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2,2,4-TRIMETHYLHYDROQUINOLINES IN THE BISCHLER–MELAU REACTION

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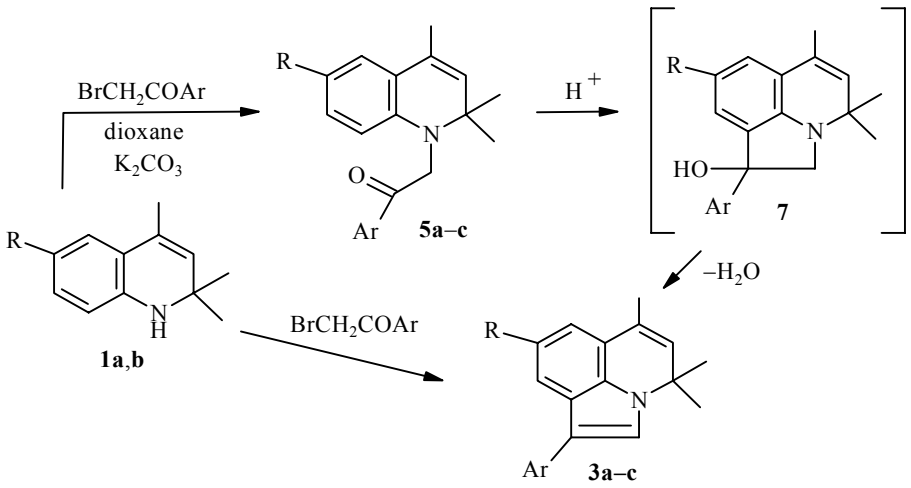
8-R-1-Aryl-4,4,6-trimethyl-4H-pyrrolo[3,2,1-ij]quinolines have been synthesized by the Bischler–Melau reaction in the series of 6-R-2,2,4-trimethylhydroquinolines.

Keywords: 8-R-1-aryl-4,4,6-trimethyl-4H-pyrrolo[3,2,1-*ij*]quinolines, 6-R-2,2,4-trimethylhydroquinolines, Bischler–Melau reaction.

The Bischler–Melau reaction is one of the convenient methods of synthesizing the indole ring from primary and secondary aromatic amines. However there are few cases in the literature of the application of this reaction for the synthesis of tricyclic systems and there is no single opinion on its mechanism [1-4].

We have studied the Bischler–Melau reaction in the series of 6-R-2,2,4-trimethyl-1,2-dihydroquinolines (**1a,b**) and 4-R^1-6-R^2-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines (**2a-c**), which are representatives of sterically hindered secondary heterocyclic amines [5,6].

It was established that carrying out the reaction in the classic variant [4,7] by melting trimethyldihydroquinolines **1a,b** and trimethyltetrahydroquinolines **2a-c** with 4-R-phenacyl bromides at ratio 2:1 at 130-150°C, leads to the formation of the corresponding 8-R-1-aryl-4,4,6-trimethyl-4H-pyrrolo[3,2,1-*ij*]-quinolines (**3a-c**) and 6-R^1-8-R^2-1-aryl-4,4,6-trimethyl-5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolines (**4a-e**) in low yield (15-25%) (Method A) (see Table 1). In this way the formation of minor rearrangement-cyclization



1 a R = H, **b** R = Me; **3 a** R = Me, Ar = Ph, **b** R = H, Ar = 4-O_2N–C_6H_4, **c** R = Me, Ar = 4-O_2N–C_6H_4; **5 a** R = H, Ar = 4-O_2N–C_6H_4, **b** R = Me, Ar = Ph, **c** R = Me, Ar = 4-O_2N–C_6H_4

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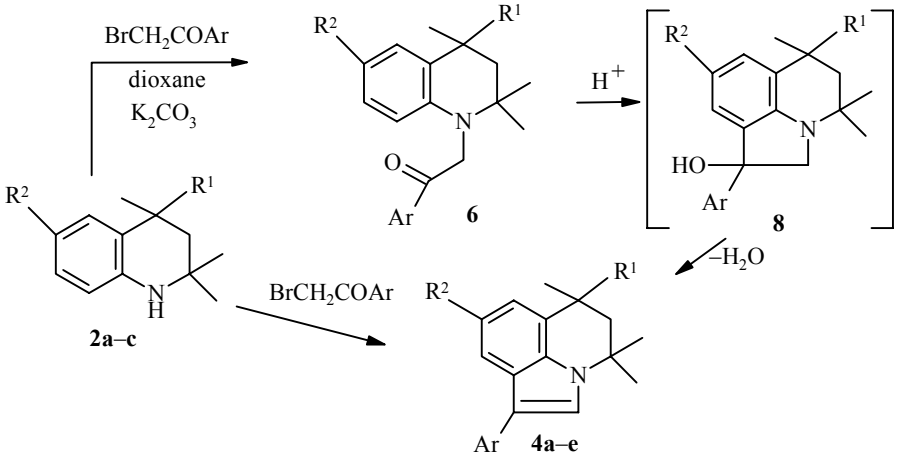
products accompanying the Bischler synthesis [4] was not detected, but the low yields of pyrroloquinolines **3a-c** and **4a-e** are evidently linked with the smooth occurrence at high temperatures of aromatization of the initial hydroquinolines **1a,b** and **2a-c** by elimination of a molecule of methane [7,8]. The occurrence of polymerization side reactions is also possible for trimethyldihydroquinolines **1a,b** under the given conditions in the presence of acid catalysts [9].



2 a $R^1 = R^2 = H$; **b** $R^1 = H$, $R^2 = Me$; **c** $R^1 = Ph$, $R^2 = H$; **4 a** $R^1 = R^2 = H$, Ar = Ph, **b** $R^1 = Ar = Ph$, $R^2 = H$, **c** $R^1 = R^2 = H$, Ar = 4-O_2N–C_6H_4, **d** $R^1 = H$, $R^2 = Me$, Ar = 4-O_2N–C_6H_4, **e** $R^1 = Ph$, $R^2 = H$, Ar = 4-O_2N–C_6H_4; **6** $R^1 = Ph$, $R^2 = H$, Ar = 4-O_2N–C_6H_4

The yields of pyrroloquinolines **3a-c** and **4a-e** were successfully increased to 35-45% on carrying out the reaction in boiling dimethylacetamide at a reactant–substrate ratio of 1:1 (method B). In this case dimethylacetamide is the acceptor of the eliminated hydrogen bromide and its hydrobromide is the acid catalyst. It was established by TLC that under these conditions the cyclization proceeds through the formation of intermediate products, evidently N-phenacyl derivatives of trimethylhydroquinolines.

With the aim of confirming the structures of the intermediate products of cyclization we synthesized the N-phenacyl derivatives of trimethylhydroquinolines **1a,b** and **2c** by the interaction of the latter with 4-R-phenacyl bromides at low temperatures and in the presence of acceptors of hydrogen bromide. The following systems were tested when selecting reaction conditions for obtaining the N-phenacyl derivatives: acetone–triethylamine; acetone–potassium carbonate; dioxane–potassium carbonate. The last system proved to be the best, permitting the use of higher temperatures. The *gem*-dimethyl groups probably screen the nitrogen atom of the hydroquinoline ring, consequently it is necessary to heat to 70-80°C to carry out the reaction at a satisfactory rate.

N-Phenacyl derivatives of 6-R-2,2,4-trimethyl-1,2-dihydroquinoline (**5a-c**) and of 2,2,4-trimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline (**6**) obtained in satisfactory yield (40-50%) were, as expected, identical according to TLC data with the intermediate products of the cyclization of trimethylhydroquinolines in the Bischler–Melau reaction.

N-Phenacyl derivatives of hydroquinolines **5a-c** and **6** were cyclized on boiling them in absolute dioxane in the presence of acid catalysts (toluenesulfonic acid, boron trifluoride etherate, etc) into the corresponding pyrroloquinolines **3a-c** and **4a-e**. Evidently the reaction goes through a stage of forming the intermediate 1-hydroxy-1,2-dihydropyrroloquinolines (**7,8**) with subsequent elimination of water. In this way the yields of the desired pyrroloquinolines also did not exceed 40% (method C).

In the ^{1}H NMR spectra of pyrroloquinolines **3a-c** and **4a-e** (Table 2), in comparison with the spectra of the corresponding hydroquinoline N-phenacyl derivatives **5a-c** and **6,** the singlet signals of the methylene protons at 4.8-4.9 ppm were absent, and in the aromatic region characteristic singlet signals were observed for the sole proton of the pyrrole ring at 7.7-7.8 ppm for the 1-phenyl derivatives and at 8.1-8.3 ppm for the 1-(4-nitrophenyl) derivatives.

So the Bischler–Melau reaction for 2,2,4-trimethylhydroquinolines was established to proceed through the stage of forming the corresponding N-phenacyl derivatives and leads to the formation of pyrrolo[3,2,1-*ij*]-quinolines.

The characteristics and yields of the synthesized compounds **3-6** are given in Table 1.

TABLE 1. Characteristics of Compounds **3-6**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
3a	$C_{21}H_{21}N$	88.00 / 87.80	7.45 / 7.32	5.10 / 4.88	98-100	15 (A), 33 (C)
3b	$C_{20}H_{18}N_2O_2$	75.73 / 75.47	5.90 / 5.66	9.10 / 8.81	169-171	23 (A), 42 (B), 37 (C)
3c	$C_{21}H_{20}N_2O_2$	76.20 / 75.90	6.34 / 6.02	8.61 / 8.43	176-178	25 (A), 40 (B), 35 (C)
4a	$C_{20}H_{21}N$	87.90 / 87.59	7.53 / 7.64	5.28 / 5.09	146-148	18 (A), 30 (C)
4b	$C_{26}H_{25}N$	79.92 / 88.88	7.26 / 7.12	4.17 / 3.99	193-195	20 (A), 39 (C)
4c	$C_{20}H_{20}N_2O_2$	75.21 / 75.00	6.58 / 6.25	9.00 / 8.75	158-160	16 (A), 33 (C)
4d	$C_{21}H_{22}N_2O_2$	75.70 / 75.45	6.87 / 6.59	8.64 / 8.38	179-181	25 (A), 40 (C)
4e	$C_{26}H_{24}N_2O_2$	79.04 / 78.79	6.31 / 6.06	7.25 / 7.07	215-217	18 (A), 45 (B), 38 (C)
5a	$C_{20}H_{20}N_2O_3$	71.50 / 71.43	6.01 / 6.95	8.54 / 8.33	142-143	41
5b	$C_{21}H_{23}NO$	82.40 / 82.62	7.67 / 7.54	4.81 / 4.60	46-47	47
5c	$C_{21}H_{22}N_2O_3$	72.14 / 72.00	6.40 / 6.29	8.27 / 8.00	154-155	45
6	$C_{26}H_{26}N_2O_3$	75.40 / 75.36	6.32 / 6.28	6.93 / 6.76	165-168	52

TABLE 2. ^{1}H NMR Spectra of Compounds **3-6**

Compound	Chemical shift, δ, ppm
1	2
3a	1.63 (6H, s, CMe_2); 2.13 (3H, s, 6-Me); 2.43 (3H, s, 8-Me); 5.70 (1H, s, 5-H); 6.8-7.8 (7H, m, H arom.); 7.71 (1H, 2-H)
3b	1.68 (6H, s, CMe_2); 2.15 (3H, s, 6-Me); 5.65 (1H, s, 5-H); 7.1-8.2 (7H, m, H arom.); 8.27 (1H, s, 2-H)
3c	1.60 (6H, s, CMe_2); 2.12 (3H, s, 6-Me); 2.48 (3H, s, 8-Me); 5.70 (1H, s, 5-H); 6.9-8.3 (6H, m, H arom.); 8.29 (1H, s, 2-H)
4a	1.48 (6H, s, CMe_2); 1.82 (3H, d, 6-Me); 1.95 (2H, qq, 5-H_2); 3.25 (1H, m, 6-H); 7.10-8.15 (7H, m, H arom.); 7.82 (1H, s, 2-H)
4b	0.85; 1.61 (3H and 3H, s and s, CMe_2); 1.80 (3H, s, 6-Me); 2.39 (2H, dd, 5-CH_2); 6.8-8.1 (13H, m, H arom.); 7.77 (1H, s, 2-H)

TABLE 2 (continued)

1	2
4c	1.38 and 1.48 (3H and 3H, s and s, CMe_2); 1.78 (3H, d, 6-Me); 1.98 (2H, qq, 5-CH_2); 3.27 (1H, m, 6-H); 7.1-8.2 (7H, m, H arom.); 8.13 (1H, s, 2-H)
4d	1.36 and 1.42 (3H and 3H, s and s, CMe_2); 1.75 (3H, d, 6-Me); 1.93 (2H, qq, 5-CH_2); 2.44 (3H, s, 6-Me); 3.21 (1H, m, 6-H); 6.9-8.2 (6H, m, H arom.); 8.09 (1H, s, 2-H)
4e	0.85 and 1.75 (3H and 3H, s and s, CMe_2); 2.83 (3H, s, 6-Me); 2.52 (2H, dd, 5-CH_2); 7.0-8.3 (12H, m, H arom.); 8.12 (1H, s, 2-H)
5a	1.35 (6H, s, CMe_2); 1.98 (3H, s, 4-Me); 4.91 (2H, s, CH_2); 5.35 (1H, s, 3-H); 5.9-8.3 (8H, m, H arom.)
5b	1.29 (6H, s, CMe_2); 1.94 (3H, s, 4-Me); 2.20 (3H, s, 6-Me), 4.79 (2H, s, CH_2); 5.32 (1H, s, 3-H); 6.0-7.7 (8H, m, H arom.)
5c	1.31 (6H, s, CMe_2); 1.95 (3H, s, 4-Me); 2.18 (3H, s, 6-Me); 4.82 (2H, s, CH_2); 5.30 (1H, s, 3-H); 5.9-8.3 (7H, m, H arom.)
6	0.98 and 1.28 (3H and 3H, s and s, CMe_2); 2.01 (3H, s, 4-Me); 2.21 (2H, dd, CH_2); 4.85 (2H, s, CH_2); 6.0-7.8 (13H, m, H arom.)

EXPERIMENTAL

The ^{1}H NMR spectra were taken in DMSO-d_6 on a Bruker AM 300 (300 MHz) instrument, internal standard was TMS. A check on the progress of reactions and the homogeneity of the compounds obtained was effected by TLC (Silufol UV-254, benzene–chloroform, 1:1, visualization with iodine vapor).

The initial 6-R-2,2,4-trimethyl-1,2-dihydroquinolines **1a,b** and 4-R^1-6-R^2-2,2,4-trimethyl-1,2,3,4-tetrahydroquinolines **2a-c** were obtained as described in [10,11].

N-Phenacyl Derivatives of Hydroquinolines 5a-c, 6. Freshly calcined potassium carbonate (2.5 g, 0.018 mol) and 4-R-phenacyl bromide (0.01 mol) were added to a solution of the appropriate hydroquinoline **1a,b** or **2a-c** (0.01 mol) in dry dioxane (20 ml). The reaction mixture was heated at 60-80°C with stirring for 3 days, poured into water, the precipitate was filtered off, and recrystallized from 2-propanol.

8-R-1-Aryl-4,4,6-trimethyl-4H-pyrrolo[3,2,1-*ij*]quinolines (3a-c) and 6-R^1-8-R^2-1-Aryl-4,4,6-trimethyl-5,6-dihydro-4H-pyrrolo[3,2,1-*ij*]quinolines (4a-e). A. Mixture of hydroquinoline **1a,b** or **2a-c** (0.02 mol) and 4-R-phenacyl bromide (0.01 mol) was mixed thoroughly, the mixture was heated to 130-150°C, and maintained at this temperature for 20-30 min. The reaction mass was poured into concentrated hydrochloric acid (20 ml), the precipitated crystals were filtered off, washed with water, dried, and purified by preparative column chromatography on Al_2O_3, using CCl_4 as eluent. After distilling off the eluent the crystals were recrystallized from methanol–petroleum ether 2:1 mixture.

B. 4-R-Phenacyl bromide (0.01 mol) was dissolved in dry dimethylacetamide (20 ml) , left for 30 min at room temperature, hydroquinoline (0.01 mol) was added, and the mixture boiled for 30 h. The reaction mixture was poured into water, the precipitated solid was filtered off, washed with water, dried, and purified by the method described in A.

C. *p*-Toluenesulfonic acid (1 g) or boron trifluoride etherate (2 ml) was added to a solution of the N-phenacyl derivative **5a-c** or **6** (0.01 mol) in absolute dioxane (30 ml) and the mixture was boiled for 20 h. The desired products were isolated and purified as described above.

REFERENCES

1. A. B. Sheremetev, I. L. Yudin, and D. E. Dmitriev*, Izv. Akad. Nauk, Ser. Khim.,* 400 (1999).
2. S. I. Zav'yalov, A. G. Zavozin, O. V. Dorofeeva, and E. E. Rumyantseva, *Izv. Akad. Nauk SSSR. Ser. Khim.*, 509 (1991).

3. L. G. Yudin, V. A. Budylin, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 704 (1967).
4. R. C. Elderfield (editor), *Heterocyclic Compounds*, Vol. 3, Wiley, New York (1952).
5. A. E. Obodovskaya, Z. A. Starikova, Yu. A. Ivanov, and I. E. Pokrovskaya, *Zh. Strukt. Khim.*, **26**, No. 5, 93 (1985).
6. A. E. Obodovskaya, Z. A. Starikova, Kh. S. Shikhaliev, and Zh. V. Shmyreva, *Kristallografiya*, **35**, 1565 (1990).
7. E. Zobian, W. Kelley, and H. Dunathan, *J. Org. Chem.*, **29**, 584 (1964).
8. T. D. Nekipelova and A. B. Gagarina, *Dokl. Akad. Nauk SSSR*, **231**, 352 (1976).
9. I. W. Elliott and H. C. Dunathan, *Tetrahedron*, **19**, 833 (1963).
10. *Syntheses of Organic Preparations*, Vol. 4 [Russian translation], Izd. Inostr. Lit., Moscow (1953), p. 186.
11. B. A. Lugovik, P. V. Borodin, L. G. Yudin, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1512 (1970).