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ANOMALOUS BECKMANN REACTION OF 4-ARYL-2,7,7-TRIMETHYL-5-OXO-5,6,7,8-TETRAHYDROQUINOLINE OXIMES IN POLYPHOSPHORIC ACID. 1. NEW SYNTHESIS OF 1-ETHOXYCARBONYL-2,5,5-TRIMETHYL-5,6-DIHYDRO-4H-PYRIDO[2,3,4-*k,l*]ACRIDINES

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Transformations of oximes of 4-aryl-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolines in PPA have been studied. It is shown that the reaction, depending on substituent at position 4 of quinoline ring, can occur in three directions: aromatization of the saturated ring (Semmler–Wolff aromatization), formation of azepinones – normal products of Beckmann rearrangement, and formation of pyridoacridines.

Keywords: 4-aryl-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolines, 1-ethoxycarbonyl-2,5,5-trimethyl-5,6-dihydro-4H-pyrido[2,3,4,-*k,l*]acridines, Semmler–Wolff aromatization, Beckmann rearrangement.

The synthesis of azepinones using the Beckmann and Schmidt reaction from heterocyclic compounds containing a dimedone fragment is commonly used for obtaining biologically active compounds [1-6]. However, the Beckmann reaction often proceeds anomalously [7]. We have recently reported the rearrangement of 3,3,6-trimethyl-1-oxo-1,2,3,4-tetrahydrobenzofuro[2,3-*c*]quinolines and 3,3,6-trimethyl-1-oxo-1,2,3,4-tetrahydrobenzoindolo[2,3-*c*]quinolines in polyphosphoric acid (PPA) [8] involves not a classical Beckmann rearrangement but rather a migration of methyl groups with Semmler–Wolff aromatization of the unsaturated ring [9]. Similar transformations have been described for oximes of 3-alkyl-4-oxo-1-phenyl-4,5,6,7-tetrahydroindazoles and 5-oxo-5,6,7,8-tetrahydrocinnolines [7, 10]. In the present study, we attempted to understand the Beckmann reaction and Semmler–Wolff aromatization for 4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolines.

The reaction was carried out by heating the corresponding oximes with a 10-fold excess of PPA at 100°C for 1 h. Under these conditions, 3-ethoxycarbonyl-2,4,7,7-tetramethyl-5-oxo-5,6,7,8-tetrahydroquinoline oxime (**1**) and 3,3-dimethyl-1-oxo-1,2,3,4,5,6,7,8-octahydroacridine oxime (**2**) were found to undergo Semmler–Wolff aromatization. The possible formation of isomeric products **3** or **4** and **5** or **6** is related to a different direction of migration of the methyl groups. In order to prove the structure of the products formed, we carried out the reductive deamination of 1-amino-2,3-dimethyl-5,6,7,8-tetrahydroacridine (**5**) to 2,3-dimethyl-5,6,7,8-tetrahydroacridine (**6**).

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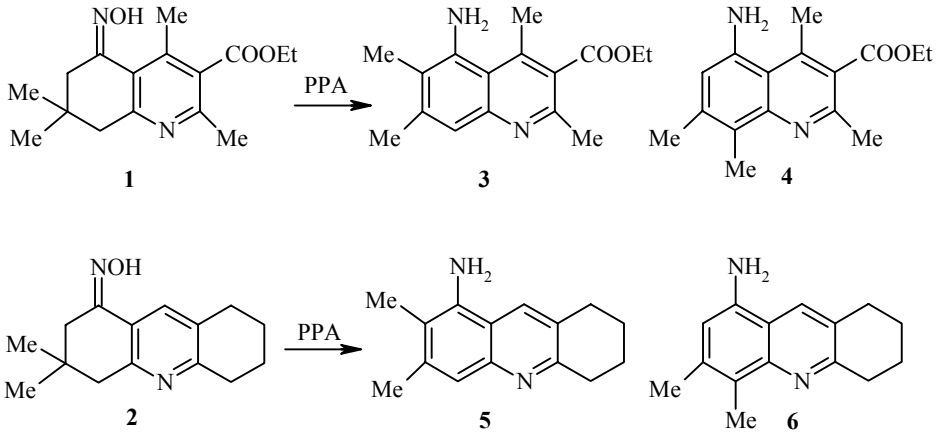
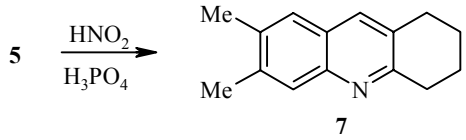


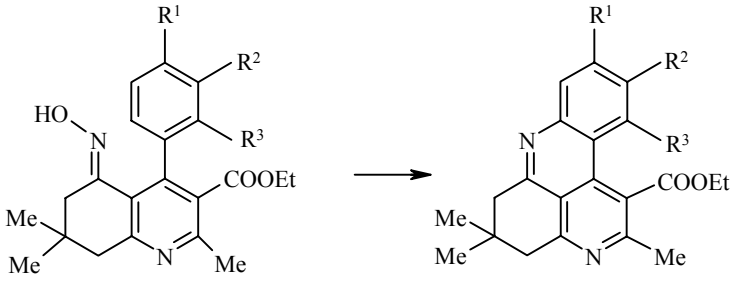
The finding of three aromatic proton singlets in the ^{1}H NMR spectrum of **7** indicates migration of the methyl group adjacent to the amino group and formation of products **3** and **5** in the reaction of oximes **1** and **2** with PPA. Otherwise, the ^{1}H NMR spectrum of **7** would have shown an aromatic proton doublet.



4-Aryl-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinoline oximes react differently under these conditions. Thus, 3-ethoxycarbonyl-2,7,7-trimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydroquinoline oxime (**8a**) gives 3-ethoxycarbonyl-2,5,5-trimethyl-5,6-dihydro-4H-pyrido[2,3,4,-*k,l*]acridine (**9a**). This transformation involves attack of the 4-phenyl substituent in starting oxime **8a** by the intermediate nitrenium cation. The ^{1}H NMR spectra show signals for the 1,2-disubstituted phenyl fragment. A similar reaction occurs for 4-(3',4'-dimethoxyphenyl)-3-ethoxycarbonyl-2,7,7-trimethyltetrahydroquinoline oxime (**8b**) with the exception that demethylation with loss of the 4-methoxy group occurs in this latter reaction. The ^{1}H NMR spectrum of pyridoacridine **9b** lacks the signal for one of the methoxy groups and shows an OH group band at 10.35 ppm.

The introduction of an electron-withdrawing substituent such as a nitro group into the benzene ring might presumably hinder the electrophilic attack of the 4-phenyl substituent by the nitrenium cation and, thus, the reaction would proceed through the classical pathway to give an azepinone. However, the formation of pyridoacridine **9c** was also discovered in this case as well.

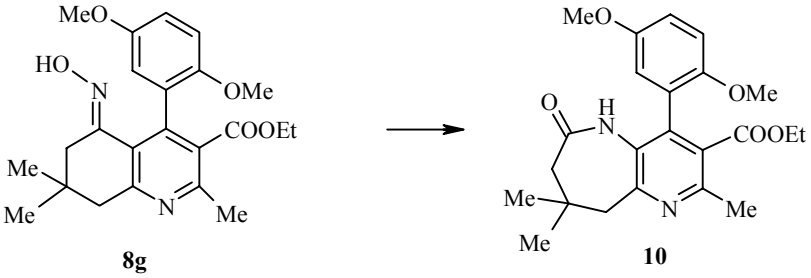
As in the case of **9a** and **9b**, the ^{1}H NMR spectra of the products formed provide considerable information. Thus, the pattern of the aromatic protons in the ^{1}H NMR spectrum of **9c** is different from that in the spectrum of starting oxime **8c**. While the ^{1}H NMR spectrum of oxime **8c** has signals for a 1,4-disubstituted aromatic system, the ^{1}H NMR spectrum of the final product **9c** has signals for a 1,2,4-trisubstituted system (Table 1). The transformations of the oximes of 4-(2'-chlorophenyl)- (**9d**), 4-(4'-methylthiophenyl)- (**9e**), and 4-(3'-bromophenyl)-5-oxo-5,6,7,8-tetrahydroquinolines (**9f**) proceed similarly. The structures of reaction products **9d-f** were demonstrated analogously.



8a–f **9a–f**

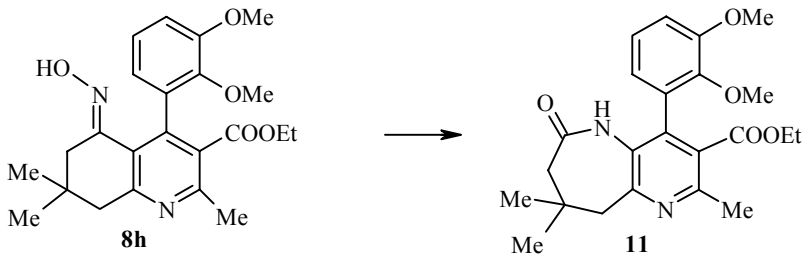
8, **9 a** $R^1 = R^2 = R^3 = H$, **8b** $R^1 = R^2 = OMe$, $R^3 = H$, **9b** $R^1 = OH$, $R^2 = OMe$, $R^3 = H$;
8, **9 c** $R^1 = NO_2$, $R^2 = R^3 = H$, **d** $R^1 = R^2 = H$, $R^3 = Cl$, **e** $R^1 = SMe$, $R^2 = R^3 = H$,
f $R^1 = R^3 = H$, $R^2 = Br$

4-(2',5'-Dimethoxyphenyl)-3-ethoxycarbonyl-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinoline oxime (**8g**) gives 9-(2',5'-dimethoxyphenyl)-8-ethoxycarbonyl-4,4,7-trimethyl-2,3,4,5-tetrahydropyrido[3,2-*b*]azepin-2-one (**10**). Hence, this reaction involves the classical Beckmann rearrangement.



8g **10**

The ^{1}H NMR spectrum of **10** shows a band for the HNC=O group at 10.78 ppm. 4-(2',3'-Dimethoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinoline oxime (**8h**) undergoes a similar reaction to give azepinone **11**. This reaction course is likely related to the noncoplanarity of the 4-phenyl substituent at $C_{(4)}$ in **8g** and **8h** due to steric hindrance created by the 2'-methoxy group. As a result, attack of the phenyl group by the nitrenium cation becomes impossible.



8h **11**

Thus, we have shown that the transformation of 2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinoline oximes in PPA depends on the substituents at $C_{(4)}$ of the tetrahydroquinoline system and may proceed in several directions involving 1) aromatization of the saturated ring (Semmler–Wolff aromatization), 2) formation of azepinones, which are the normal products of the Beckmann rearrangement, and 3) attack of the 4-phenyl substituent by the intermediate nitrenium ion to give pyridoacridines.

TABLE 1. ^{1}H NMR Spectra of Products

Compound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)			
	2-CH_3 (7-CH_3) (3H, s)	$COOC_2H_5$ (3H, t, 2H, q)	H arom.	Other protons
2	—	—	7.78 (1H, s, 9-H)	1.00 (6H, s, 3-, 3-CH_3); 1.78 (2H, m, 6-CH_2); 1.86 (2H, m, 7-CH_2); 2.62 (2H, s, 2-CH_2); 2.74 (4H, m, 5-, 8-CH_2); 2.90 (2H, s, 4-CH_2); 10.73 (1H, s, NOH)
3	2.44 (2.35)	1.34 (*J* = 7.0), 4.40 (*J* = 7.0)	7.06 (1H, s, 8-H)	2.14 (3H, s, 6-CH_3); 2.85 (3H, s, 4-CH_3); 5.20 (2H, s, NH_2)
5	2.11	—	8.17 (1H, s, 9-H)	1.83 (4H, m, 6-, 7-CH_2); 2.32 (3H, s, 3-CH_3); 2.89 (4H, m, 5-, 8-CH_2); 5.20 (2H, s, NH_2); 6.95 (1H, s, 4-H)
7	2.31	—	7.55 (1H, s, 1-H); 7.60 (1H, s, 4-H); 7.80 (1H, s, 9-H)	1.83 (4H, m, 6-, 7-CH_2); 2.46 (3H, s, 3-CH_3); 2.89 (4H, m, 5- and 8-CH_2)
9a	2.64	1.36 (*J* = 7.1), 4.59 (*J* = 7.1)	7.69 (1H, t, 10-H); 7.87 (1H, t, 9-H); 8.06 (1H, d, *J* = 8.1, 8-H); 8.15 (1H, d, *J* = 8.1, 11-H)	1.06 (6H, s, 5-, 5-CH_3); 3.09 (2H, s, 6-CH_2); 3.11 (2H, s, 4-CH_2)
9b	2.58	1.36 (*J* = 7.1), 4.59 (*J* = 7.1)	7.35 (1H, s, 11-H); 7.45 (1H, s, 8-H)	1.04 (6H, s, 5-, 5-CH_3); 3.02 (2H, s, 6-CH_2); 3.06 (2H, s, 4-CH_2); 3.86 (3H, s, OCH_3); 10.36 (1H, s, 9-OH)
9c	2.69	1.39 (*J* = 7.1), 4.63 (*J* = 7.1)	8.32 (1H, d, *J* = 9,2 11-H,); 8.48 (1H, dd, J_1 = 9.2, J_2 = 2.56, 10-H); 8.73 (1H, d, *J* = 2.56, 8-H)	1.10 (6H, s, 5-, 5-CH_3); 3.18 (4H, s, 4- and 6-CH_2)
9d	2.85	1.04 (*J* = 7.1), 4.18 (*J* = 7.1)	7.66 (1H, dd, J_1 = 7.66, J_2 = 1.36, 10-H,); 7.78 (1H, t, 9-H); 7.96 (1H, dd, J_1 = 8.02, J_2 = 1.36, 8-H)	1.04 (6H, s, 5-, 5-CH_3); 3.06 (2H, s, 6-CH_2); 3.12 (2H, s, 4-CH_2)
9e	2.60	1.35 (*J* = 7.1), 4.54 (*J* = 7.1)	7.56 (1H, dd, J_1 = 8.80, J_2 = 1.96, 10-H); 7.77 (1H, d, *J* = 1.96, 8-H); 7.97 (1H, d, *J* = 8.80, 11-H)	1.04 (6H, s, 5-, 5-CH_3); 2.63 (3H, s, 9-SCH_3); 3.04 (2H, s, 6-CH_2); 3.08 (2H, s, 4-CH_2)
9f	2.63	1.41 (*J* = 7.1), 4.54 (*J* = 7.1)	7.97 (2H, s, 8-H and 9-H); 8.21 (1H, s, 11-H)	1.04 (6H, s, 5-, 5-CH_3); 3.05 (2H, s, 6-CH_2); 3.10 (2H, s, 4-CH_2)
10	(2.69)	0.92 (*J* = 7.1), 3.95 (*J* = 7.1)	6.57 (1H, d, *J* = 2.8 6-H); 6.84 (1H, dd, J_1 = 11, J_2 = 2,8, 4-H); 6.90 (1H, d, *J* = 11, 3-H)	0.92 (3H, s, 4-CH_3); 1.07 (3H, s, 4-CH_3); 2.42 (2H, s, 3-CH_2); 2.52 (2H, s, 5-CH_2); 3.53 (3H, s, OCH_3); 3.67 (3H, s, OCH_3); 10.78 (1H, s, NHCO)
11	(2.42)	0.88 (*J* = 7.1), 3.92 (*J* = 7.1)	6.60 (1H, t, 5'-H); 6.97 (1H, d, 4'-H, *J* = 11); 7.00 (1H, d, 6'-H, *J* = 11)	0.91 (3H, s, 4-CH_3); 1.07 (3H, s, 4-CH_3); 2.53 (2H, d, 5-CH_2, *J* = 3.64); 2.73 (2H, d, 3-CH_2, *J* = 3.64); 3.46 (3H, s, OCH_3); 3.79 (3H, s, OCH_3); 10.78 (1H, s, NHCO)

TABLE 2. Physicochemical Characteristics of **3, 5, 7-11**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C*	R_f*[2]	Yield, %
		C	H	N	Hal (S)			
3	$C_{16}H_{20}N_2O_2$	70.81 / 70.59	7.23 / 7.35	10.52 / 10.29	—	77-78	0.47	48.4
5	$C_{15}H_{18}N_2$	79.91 / 79.65	7.74 / 8.02	12.20 / 12.39	—	230-231	0.3	48
7	$C_{15}H_{17}N$	85.10 / 85.30	8.10 / 8.06	6.57 / 6.64	—	124-125	—	43
8a	$C_{21}H_{24}N_2O_3$	71.84 / 71.59	7.00 / 6.86	7.72 / 7.95	—	187		75
8b	$C_{23}H_{28}N_2O_5$	67.00 / 66.97	6.81 / 6.84	7.00 / 6.78	—	214		80.4
8c	$C_{21}H_{23}N_3O_5$	63.20 / 63.48	5.93 / 5.83	10.30 / 10.58	—	222		48.1
8d	$C_{21}H_{23}ClN_2O_3$	65.43 / 65.20	6.15 / 5.99	7.12 / 7.24	9.32 / 9.18	210		70.3
8e	$C_{22}H_{26}N_2O_3S$	66.56 / 66.33	6.37 / 6.53	7.20 / 7.04	(8.31) / (8.04)	207		94
8f	$C_{21}H_{23}BrN_2O_3$	58.62 / 58.47	5.15 / 5.34	6.69 / 6.50	18.30 / 18.56	210-211		31
8g	$C_{23}H_{28}N_2O_5$	67.10 / 66.97	6.87 / 6.84	6.90 / 6.78	—	235		78
8h	$C_{23}H_{28}N_2O_5$	67.00 / 66.97	6.85 / 6.84	7.00 / 6.78	—	215		80.4
9a	$C_{21}H_{22}N_2O_2$	75.70 / 75.45	6.41 / 6.59	8.52 / 8.38	—	111-112	0.65	20.8
9b	$C_{22}H_{24}N_2O_4$	69.80 / 69.47	6.10 / 6.32	7.20 / 7.39	—	166	0.52	26
9c	$C_{21}H_{21}N_3O_4$	66.23 / 66.49	5.31 / 5.54	11.00 / 11.08	—	196	0.73	67
9d	$C_{21}H_{21}ClN_2O_2$	68.1 / 68.39	5.44 / 5.70	7.81 / 7.60	9.42 / 9.63	104	0.75	25
9e	$C_{21}H_{24}N_2O_2S$	69.60 / 69.47	6.44 / 6.36	7.52 / 7.39	(8.60) / (8.42)	94	0.55	22
9f	$C_{21}H_{21}BrN_2O_2$	61.25 / 61.02	5.14 / 5.12	6.89 / 6.78	19.48 / 19.33	204	0.22	35.7
10	$C_{23}H_{28}N_2O_5$	66.72 / 66.99	6.71 / 6.84	6.78 / 6.80	—	227	0.45	46
11	$C_{23}H_{28}N_2O_5$	66.75 / 66.99	6.64 / 6.84	6.79 / 6.80	—	205	0.71	44

*Crystallization solvents: ethanol for **3** and **5**, acetone–water for **9a**, benzene–hexane for **9b**, acetone for **9c**, and acetone–hexane for **7, 9d-f, 10, 11**.

*[2] Eluent: 5:10:1 chloroform–benzene–ethanol for **3** and **9c**, 10:1 benzene–2-propanol for **5, 9a,e,f**, 8:1:2 benzene–2-propanol–ethyl acetate for **9b**, and 4:1 ethyl acetate–benzene for **9d, 10, 11**.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Varian VXR-300 spectrometer at 300 MHz and a Gemini-200 spectrometer at 200 MHz in DMSO-d_6 with TMS as the internal standard. The purity of the products was monitored by thin-layer chromatography on Silufol UV-254 plates with detection by UV light or iodine.

Oximes **1, 2,** and **8a-f** were obtained by the well-known method from the corresponding 4-aryl-3-ethoxycarbonyl-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinolines [11-13]. The configuration of the oximes was not determined.

General Method for the Preparation of Products 3, 5, 9a-f, 10, and 11. A mixture of PPA (10 g) and oxime (1 g) was heated for 1 h at 100°C. The reaction mixture was poured into water (100 ml) and neutralized by adding aqueous ammonia. The precipitate formed was filtered off or extracted with chloroform. The products were purified by chromatography on silica gel.

2,3-Dimethyl-5,6,7,8-tetrahydroacridine (7). A solution of $NaNO_2$ (0.60 g, 0.01 mol) in water (5 ml) was added to a solution of 1-amino-2,3-dimethyl-5,6,7,8-tetrahydroacridine (**5**) (2.26 g, 0.01 mol) in hypophosphoric acid (20 ml) at 5°C. The mixture was maintained at room temperature for 5 h and then heated at 60°C for 1 h, cooled, neutralized by adding ammonia, and filtered to give 0.9 g of compound **7**. The product was crystallized from acetone–hexane.

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