quinolinium salts. The IR spectra contain aromatic stretching absorption bands at 1650–1500 cm^{-1}. In the region of out-of-plane deformation vibrations of an isolated H atom, there is a band near 900 cm^{-1}. Bands characteristic of CH_2 groups and ClO_4^- anions are present near 1400 and 1090 cm^{-1}, respectively. However, the UV and IR spectra provide insufficient evidence to determine the site of condensation of the cyclopentane ring to the quinoline ring ([*b*] or [*c*]).

The structures of the condensation products of secondary aromatic amines in the presence of perchloric acid was proved by their ^{1}H NMR spectra, as described for *N*-alkyl- and *N*-arylquinolinium salts [8] and phenanthridine [9, 10] and tetrahydrophenanthridine derivatives [11, 12].

In the spectra of salt **I**, the aliphatic proton signals are three multiplets at 2.41, 2.50, 2.59, and 3.34 ppm (3H, NCH_3). When methyl is replaced by ethyl (compound **II**), the 3-CH_2 and aromatic H^4 signals shift slightly downfield. Replacement of the *N*-alkyl substituent with phenyl (compound **IV**) or benzyl (compound **III**) produces no significant shifts of signals of the heterocyclic fragment.

Annelation of the aromatic ring in position [*f*] (compound **V**) gives rise to a slight downfield shift of the active 1-CH_2 methylene signal (4.17 ppm), under the effect of ring π-electron currents of the phenyl substituent, as it occurs in quinaldinium salts [7].

Evidence for the angular structure is provided by the fact that the quinoline ring signal is observed at 9.1-9.7 ppm, whereas the respective signal of the acridine structure is at 10.00–10.40 ppm [3].

EXPERIMENTAL

The UV spectra were taken on a Specord M-40 instrument in ethanol. The IR spectra were obtained

on a Specord-80 spectrometer in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury-400 spectrometer (400 MHz) in ethanol against internal TMS.

5-Methyl-2,3-dihydro-1*H*-cyclopenta[*c*]quinolinium perchlorate (I). A mixture of 0.1 mol of *N*-methylaniline, 0.5 mol of cyclopentanone, 0.15 mol of 57% perchloric acid, 0.5 mol of 1-butanol, and 0.2 mol of nitrobenzene was heated to 100°C under stirring. A solution of 0.1 mol of formaldehyde obtained by depolymerization of Paraform, in 1-butanol was then added over the course of 30 min in the presence of catalytic amounts of perchloric acid. The reaction mixture was heated for 6 h, after which 1-butanol and nitrobenzene were removed by steam distillation. The precipitate that formed was treated with 2-propanol. The tarry material that formed after distillation was refluxed with small portions of water. The precipitates were combined and crystallized from 2-propanol.

Salts **II**–**VI** were prepared in a similar way.

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