

Arylaliphatic 3-Aza-1,5-diketones: Reactions with N-Nucleophiles

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Abstract—1-Substituted 3,5-diphenylpyrazinium salts were obtained by reactions of tertiary bis(phenacyl)-amines with ammonium acetate, hydroxylamine hydrochloride, and hydrazine hydrate in acid medium. The reaction of quaternary dimethylbis(phenacyl)ammonium bromide with hydrazine hydrate afforded 3,6-diphenylpyridazine.

Bis(phenacyl)amines like **I–III** have been reported for the first time at the beginning of the past century [1]. Gabriel [1] studied the reaction of bromoacetophenone with ammonia and obtained bis(phenacyl)-amine (R = H) which was then brought into reaction with ammonia in alcoholic solution. The structure of the resulting cyclization product was refined later [2] as 2,6-dihydropyrazine.

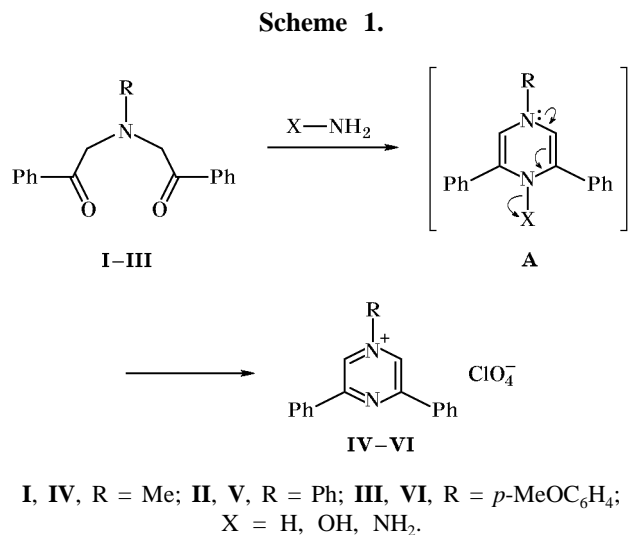
While studying the chemistry of 1,5-diketones, we turned to their 3-aza analogs, among which the simplest and most accessible were bis(phenacyl)-amines **I–III**. However, these compounds appeared to be studied very poorly, though they attract a certain interest, in particular as initial compounds for the synthesis of heterocycles with two heteroatoms. There are some published data on the preparation from such diketones of oxazine [3] and dihydropyrazine derivatives [4]. The latter were obtained via reaction with amines in toluene. It should be noted that common 1,5-diketones are known to react with N-nucleophiles to give a variety of products [5]. Depending on the conditions, dihydropyridine or pyridine derivatives, pyridinium salts, or mixtures of these compounds could be obtained.

Using compounds **I–III** as examples (diketone **I** was taken as the corresponding salt with perchloric acid, and amines **II** and **III** were free bases), we examined their reactions with ammonia and its derivatives, namely with ammonium acetate in acetic acid and with hydroxylamine hydrochloride and hydrazine hydrate in isopropyl alcohol in the presence of perchloric acid. Regardless of the N-nucleophile, compounds **I–III** gave rise to the same products, pyrazi-

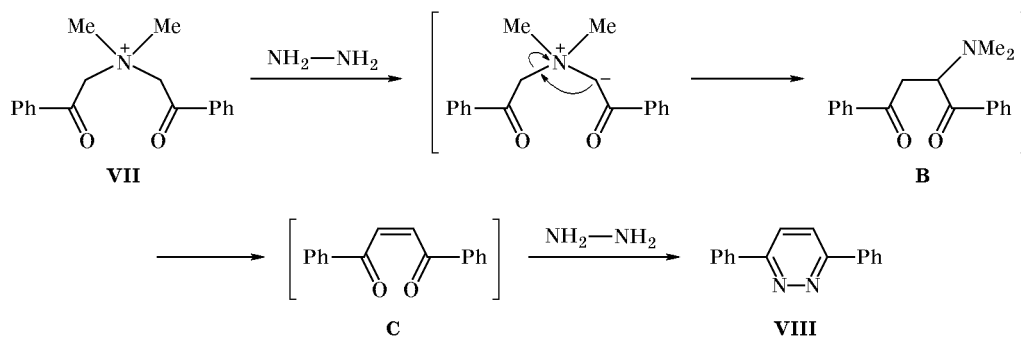
nium perchlorates **IV–VI** (Scheme 1). It should be noted that we have found no published data on such pyrazinium salts.

In the reaction with ammonium acetate in acetic acid, no effect of the R substituent on the rate of the process was observed: in all cases the reaction was complete in 2 h. With the other nucleophiles in alcoholic medium, the reaction was the most difficult to occur with diketone **II** (5–8 h); the process was more ready in the case of diketone **I** (3–4 h), and the fastest reaction was that with diketone **III** (20 min). In the latter case, the reason is not the substituent effect but poor solubility of product **VI** which precipitates from the reaction mixture during the process.

The structure of the products was confirmed by the IR, ¹H NMR, and mass (HPLC–MS) spectra. Unlike



Scheme 2.



initial 3-aza-1,5-diketones **I–III**, the IR spectra of products **IV–VI** lack carbonyl absorption ($1685\text{--}1689\text{ cm}^{-1}$) but contain absorption bands belonging to stretching vibrations of the aromatic fragments ($1600\text{--}1500\text{ cm}^{-1}$) and perchlorate ion (a strong band at $1088\text{--}1094\text{ cm}^{-1}$). In the $^1\text{H NMR}$ spectra ($\text{DMSO-}d_6$) we observed signals from aromatic protons at δ 7.3–8.5 ppm and a singlet at δ 9.8 ppm (2H), which was assigned to protons of the pyrazinium ring [6]. Compounds **IV** and **VI** also showed in the $^1\text{H NMR}$ spectra singlets from the methyl and methoxy groups, respectively, at δ 4.49 and 3.94 ppm.

The molecular weights of cations **IV–VI** determined from the mass spectra (HPLC–MS) were in agreement with the calculated values.

We also examined the reactions of quaternary salt **VII** with the same nucleophiles under analogous conditions. It might be expected that the reaction would stop at the stage of formation of dihydropyridazine **A**. However, such compounds were not isolated. The reaction of **VII** with hydrazine hydrate in the absence of an acid afforded 3,6-diphenylpyridazine **VIII**. This result may be explained by the occurrence of Stevens rearrangement by the action of a base (NH_2NH_2). As shown in [7], phenacylammonium salts readily undergo Stevens rearrangement to give bis-arylethenes even by the action of an amine. Presumably, in our case intermediate diketone **C** reacts with hydrazine hydrate with formation of compound **VIII**. The structure of the product was confirmed by the IR and GC–MS data. Its melting point coincided with that given in [8].

EXPERIMENTAL

The IR spectra were recorded on a Perkin–Elmer Spectrum BX-II spectrophotometer from samples pelleted with KBr (compounds **IV–VI**) or dispersed in mineral oil (**VIII**). The $^1\text{H NMR}$ spectra were obtained on a Bruker AC-250 spectrometer (operating

frequency 250 MHz) from solutions in $\text{DMSO-}d_6$ with addition of tetramethylsilane as internal reference. The mass spectra of compounds **IV–VI** were recorded on an HP 1100 LS/MSD HPLC–MS system, and of **VIII**, on an Agilent 5973N GC–MS system (HP5-ms column; carrier gas helium, flow rate 1 ml/min; detector temperature 280°C). The progress of the reactions was monitored by TLC using Sorbfil as sorbent and ethanol as eluent and by IR spectroscopy (following disappearance of the carbonyl absorption band in the spectrum of the reaction mixture).

1-Substituted 3,5-diphenylpyrazinium salts IV–VI. *a. Reaction with ammonium acetate.* A mixture of 0.3 g (8.2×10^{-4} mol) of diketone **I** perchlorate, 0.19 g (24.5×10^{-4} mol) of ammonium acetate, and 2 ml of glacial acetic acid was heated for 2 h under reflux. The mixture was cooled, and the precipitate of **IV** was filtered off and washed with 50% ethanol. Yield 0.12 g. An additional 0.08 g of the product was isolated from the filtrate by adding 1 ml of a saturated solution of NH_4ClO_4 . Recrystallization from acetic acid gave 0.17 g (60.7%) of salt **IV**. The reactions with diketones **II** and **III** taken as free bases were carried out in a similar way. The mixture was cooled to room temperature, and 1 ml of a saturated solution of ammonium perchlorate was added. The solution was separated from tarry material by decanting, and the latter was ground with water to obtain a powder which was filtered off. Recrystallization gave 0.21 g (57%) of **V** or 0.28 g (80%) of **VI**.

b. Reaction with hydroxylamine hydrochloride. A mixture of 0.3 g (8.2×10^{-4} mol) of diketone **I** perchlorate, 0.28 g (40.8×10^{-4} mol) of hydroxylamine hydrochloride, and 5 ml of isopropyl alcohol was heated to the boiling point, and 65% perchloric acid was added to pH 3–4. The mixture was heated for 3 h under reflux and cooled, and the precipitate of **IV** was filtered off and washed with isopropyl alcohol. Yield 0.2 g. Recrystallization from methanol afforded 0.18 g (64%) of the product. The reactions with compounds

II and **III** were carried out in a similar way. The mixture was heated under reflux for 5 h (with **II**) or 20 min (**III**). The yields of salts **V** and **VI** were 49% and 50%, respectively.

c. Reaction with hydrazine hydrate. A mixture of 0.3 g (8.2×10^{-4} mol) of diketone **I** perchlorate, 0.2 g (25×10^{-4} mol) of hydrazine hydrate, and 5 ml of isopropyl alcohol was acidified to pH 3–4 by adding perchloric acid. The mixture was heated for 4 h under reflux and cooled, and the precipitate of salt **IV** was filtered off and washed with isopropyl alcohol. Yield 0.37 g [after recrystallization, 0.24 g (86%)]. The reactions with compounds **II** and **III** were carried out in a similar way: the mixture was heated under reflux for 8 h (**II**) or 20 min (**III**); yield 68% (**V**), 61% (**VI**).

1-Methyl-3,5-diphenylpyrazinium perchlorate (IV). Beige crystals, mp 269–271°C. IR spectrum, ν , cm^{-1} : 1624, 1600, 1548, 1508 (C–C_{arom}); 1276, 1238 (C–N); 1090 (ClO₄⁻). ¹H NMR spectrum, δ , ppm: 4.49 s (3H, CH₃); 7.72 t (6H) and 8.37 m (4H) (C₆H₅); 9.7 s (2H, pyrazine). Mass spectrum, m/z : 247 [M]⁺; calculated for the cation: 247. Found, %: C 58.64; H 4.42; N 8.24. C₁₇H₁₅ClN₂O₄. Calculated, %: C 58.87; H 4.33; N 8.08.

1,3,5-Triphenylpyrazinium perchlorate (V). Light brown crystals, mp 249–250°C (from methanol). IR spectrum, ν , cm^{-1} : 1608, 1523, 1489 (C–C_{arom}); 1276, 1205 (C–N); 1093 (ClO₄⁻). ¹H NMR spectrum, δ , ppm: 7.72 t (6H), 7.86 t (3H), 8.12 m (2H), and 8.54 m (4H) (C₆H₅); 9.89 s (2H, pyrazine). Mass spectrum, m/z : 309 [M]⁺; calculated for the cation: 209. Found, %: C 64.35; H 4.32; N 7.14. C₂₂H₁₇ClN₂O₄. Calculated, %: C 64.63; H 4.16; N 6.85.

1-p-Methoxyphenyl-3,5-diphenylpyrazinium perchlorate (VI). Green crystals, mp 246–248°C (from methanol–DMF, 10:1). IR spectrum, ν , cm^{-1} : 1590, 1520, 1505 (C–C_{arom}); 1267 (C–N); 1089 (ClO₄⁻). ¹H NMR spectrum, δ , ppm: 3.94 s (3H,

OCH₃); 7.38 d (2H), 7.72 m (6H), 8.09 d (2H), and 8.52 m (4H) (C₆H₅); 9.8 s (2H, pyrazine). Mass spectrum, m/z : 339 [M]⁺; calculated for the cation: 339. Found, %: C 62.68; H 4.51; N 6.52. C₂₃H₁₉ClN₂O₅. Calculated, %: C 62.94; H 4.33; N 6.38.

3,6-Diphenylpyridazine (VIII). A mixture of 0.35 g (9×10^{-4} mol) of compound **VII** in 6 ml of ethanol and 0.1 g (10×10^{-4} mol) of hydrazine hydrate was heated under reflux for 4 h. The mixture was cooled, and the precipitate was filtered off and washed with ethanol. Yield 0.15 g (30%). mp 220–222°C (from ethanol); published data [8]: mp 225°C. IR spectrum, ν , cm^{-1} : 1582, 1548 (C–C_{arom}). Mass spectrum, m/z (I_{rel} , %): 232 (42) [M]⁺, 204 (10.2), 102 (100), 76 (14). Found, %: C 82.93; H 5.25; N 12.28. C₁₆H₁₂N₂. Calculated, %: C 82.76; H 5.17; N 12.07. M 232.

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