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CONDENSED ISOQUINOLINES.
PART 6.* SYNTHESIS OF 5-ARYL-7,12-DIHYDROISOQUINO[2,3-*a*]QUINAZOLINIUM SALTS

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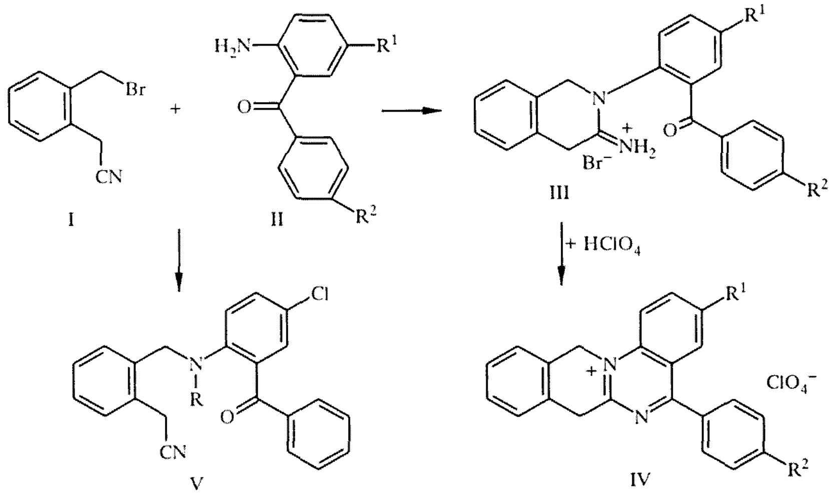
*2-(o-Aroyl)phenyl-1,4-dihydroisoquinolin-3(2H)-imine hydrobromides have been synthesized by the reaction of o-bromomethylphenylacetonitrile with o-aminobenzophenones. The products were cyclized into 5-aryl-7,12-dihydroisoquino[2,3-*a*]quinazolinium perhclorates.*

In spite of the fact that the isoquino[2,3-*a*]quinazoline heterocyclic system has become known only recently [2, 3], there is already information [4, 5] on the prospects of searching for new biologically active compounds among its derivatives. Only two approaches to the synthesis of this system have been described. In one of them [2], 5-phenyl-12-oxoisoquino[2,3-*a*]quinazoline was obtained using 4-phenylquinazoline as starting material. It is the sole representative of this system and was obtained by the given method. The other approach is based on the reaction o-(bromomethyl)phenylacetonitrile (I) with esters and the nitrile of anthranilic acid and leads to 5-oxo- and 5-imino-7,12-dihydro-5H-isoquino[2,3-*a*]quinazolines [3, 6]. In view of the prospects of extending the range of the latter approach to other o-aminocarbonyl compounds, we have studied the reaction of the bromonitrile (I) with the o-aminobenzophenones (II) in the present work.



II–IV a R^1 = Cl, R^2 = H; б R^1 = R^2 = Br; в R^1 = Br, R^2 = NO_2;
V a R = H; b R = $COCH_3$

It was found that heating a mixture of bromonitrile (I) with the aminobenzophenones (II) in acetonitrile leads to the hydrobromide of the corresponding 2-(aroylphenyl)-1,4-dihydroisoquinolin-3(2H)-imine (III). The band for the stretching

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*For part 5 see [1].

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vibration of the nitrile group was absent from the IR spectra of these compounds but intense bands were observed for the symmetric (2930 cm^{-1}) and asymmetric (3155 cm^{-1}) stretching vibrations of a $=^{-}N^{+}H_2$ group. There was also an intense band at 1630 cm^{-1} evidently due to the presence of the stretching vibrations of C=O and $C=N^{+}$ groups. A similar picture was observed previously [7] in the IR spectra of the structurally similar 2-aryl-1,4-dihydroisoquinolin-3(2H)-imines. We were unsuccessful in recording the PMR spectra of the isoquinolinimine salts (III), due on the one hand to their extremely unsatisfactory solubility in the majority of solvents, and on the other to their lability in those events in which they would dissolve. An unexpected conversion of these salts occurred in DMSO-D_6. On first adding solvent the bright yellow crystals acquired an intense blue coloration. Consequently the spectra obtained with the solutions did not correspond to an individual substance. In the high field region of the spectra of freshly prepared solutions of these compounds it was possible to discern signals for the protons of the methylene groups as two AB spin systems. The protons at $C_{(1)}$ give two doublets at 5.3 and 5.6 ppm with a coupling constant of 14 Hz and the protons at $C_{(4)}$ two doublets at 4.2 and 4.5 ppm with a coupling constant of 18 Hz. The diastereotopicity of the indicated pairs of protons and their magnetic nonequivalence caused by this is characteristic for salts of 2-aryl-1,4-dihydroisoquinolin-3(2H)-imines with unsymmetrical substitution in the 2-aryl residue and is caused by hindrance to free rotation about the $N_{(2)}-C_{Ar}$ bond [6].

Attempts to record the spectra of isoquinolinimines (III) in deuterotrifluoroacetic acid also proved to be unsuccessful, since cyclization of these compounds into 5-aryl-7,12-dihydroisoquino[2,3-*a*]quinazolinium salts (IV) occurs very readily in it. Preparatively, this transformation was effected by short heating of solutions of the isoquinolines (III) in a mixture of acetic and perchloric acids which leads to the perchlorates of isoquinoquinoxalines (IV). There was no absorption in their IR spectra for carbonyl and protonated imino groups. The PMR spectra, which were recorded in CD_3CN, were characterized by the presence of two two-proton triplets at 4.9 and 6.0 ppm for the protons at $C_{(7)}$ and $C_{(12)}$ respectively, having a homoallyl type of mutual interaction with a long range (through 5 bonds) coupling constant of 2.5 Hz. The special feature of the spectra recorded in deuterotrifluoroacetic acid proved to be the significant reduction in the signal intensity from the methylene protons at $C_{(7)}$, complete exchange of these protons with deuterium occurring after a certain time.

We studied the reaction of bromonitrile (I) with aminobenzophenone (IIa) with the aim of searching for an optimum one-stage method of synthesis of isoquino-quinoxalinium salts (IV) under various conditions, but this did not lead to the desired result. On replacing acetonitrile by acetic acid the isoquinolinimine salt (IIIa) was obtained in unsatisfactory yield. Reaction in propan-2-ol in the presence of sodium acetate as auxiliary base leads to 5-chloro-2-[o-(cyanomethyl)benzyl-amino]-benzophenone (Va) which was characterized as the N-acetyl derivative (Vb).

EXPERIMENTAL

The IR spectra of compounds were recorded with a Pye Unicam SP3-300 instrument in KBr. The PMR spectra were obtained on a Bruker WP-100 SY (100 MHz) instrument, internal standard was TMS.

The data of elemental analysis for the compounds synthesized corresponded to calculated values.

2-(o-Aroylphenyl)-1,4-dihydroisoquinolin-3(2H)-imine Hydrobromides (IIIa, $C_{22}H_{17}ClN_2O \cdot HBr$; IIIb, $C_{22}H_{16}Br_2N_2O \cdot HBr$; IIIc, $C_{22}H_{16}BrN_3O_3 \cdot HBr$). Bromonitrile (I) (3.7 mmole) was added to a solution of the aminobenzophenone (II) (3 mmole) in acetonitrile (10 ml) and the mixture boiled for 12 h. The solid which precipitated on cooling the mixture was filtered off, washed with acetonitrile, and recrystallized from acetic acid. Yield was 65-70%.

Compound (IIIa) had mp 293-295°C, (IIIb) mp 304.5-307°C (with decomposition), and (IIIc) mp 252-253°C (with decomposition).

5-Aryl-3-R-7,12-dihydroisoquino[2,3-*a*]quinazolinium Perchlorates (IVa, $C_{22}H_{16}Cl_2N_2O_4$; IVb, $C_{22}H_{15}Br_2ClN_2O_4$; IVc, $C_{22}H_{15}BrClN_3O_6$). A solution of isoquinolinimine (III) (2 mmole) in acetic acid (30 ml) and 70% perchloric acid solution (3 ml) was boiled for 10 min, cooled, the precipitated solid was filtered off, washed with acetic acid, and recrystallized from acetic acid. Yield was 85-88%.

Compound (IVa) had mp 205-207°C, (IVb) mp 334-337°C, and (IVc) mp > 350°C (with decomposition).

5-Chloro-2-[o-(cyanomethyl)benzylamino]benzophenone (Va, $C_{22}H_{17}ClN_2O$). Fused sodium acetate (0.74 g: 9 mmole) and bromonitrile (I) (0.79 g: 3.7 mmole) were added to a solution of aminobenzophenone (IIa) (0.69 g: 3 mmole) in propan-2-ol (20 ml). The mixture was boiled for 20 h, filtered hot, the solid which precipitated on cooling the filtrate was filtered off, and washed with propan-2-ol. Yield was 0.54 g (50%), mp 83-84°C (from propan-2-ol). PMR spectrum (DMSO-D_6): 4.16 (2H, s, $\underline{CH_2}CN$), 4.60 (2H, d, $\underline{CH_2}-NH$, J = 5.5 Hz), 6.81 (1H, d, 3-$\underline{H}$, J = 8.5 Hz), 7.3-7.7 (11H, m, arom.), 8.65 ppm (1H, t, $\underline{NH}-CH_2$, J = 5.5 Hz, exchanged in D_2O when the doublet at 6.81 is converted into a singlet). IR spectrum: 3300 (NH), 2245 ($C\equiv N$), 1620 cm^{-1} (C=O).

N-Acetyl-5-chloro-2-[o-(cyanomethyl)benzylamino]benzophenone (Vb, $C_{24}H_{19}ClN_2O_2$) was obtained by the action of acetyl chloride on amine (Va) in anhydrous dioxan in the presence of an excess of fused sodium acetate. PMR spectrum ($DMSO-D_6$): 1.84 (3H, s, $CO\underline{CH_3}$), 3.75 (1H, d), 3.98 (1H, d, $\underline{CH_2}CN$, J = 18 Hz), 4.29 (1H, d), 5.01 (1H, d, $\underline{CH_2}-N$, J = 14 Hz), 6.8-7.8 ppm (12H, m, arom.). IR spectrum: 2245 ($C\equiv N$), 1660 cm^{-1} (C=O).

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