REACTIONS OF CYCLIC AMMONIUM CATIONS

X.* REACTION OF ISOQUINOLINE WITH DIALKYLANILINES, 1-ALKYL-1,2,3,4-TETRAHYDROQUINOLINES, AND THEIR ANALOGS IN THE PRESENCE OF ACYL HALIDES

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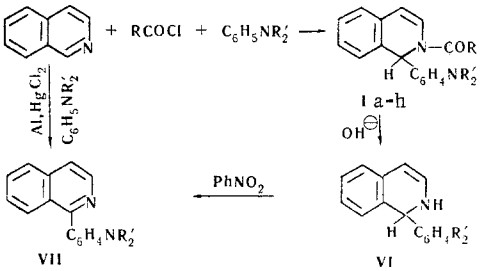
A method has been developed for the introduction of an isoquinolinium residue into an activated aromatic ring by means of N-acylisoquinolinium salts formed in the reaction of acyl halides with isoquinoline. 1-Substituted 2-acyl-1,2-dihydroisoquinolines with dialkylaniline, N-phenyl morpholine, N,N'-diphenylpiperazine, 1-alkyl-1,2,3,4-tetrahydroquinoline, and 1-alkylindoline residues in the 1 position were synthesized via this route. The structures of the compounds obtained were proved by alternative syntheses.

Pyridine, quinoline, and acridine react with acyl halides to form N-acyl cyclic ammonium salts which in situ are convenient electrophilic reagents for the introduction ot a heterocyclic residue into an activated aromatic ring [2-4]. It turned out that isoquinoline is even more reactive in this respect and forms 1-acyl-2-(p-dialkylaminophenyl)-1,2-dihydroisoquinolines (I) at room temperature when mixed with acyl halides and dialkylanilines:



We proved structure I in the case of Ib by converting it to the previously described 1-(p-dimethylaminophenyl)isoquinoline (VII). In addition, we obtained VII by the reaction of isoquinoline with dimethylaniline in the presence of aluminum dust and mercuric chloride.

The nature of the acyl residue has little effect on the yields of I (Table 1) in the reactions of N-acylisoquinolinium salts and N-acylquinolinium salts [4]. The reaction proceeds smoothly both without solvents (70-80% yields) and in anhydrous, aprotic media [in benzene or dimethylformamide (DMF)]; in a nitrogen atmosphere the reaction products obtained are considerably purer, although the yields are lower (60-65%). Increased yields can be achieved by UV irradiation† of the reaction mass (the yield in DMF at 50° was 85%).

*See [1] for communication IX.

†The UV light source was a 375-W PRK-2M quartz-mercury lamp.

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TABLE 1. 1-Aryl-2-acyl-1,2-dihydroisoquinolines (I-III)

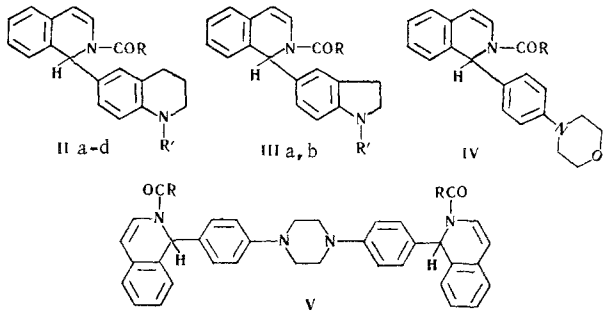
Compound	R	R′	Mp, °C *	UV spectra in ethanol		Empirical formula	Found, %			Calculated, %			Yield, %
				λ_{max}, nm	lg ε		C	H	N	C	H	N	
Ia	CH_3	CH_3	126—127	259, 290, 225	4,33; 4,27; 4,43	$C_{19}H_{20}N_2O$	78,1	7,0	9,4	78,1	6,9	9,6	78
Ib	C_6H_5	CH_3	113—114	264, 225	4,27; 4,43	$C_{24}H_{22}N_2O$	81,8	6,6	7,9	81,4	6,3	7,9	77
Ic	p-$O_2N{=}C_6H_4$	CH_3	152—153	260, 225	4,70; 4,43	$C_{24}H_{21}N_3O_3$	71,9	5,4	10,3	72,2	5,3	10,5	78
Id	p-$C_6H_5C_6H_4$	CH_3	173—174	270, 225	4,42; 4,43	$C_{30}H_{26}N_2O$	83,1	6,2	6,2	83,6	6,1	6,6	87
Ie	γ-Pyridyl	CH_3	174—175	270, 300, 225	4,76; 4,62; 4,43	$C_{23}H_{21}N_3O$	77,5	6,1	11,6	77,7	6,0	11,8	88
If	α-Furyl	CH_3	105—106	260, 300, 225	4,52; 4,34; 4,43	$C_{22}H_{20}N_2O_2$	76,7	5,8	8,1	76,7	5,8	8,1	30
Ig	C_6H_5	C_2H_5	131—132	270, 225	4,23; 4,43	$C_{16}H_{26}N_2O$	81,6	6,8	7,3	81,6	6,8	7,3	65
Ih	C_6H_5	C_4H_9	83—84	265, 300, 225	4,69; 4,55; 4,43	$C_{30}H_{34}N_2O$	82,0	7,8	6,3	82,1	7,8	6,4	52
Ii	$(C_6H_5)_2N$	CH_3	195—196	270, 300, 225	4,42; 4,58; 4,43	$C_{30}H_{27}N_3O$	87,7	6,0	9,4	80,9	6,1	9,4	82
IIa	C_6H_5	CH_3	97—98	272, 225	4,38; 4,43	$C_{26}H_{24}N_2O$	81,9	6,2	7,3	82,1	6,3	7,4	56
IIb	C_6H_5	C_2H_5	112—113	280, 225	4,15; 4,43	$C_{27}H_{26}N_2O$	82,2	6,5	7,0	82,2	6,6	7,1	41
IIc	C_6H_5	C_3H_7	87—88	270, 225	4,46; 4,43	$C_{28}H_{28}N_2O$	82,6	7,0	6,8	82,3	6,9	6,8	85
IId	C_6H_5	CH_3 †	119—120	275, 300, 225	4,53; 4,46; 4,43	$C_{28}H_{28}N_2O$	82,2	6,8	6,8	82,3	6,9	6,8	83
IIIa	C_6H_5	CH_3	86—87	294, 225	4,07; 4,43	$C_{25}H_{22}N_2O$	81,8	6,1	7,6	82,0	6,0	7,6	66
IIIb	C_6H_5	C_2H_5	72—73	270, 300, 225	4,48; 4,40; 4,43	$C_{26}H_{24}N_2O$	81,9	6,2	7,2	82,1	6,3	7,4	84

*Ia, Ie, Ig, and IId were recrystallized from methanol, Ic was recrystallized from aqueous methanol, Ih from ethanol, Id from butanol, Ii from acetone, and the remaining compounds were recrystallized from petroleum ether.

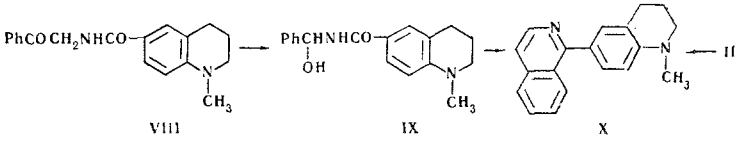
†CH_3 in the 2 position of the tetrahydroquinoline ring.

It is curious that carrying out this reaction in a constant 3000-Oe magnetic field at room temperature or with slight heating consistently increases the yields of I by an average of 20-25% as compared with a control.

It turned out that the proposed method for the introduction of an isoquinolinium residue has extremely broad synthetic possibilities. We have previously reported the possibility of obtaining isoquinoline derivatives of pyrrole [5] and thiazolidones [6] via this route. Under similar conditions, an isoquinoline residue can be introduced into the benzene rings of 1-alkyl-1,2,3,4-tetrahydroquinolines (II), 1-alkyl-2,3-dihydroindoles (III), N-phenylmorpholine (IV), and N,N'-diphenylpiperazine (V) (Table 1).



The UV and IR spectra of IV and V were similar to the spectra of I; this makes the structure assigned to them extremely likely. To prove the structures of II and III we used an independent route to obtain 1-methyl-6-(1-isoquinolinyl)-1,2,3,4-tetrahydroquinoline (X), which turned out to be identical to the compound obtained by hydrolysis of the product of the reaction of N-benzoylisoquinolinium chloride with 1-methyl-1,2,3,4-tetrahydroquinoline (II, R = CH_3). We accomplished the alternative synthesis as follows. Willsmeyer formylation of 1-methyl-1,2,3,4-tetrahydroquinoline yielded 1-methyl-6-formyl-1,2,3,4-tetrahydroquinoline; this was oxidized to 1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid, from which the acid chloride was obtained and used to acylate ω-aminoacetophenone; the resulting VIII was reduced with sodium amalgam and the product (IX) was converted to X by the Pictet-Gams method.



Thus,the reaction of N-acylisoquinolinium salts with dialkylanilines and their analogs always involves ring fusion at the 1 position of the isoquinoline and the para position of the aromatic ring relative to the amino group, as in the reactions of N-acyl salts of other six-membered heterocycles. The synthesized 1,2-dihydroisoquinoline derivatives turned out to be effective heat stabilizers for polyolefins and raw and cured rubbers; this will be the subject of a separate communication.

EXPERIMENTAL

The purity of the isoquinoline used in this study was checked by gas-liquid chromatography and was no less than 99%. In all cases, the chromatography on aluminum oxide (activity II) was carried out by elution with benzene-hexane-chloroform (6:1:30); the chromatograms were developed with iodine vapors in UV light. The UV spectra in ethanol were obtained with an SF-4a spectrometer; the IR spectra (KBr pellets and chloroform solutions) were obtained with a UR-20 spectrometer.

1-Aryl-2-acyl-1,2-dihydroisoquinolines (Ia-h, IIa-d, and IIIa, b, Table 1). A reaction mixture consisting of 0.05 mole of isoquinoline, 0.05 mole of freshly distilled acyl chloride, and 0.1 mole of dialkylaniline was heated at 100° for 8 h. The reaction mass was then made alkaline and steam-distilled. The light-colored, amorphous residue was extracted, dried, and recrystallized. The reaction proceeded similarly in anhydrous dimethylformamide or benzene. IR spectra: 1680-1690 cm^{-1} (C=O, the position varies only slightly with a change in the nature of the acyl residue); 1650 cm^{-1} (C=C in the dihydropyridine ring); 1500, 1550, and 1600 cm^{-1}.

Hydrolysis of 1-(p-Dimethylaminophenyl)-2-benzoyl-1,2-dihydroisoquinoline (Ib). A solution of 2 g (5.6 mmole) of Ib and 8 g of KOH in 30 ml of 70% ethanol was refluxed for 5 h, 30 ml of water was added, and the ethanol was removed by distillation. The residual suspension was extracted with 20 ml of benzene, 10 ml of nitrobenzene was added to the benzene extract, and the mixture was refluxed for 3 h. The reaction mixture was then extracted with hydrochloric acid, the acid extracts were made alkaline, and the resulting precipitate was filtered and chromatographed on a column filled with aluminum oxide to give 0.4 g (30%) of 1-(p-dimethylaminophenyl)isoquinoline (VII) and 0.84 g (60%) of 1-(p-dimethylaminophenyl)-1,2-dihydroisoquinoline (VI). VII had mp 114-115° (from petroleum ether) and R_f 0.40 (blue fluorescence on irradiation with UV light). The picrate of VII had mp 221-222° (from ethanol). Found %: N 14.7. $C_{17}H_{16}N_2 \cdot C_6H_3N_3O_7$. Calc. %: N 14.6. VI had mp 111-112° (from petroleum ether) and R_f 0.30 (no fluorescence in UV light). IR spectrum: 3440 cm^{-1} (N–H), 1620 cm^{-1} (C=C in the dihydropyridine ring). Found %: C 81.2; H 7.8; N 11.0. $C_{17}H_{18}N_2$. Calc. %: C 81.6; H 7.2; N 11.2. The picrate of VI had mp 201-202° (from ethanol). Found %: N 14.4. $C_{17}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calc. %: N 14.6. Only VII (50%) was isolated by chromatography from the hydrolysis of Ib with dilute H_2SO_4.

Reaction of Isoquinoline with Dimethylaniline in the Presence of Aluminum Dust. A mixture of 16 g (0.12 mole) of isoquinoline, 15.14 g (0.124 mole) of dimethylaniline, 3.35 g (0.124 g-atom) of aluminum dust, and 1 g (0.00368 mole) of mercuric chloride was heated under nitrogen at 180-190° for 8 h. The hot reaction mixture was dissolved in 60 ml of nitrobenzene, the aluminum dust was separated from it, and the filtrate was refluxed for 3 h. The nitrobenzene was then removed by vacuum distillation, and the residue was chromatographed on a column filled with aluminum oxide to give 13.18 g (30%) of VII, which was identical to that described above.

1-Methyl-6-(1-isoquinolinyl)-1,2,3,4-tetrahydroquinoline (X). A) A solution of 2 g (0.005 mole) of 1-(1-methyl-1,2,3,4-tetrahydro-6-quinolinyl)-2-benzoyl-1,2-dihydroisoquinoline (IIa) in 50 ml of concentrated HCl was refluxed for 5 h, cooled, and 0.57 g (90%) of benzoic acid was obtained by filtration. The filtrate was made alkaline and extracted with benzene. The benzene extracts were dried, and the solvent was removed by distillation. The residue was chromatographed on a column filled with aluminum oxide to give 1.2 g (87.5%) of X with R_f 0.44 (blue luminescence on irradiation with UV light) and mp 117-118° (from petroleum ether). Found %: C 83.0; H 6.6; N 10.2. $C_{19}H_{18}N_2$. Calc. %; C 83.2; H 6.6; N 10.2. The picrate of X was obtained as red crystals with mp 183-184° (from ethanol). Found %: C 59.7; H 4.2; N 13.8. $C_{19}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calc. %: C 59.6; H 4.2; N 13.9.

B) A solution of 2 g (6.48 mmole) of VIII in 20 ml of absolute alcohol was reduced with 3 g of 3% sodium amalgam as described in [7], after which 1 g (3.24 mmole) of the IX obtained after the reduction was dissolved, without prior purification, in 25 ml of dry xylene, 5 g of phosphorus pentoxide and 10 g of $POCl_3$ were added, and the mixture was refluxed for 3 h. The excess phosphorus oxychloride and phosphorus pentoxide were decomposed with ice, and the aqueous layer was separated, made alkaline, and extracted with benzene. The extract was dried and vacuum-evaporated, and the residue was chromatographed on a column filled with aluminum oxide to give 1.6 g (90%) of X, which was identical to that obtained via method (A).

Alkaline hydrolysis of IIa yielded 30% of X and 65% of 1-methyl-6-(1,2-dihydro-1-isoquinolinyl)-1,2,-3,4-tetrahydroquinoline (XI) with R_f 0.19 (no fluorescence in UV light) and mp 87-88° (from petroleum ether). IR spectrum: 3440 cm^{-1} (N–H), 1620 cm^{-1} (C=C of the dihydropyridine ring). Found %: C 82.5; H 7.3; N 10.1. $C_{19}H_{20}N_2$. Calc. %: C 82.6; H 7.3; N 10.3. The picrate of XI was obtained as red crystals with mp 159-160°. Found %: N 5.9. $C_{19}H_{20}N_2 \cdot C_6H_3N_3O_7$. Calc. %: N 6.0.

1-Methyl-6-carboxy-1,2,3,4-tetrahydroquinoline. A mixture of 5 g (0.0261 mole) of 1-methyl-6-formyl-1,2,3,4-tetrahydroquinoline [8], 8 g of potassium hydroxide, and 5.2 g of sodium hydroxide was ground thoroughly in a mortar and calcined until vapor evolution ceased. The calcined mixture was dissolved in 200 ml of water, and the solution was boiled with activated charcoal, filtered, and acidified with hydrochloric acid until the initially formed precipitate dissolved completely. The acid solution was again boiled with charcoal, filtered, and carefully made alkaline to pH 2 with ammonium hydroxide. The resulting precipitate was evacuated, dried, and recrystallized from benzene to give 2 g (40%) of a product with mp 223-224° [9].

1-Methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic Acid Chloride. Thionyl chloride [2.05 g (17.2 mmole)] was added to a solution of 1.5 g (7.84 mmole) of 1-methyl-6-carboxy-1,2,3,4-tetrahydroquinoline in 50 ml of absolute benzene, and the mixture was refluxed for 6 h. The excess thionyl chloride and sol-

vent were removed by distillation to give 0.99 g (60%) of the crystalline, white acid chloride with mp 204-205° (from petroleum ether) and R_f 0.22. Found %: N 6.7; Cl 16.3. $C_{11}H_{12}ClNO$. Calc. %: N 6.7; Cl 16.9.

1-Methyl-6-phenacylaminocarbonyl-1,2,3,4-tetrahydroquinoline (VIII). Dry pyridine (5 ml) was added to a solution of 1.7 g (8.1 mmole) of 1-methyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid chloride in 15 ml of anhydrous toluene, the mixture was stirred for 30 min, and 1.39 g (8.1 mmole) of ω-aminoacetophenone hydrochloride was added gradually. The resulting mixture was then held at room temperature for 3.5 h and then refluxed for 2.5 h. The reaction mixture was made alkaline and steam-distilled. The residue was separated, dried, and recrystallized from methanol and then toluene to give 2.2 g (90%) of VIII with mp 218-220° and R_f 0.78. Found %: C 73.8; H 6.4; N 8.9. $C_{19}H_{20}N_2O_2$. Calc. %: C 74.0; H 6.5; N 9.0.

1-(p-Morpholinophenyl)-2-benzoyl-1,2-dihydroisoquinoline (IV). This compound [9.6 g (80%)] was obtained like I-III by the reaction of 10.6 g (0.05 mole) of isoquinoline, 4 g (0.025 mole) of N-phenylmorpholine, and 2.3 g (0.025 mole) of benzoyl chloride and had mp 213-214° (from aqueous methanol) and R_f 0.14; λ_{max} 268 nm, log ε 4.2. Found %: C 78.8; H 5.8; N 6.9. $C_{26}H_{24}N_2O_2$. Calc. %: C 78.8; H 6.1; N 7.0.

1,4-Bis[4-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)phenyl]piperazine (V). This compound [3 g (50%)] was similarly obtained by the reaction of 2.6 g (0.025 mole) of isoquinoline, 2.98 g (0.0125 mole) of N,N'-diphenylpiperazine, and 1.2 g (0.0125 mole) of benzoyl chloride and had mp 82-83°(from ethanol) and R_f 0.33. Found %: C 81.5; H 6.0; N 7.5. $C_{48}H_{40}N_4O_2$. Calc. %: C 81.8; H 5.7; N 7.9.

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