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SYNTHESIS OF 3,4-DIHYDRO-QUINAZOLINES IN THE REACTION OF *o*-AMINOPHENYLDIPHENYL-CARBINOL WITH NITRILES

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The reaction of o-aminophenyldiphenylcarbinol with nitriles of various structure in the presence of perchloric acid has been investigated. Optimal conditions have been developed for the synthesis of 3,4-dihydroquinazolinium perchlorates, from which the corresponding 3,4-dihydroquinazolines are obtained by treatment with bases. Certain compounds with an active methylene group bound directly to the heterocycle are able to exist in tautomeric forms with migration of the multiple bond into an exocyclic position.

Keywords: 3,4-dihydroquinazolines, alkylation, acylation, tautomerism.

There is only sparse information in the literature on the methods of obtaining and the properties of 3,4-dihydroquinazoline derivatives [1-8]. The 3,4-dihydroquinazolines are the most widespread of the dihydro derivatives of quinazoline. They may exist in equilibrium with the tautomeric 1,4-dihydro form [1], however 1,4-dihydroquinazolines are successfully obtained only in those cases when positions 1 and 2 of the heterocycle are substituted by alkyl and aryl groups.

3,4-Dihydroquinazolines are obtained by the selective reduction of the quinazoline ring, by heterocyclization of *o*-aminobenzylamines or *o*-nitrobenzylamines [1], and also by the reaction of *o*-acylanilines with formamide or ureas in formic acid [2,3]. The synthesis of dihydroquinazolines has been reported by the cyclocondensation of *o*-carbodiimidocinnamic acid derivatives with alcohols, thiols, or amines [4], of N-(2-bromophenyl)ethylimidates with aldehydes, ketones, and isothiocyanates in the presence of lithium [5], and of 2-azidomethylanilines with aromatic aldehydes [6]. A method of obtaining quinazoline derivatives (including dihydroquinazolines) by the amination of the appropriate benzoxazines is known [7,8]. There is information on the pharmacological activity of a set of representatives of this class of compound [7,9-13].

To search for new methods of synthesizing nitrogen-containing heterocyclic compounds we investigated the reaction of *o*-aminophenyldiphenylcarbinol (APC) with nitriles of various structure. It was established that, in the presence of an equimolar quantity of perchloric acid, 3,4-dihydroquinazolinium perchlorates are formed, which on treatment with aqueous alkali are converted into the corresponding bases (Scheme 1). It should be noted that 3,4-dihydroquinazolines are the N-hetero analogs of 4H-3,1-benzoxazines, which we described previously in [14].

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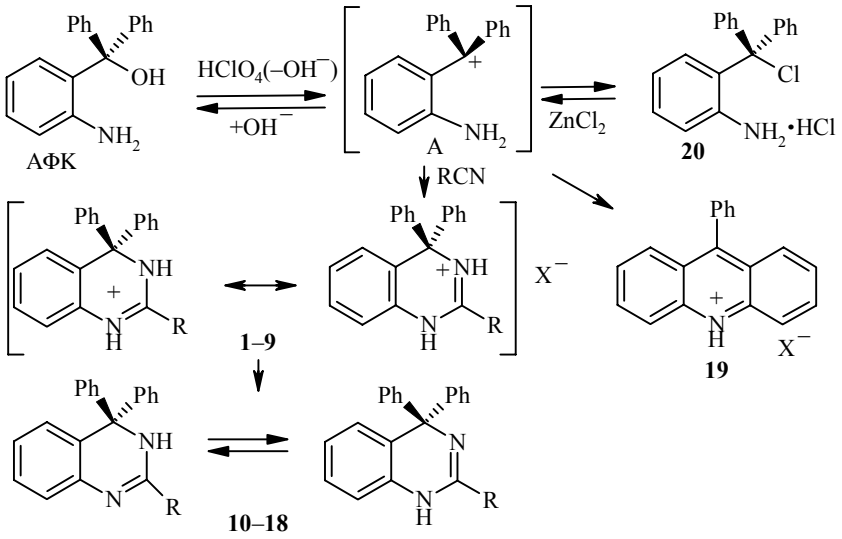
Scheme 1



1, **10** R = Me; **2**, **11** R = vinyl; **3**, **12** R = Ph; **4**, **13** R = *p*-$C_6H_4NO_2$;
5, **14** R = *p*-$C_6H_4NH_2$; **6**, **15** R = CH_2Ph; **7**, **16** R = *p*-nitrobenzyl;
8, **17** R = *p*-aminobenzyl; **9**, **18** R = CH_2COOEt; X = ClO_4

It is evident that the triarylcarbenium cation A and not APC itself participates in the reaction with nitrile (see Scheme 1). This cation is readily formed from APC in the presence of perchloric acid, as it occurs in other similar reactions [15-17]. The cation A is able to convert into the acridinium ion **19** [18] (Scheme 1). To prevent this process the reaction with nitrile was carried out with a constant deficit of APC in the reaction mixture. Liquid nitriles are used in the synthesis as both reactant and solvent providing an excess of nitrile in the reaction mixture. In those cases when a crystalline nitrile was used the reaction was carried out in nitromethane by slow addition of APC to the reaction mixture.

The isolation of perchlorates **1-9** from the reaction mixture was carried out by precipitation with dry ether. The corresponding free bases **10-18** were obtained by neutralizing salts **1-9** with aqueous ammonia with subsequent recrystallization from ethanol. Compound **13** was obtained both by the method described above and by an alternate synthesis, *viz*. by the interaction of 2-aminophenychloromethane hydrochloride (**20**) [19] and *p*-nitrobenzonitrile in the presence of $ZnCl_2$. This confirms the possibility of reaction proceeding through the triarylmethyl cation A. The structures of compounds **1-18** were proved by the data of elemental analysis and by spectral methods (Tables 1-3).

Compounds **15-18**, with an active methylene group bonded directly to the heterocycle, are of particular interest.

In the ^{1}H NMR spectra of the corresponding perchlorates **6-9** a singlet was observed for the methylene group. In the spectrum of benzylquinazoline **15** there were four singlets of various intensity with a total integral of 2H. Two resonances corresponded to a methylene groups and two signals to a methine groups, indicating the existence of the four tautomeric forms **15a-d** in solution (Scheme 2).

The surprising thing is that no methine proton signals were detected in the ^{1}H NMR spectra of the *p*-nitro and *p*-aminobenzyl derivatives **16** and **17**, but the tautomeric transformation between the 1H and 3H forms in solution are rapid on NMR time scale so that the only one signal for the methylene group was observed in the spectrum.

TABLE 1. Characteristics of 3,4-Dihydroquinazolinium Perchlorates **1-9**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	IR spectrum, ν, cm^{-1}			^{1}H NMR spectrum ($(CD_3)_2CO$), δ, ppm, *J* (Hz)				Yield, %
		C	H	N	Cl		HN=C=NH	ClO_4^-	NO_2, NH_2	CH_2 (2H, s)	H_{arom}	H (R)	H–N (2H, s)	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	$C_{21}H_{19}ClN_2O_4$	63.32 / 63.24	4.85 / 4.80	7.05 / 7.02	8.93 / 8.89	272-276	3200, 1670	1140, 1110, 1060	—	—	7.25 (14H, m)	2.63 (3H, s)	5.95 (br. s)	65.0
2	$C_{22}H_{19}ClN_2O_4$	64.29 / 64.31	4.60 / 4.63	6.80 / 6.83	8.62 / 8.65	242-245	3160, 1660	1150, 1110, 1040	—	—	7.32 (14H, m)	6.75 (3H, m)	5.60 (br. s)	62.0
3	$C_{26}H_{21}ClN_2O_4$	67.35 / 67.70	4.32 / 4.60	6.42 / 6.10	7.51 / 7.72	215 (dec.)	3220, 1650	1120, 1070	—	—	7.30 [10H, s, $(C_6H_5)_2$]	7.50 (9H, m, C_6H_4+ 2-C_6H_5)	5.80 (br. s)	73,0
4	$C_{26}H_{20}ClN_3O_6$	61.82 / 61.79	4.03 / 3.99	8.37 / 8.31	7.03 / 7.01	>160 (dec.)	3300, 1645	1120, 1070	1530, 1370	—	7.33 (14H, m)	8.62 8.95 [4H, dd, H_{arom} ($2H_B$+$2H_A$)] $^3J_{AB}$ = 8.0	4.50 (br. s)	65.0

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
5	$C_{26}H_{22}ClN_3O_4$	65.71 / 65.62	4.74 / 4.66	8.92 / 8.83	7.36 / 7.45	>190 (dec.)	3180, 1640	1130, 1110, 1090	3320 (NH_3^+)	—	—	—	*	55.0
6	$C_{27}H_{23}ClN_2O_4$	68.60 / 68.71	4.42 / 4.81	5.63 / 5.92	7.35 / 7.53	>120 (dec.)	3220, 1650	1160, 1020	—	4.30	7.30 (19H, m)	—	5.8 (br. s)	70.0
7	$C_{27}H_{22}ClN_3O_6$	62.75 / 62.43	4.45 / 4.22	8.55 / 8.11	6.44 / 6.83	>250 (dec.)	3220, 1635	1170, 1100, 1075	1520, 1330	4.46	7.36 (14H, m)	7.63 8.13 [4H, dd, H_{arom} ($2H_B$+$2H_A$)] $^3J_{AB}$ = 9.0	5.65	60.0
8	$C_{27}H_{24}ClN_3O_4$	66.25 / 66.19	4.97 / 4.94	8.64 / 8.58	7.15 / 7.29	177-179	3170, 1650	1150, 1100, 1080	3300 (NH_3^+)	—	—	—	*	52.0
9	$C_{24}H_{23}ClN_2O_6$	61.66 / 61.24	4.52 / 4.83	6.14 / 5.92	7.33 / 7.51	215 (dec.)	3200, 1620	1130, 1020	1730 (C(O)O–)	3.96	7.23 (14H, m)	1.23 (3H, t, CH_3) 4.20 (2H, q, CH_2)	6.60*[2]	70.0

*[1] H NMR spectra are not presented due to decomposition of these salts in the solvent.

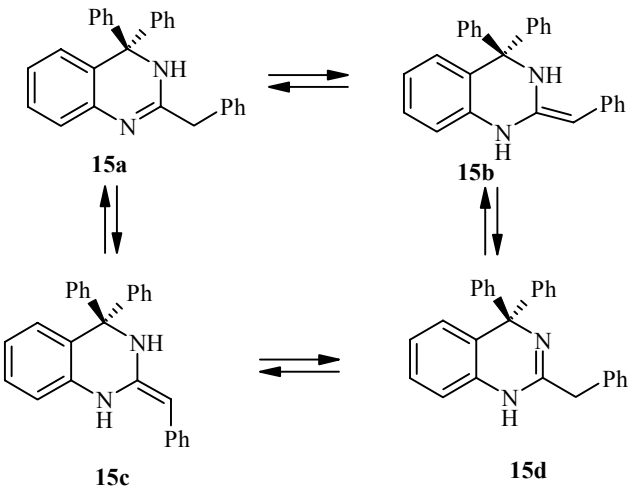
*[2] In CD_2Cl_2.

TABLE 2. Characteristics of the Synthesized Compounds **10-18, 21,** and **23**

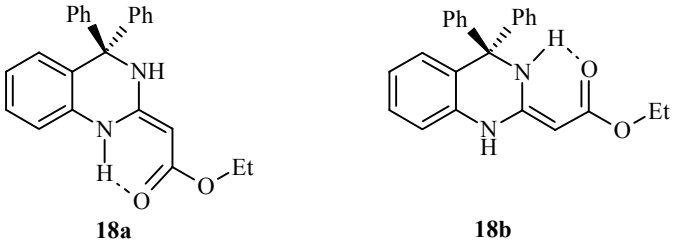
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f, (benzene–ether)	UV spectrum (ethanol), λ_{max}, nm (log ε)	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N					
10*	$C_{21}H_{18}N_2$	84.66 / 84.50	6.35 / 6.04	9.00 / 9.40	168-170	0.08	277 (3.82)	3280 (NH); 1645 (C=N)	75
11*[2]	$C_{22}H_{18}N_2$	85.32 / 85.16	5.61 / 5.82	8.64 / 9.04	135-136	0.09	313 (3.71)	3230 (NH); 1640 (C=N)	72
12	$C_{26}H_{20}N_2$	86.51 / 86.70	5.52 / 5.91	7.94 / 7.85	163-165	0.42	237 (4.31) 305 (3.83)	3440 (NH); 1630 (C=N)	75
13	$C_{26}H_{19}N_3O_2$	77.15 / 77.02	4.78 / 4.72	10.43 / 10.36	193-196	0.70	268 (4.22) 362 (3.63)	3470 (NH); 1625 (C=N) 1530; 1370 (NO_2)	70
14	$C_{26}H_{21}N_3$	83.36 / 83.17	5.53 / 5.64	11.01 / 11.19	115-118	0.17	—	3220 (NH); 1610 (C=N) 3380; 3370 (NH_2)	58
15*[3]	$C_{27}H_{22}N_2$	86.30 / 86.61	5.61 / 5.90	7.82 / 7.53	140-142	0.25	284 (3.86)	3288 (NH); 1624 (C=N)	72
16	$C_{27}H_{21}N_3O_2$	77.51 / 77.33	5.28 / 5.01	10.15 / 10.02	80-81	0.16	278 (4.14)	3380 (NH); 1620 (C=N) 1520; 1330 (NO_2)	70
17	$C_{27}H_{23}N_3$	83.13 / 83.26	5.62 / 5.95	10.71 / 10.79	106	0.06	—	3200 (NH); 1620 (C=N) 3330; 3410 (NH_2)	52
18	$C_{24}H_{22}N_2O_2$	77.52 / 77.81	5.63 / 5.90	7.32 / 7.63	157-159	0.57	253 (3.67) 306 (4.49)	3310 (NH); 1612 (C=N) 1628 ($COOC_2H_5$)	71
21	$C_{29}H_{25}N_3O_2$	77.86 / 77.83	5.58 / 5.63	9.37 / 9.39	87-89 (dec.)	0.05 0.28*[4]		1590 (C=C); 1520, 1350 (NO_2)	52
22*[5]	$C_{26}H_{26}N_2O_2$	78.40 / 78.36	6.53 / 6.58	7.01 / 7.03	143-145	0.34		1625 (C=C); 1725 ($COOC_2H_5$)	60

* $M^{+\cdot}$ 298.
*[2] $M^{+\cdot}$ 310.
*[3] $M^{+\cdot}$ 374.
*[4] Eluent benzene–acetone, 1 : 2.6.
*[5] $M^{+\cdot}$ 398.

Scheme 2



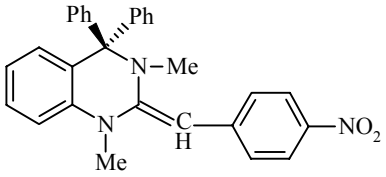
On the contrary no signal was detected for the methylene group in the ^{1}H NMR spectrum of compound **18**, in which the methylene group is linked with an ethoxycarbonyl group. In its place the spectrum shows two singlets for methine protons of total intensity 1H. Evidently compound **18** exists as a mixture of two geometric isomers with an exocyclic multiple bond (structures **18a** and **18b**).



These structures are possibly stabilized by intramolecular hydrogen bonds (IMHB). Conjugation of the lone electron pairs of the nitrogen atoms with the carbonyl group through the multiple bond and the presence of IMHB lower the ν_{CO} stretching to 1628 cm^{-1} (Table 2).

Attempts were undertaken to fix the tautomeric forms of compounds **15**, **16**, and **18** by alkylation with dimethyl sulfate by the procedure of [20, p. 465]. It is evident from analysis of the ^{1}H NMR spectra that alkylation of dihydroquinazoline **16** leads to the N,N-dimethyl derivative **21** with a fixed exocyclic double bond.

Alkylation of the tetrahydroquinazoline **18** occurs as N- and C-alkylation with endocyclic migration of the multiple bond and the formation of the dihydroquinazoline **22** (Table 3). Under the same conditions the benzyl derivative **15** forms a mixture of two mono and one dimethyl substituted quinazolines **23-25**. Analysis of this mixture by HPLC shows that it consists of 60% dimethylation product **23** and 40% monomethylation products **24** and **25**, which is in good agreement with the data of ^{1}H NMR spectroscopy.



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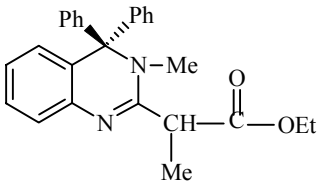

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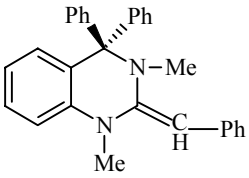
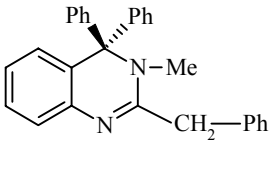


23



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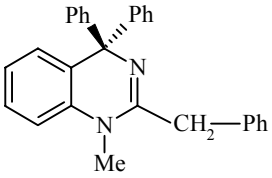

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TABLE 3. ^{1}H NMR spectra of Compounds **10-18, 21,** and **22**

Com-pound	Solvent	δ, ppm	SSCC, *J*, Hz
10	$CDCl_3$	2.05 (3H, s, CH_3); 3.75 (1H, br. s, NH); 6.80 (4H, m, C_6H_4); 7.15 [10H, s, $(C_6H_5)_2$]	—
11	$CDCl_3$	3.90 (1H, br. s, NH); 5.46 (1H, d, H_β); 5.77 (1H, d, H_γ); 6.32 (1H, dd, H_α); 6.73 (4H, m, C_6H_4); 7.20 [10H, s, $(C_6H_5)_2$]	$^3J_{\alpha\beta}$ = 10.5 $^3J_{\alpha\gamma}$ = 17.0
12	$CDCl_3$	2.92 (1H, br. s, NH); 7.18 (19H, m, H_{arom})	—
13	$CDCl_3$	3.95 (1H, br. s, NH); 7.35 (4H, m, C_6H_4); 7.80 [10H, s, $(C_6H_5)_2$]; 8.57 and 8.90 [4H, dd, H_{arom}, ($2H_B$+$2H_A$)]	$^3J_{AB}$ = 8.0
14	$CDCl_3$	4.90 (2H, br. s, NH_2); 7.65 [10H, s, $(C_6H_5)_2$]; 7.90 (4H, m, C_6H_4); 8.00 and 8.30 [5H, m, ($2H_B$+$2H_A$+NH)]	$^3J_{AB}$ = 7.0
15	$CDCl_3$	3.53, 3.68, 4.30, 4.40 (2H, four s, CH_2); 7.13 (20H, m, $19H_{arom}$+NH)	—
	$(CD_3)_2CO$	3.34 (1H, br. s, NH); 3.55, 3.68, 4.38, 4.41 (2H, four s, CH_2); 7.20 (19H, m, H_{arom})	—
	CF_3COOH	3.57, 3.67, 4.12, 4.20 (2H, four s, CH_2); 6.77 (19H, m, H_{arom}); 7.83 and 8.04 (1H, two s, NH)	—
	DMSO	3.48, 4.25, 4.27 (2H, three s, CH_2); 6.95 (19H, m, H_{arom}); 8.45, 8.60, 9.50 (1H, three s, NH)	—
16	$CDCl_3$	3.76 (2H, s, CH_2); 5.70 (1H, s, NH); 7.16 {16H, m, H_{arom}, [$(C_6H_5)_2$+ C_6H_4+$2H_B$)]}; 7.90 (2H, d, H_A)	$^3J_{AB}$ = 7.0
	$(CD_3)_2CO$	3.90 (2H, s, CH_2); 6.90 (4H, m, C_6H_4); 7.33 [10H, s, $(C_6H_5)_2$]; 7.63 and 8.23 [4H, dd, H_{arom} ($2H_B$+$2H_A$)]	$^3J_{AB}$ = 7.0
17	$CDCl_3$	3.90 (4H, br. s, NH_2+CH_2); 7.10 and 7.34 [4H, dd, H_{arom} ($2H_B$+$2H_A$)]; 7.65 (15H, m, H_{arom} +NH)	$^3J_{AB}$ = 8.0
18	$CDCl_3$	1.21 (3H, t, CH_3); 4.08 (2H, q, CH_2); 5.35 (1H, br. s, 3-NH); 6.75 (4H, m, C_6H_4); 6.88 (1H, s, =CH); 7.18 [10H, s, $(C_6H_5)_2$]; 10.75 (1H, br. s, 1-NH)	—
	$(CD_3)_2CO$	1.15 (3H, t, CH_3); 3.60 (2H, q, CH_2); 3.90 and 8.65 (1H, two s, 3-NH); 4.21 and 9.48 (1H, two s, 1-NH); 6.52 (4H, m, C_6H_4); 6.61 and 6.67 (1H, two s, =CH); 6.88 [10H, s, $(C_6H_5)_2$]	
21	$(CD_3)_2CO$	2.85 [6H, s, $(N–CH_3)_2$]; 4.90 (1H, s, =CH); 7.15 {16H, m, H_{arom}[$(C_6H_5)_2$+C_6H_4+$2H_B$]}; 7.90 (2H, d, $2H_A$)	$^3J_{AB}$ = 9.0
22	DMSO-d_6	1.13 (3H, t, CH_3); 1,45 (3H, d, C–CH_3); 3.25 (3H, s, N–CH_3); 3.88 (1H, q, C–H); 4.09 (2H, q, CH_2); 6.95 (14H, m, H_{arom})	$^3J_{CH_2CH_3}$ = 7.0 $^3J_{CH_2CH_3}$ = 6.5

Compound **21**, in contrast to the other analogs, has a bright red color. The color disappears in an acidic medium probably as a result of protonation of the amine nitrogen atoms of the heterocycle. This confirms the presence of charge transfer in the initial structure from the amino groups to the acceptor nitro group through the benzylidene moiety. The experimental material extends the insight on the possibilities of synthesis and properties of dihydroquinazoline derivatives and opens the possibilities for further investigations in this series of interesting compounds.

EXPERIMENTAL

The IR spectra were recorded in Nujol on a Specord IR 75 instrument at room temperature, and the ^{1}H NMR spectra on Tesla B3-467 (60 MHz) and Bruker AC-200 (200 MHz) instruments. Electronic spectra were recorded on a Specord UV-vis spectrometer in ethanol. TLC was carried out in the system benzene–ether, 4 : 1, on Silufol UV 254 plates, visualization by iodine vapor. Analysis of the mixture of compounds **23-25** was carried out by HPLC.

4,4-Diphenyl-2-vinyl-3,4-dihydroquinazolinium Perchlorate (2). A mixture of APC (0.27 g, 0.001 mol), and 70% $HClO_4$ (0.1 ml, 0.001 mol) in acrylonitrile (5 ml) was refluxed with stirring for 30 min. The mixture was then cooled (ice bath), and the salt obtained was precipitated with ether. Yield 0.25 g.

Salts **1**, **3**, **6**, and **9** were obtained by a similar method, maintaining the temperature of the reaction mixture at 80-85°C.

2-(*p*-Nitrophenyl)-4,4-diphenyl-3,4-dihydroquinazolinium Perchlorate (4). A solution of APC (0.27 g, 0.001 mol) in nitromethane (5 ml) was added dropwise to a refluxed mixture of *p*-nitrobenzoic acid nitrile (0.15 g, 0.001 mol) and 70% $HClO_4$ (0.1 ml, 0.001 mol) in nitromethane (5 ml) during 30 min. After cooling (ice bath), the salt formed was precipitated from the reaction mixture by adding ether. Yield 0.33 g.

Salts **5, 7,** and **8** were obtained analously.

2-(*p*-Nitrophenyl)-4,4-diphenyl-3,4-dihydroquinazoline (13). A. Salt **4** (1 g, 0.002 mol) was stirred with an excess of 25% aqueous ammonia (10 ml), and the mixture was heated at reflux for 10 min. The precipitate was then filtered off, washed with water, and dried in the air. Yield 0.56 g.

Bases **10**, **11**, and **14-18** were obtained analogously.

B. A mixture of *o*-aminophenyl(diphenyl)chloromethane hydrochloride (1.02 g, 0.0031 mol), *p*-nitrobenzoic acid nitrile (0.46 g, 0.0031 mol), and anhydrous $ZnCl_2$ (0.42 g, 0.0031 mol) in absolute chloroform (5 ml) was heated at reflux for 15 min until disappearance of the dark blue color of the reaction mixture (the color of the carbenium cation A, Scheme 1). At the end of the reaction, aqueous ammonia (10 ml) was added, and the mixture was heated to 50°C with stirring for 10 min. The organic layer was then separated, washed with water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue recrystallized from alcohol. Yield 0.75 g (60%).

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