The structure of the products resulting from dehydroacetic acid and hydrazines

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Abstract: Dehydroacetic acid, 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one, a biologically active compound, undergoes a variety of reactions with alkyl, aryl and heteroaryl hydrazines producing various products (pyranopyrazoles, bipyrazoles, pyrazolyl 1,3-diketones, pyrazolones, etc.) under different experimental conditions. The structure of these products has been established by employing NMR spectroscopy, mass spectrometry, theoretical calculations and X-ray crystallography.

Keywords: Dehydroacetic acid, bipyrazole, hydrazines, pyrazole.

Dehydroacetic acid (1, 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one, DHAA), a biologically active compound, has shown to have good antibiotic and fungicidal effects besides showing strong antiseptic properties. It has also been used to enhance vitamin C stability, in vegetable food processing and as a preservative. Dehydroacetic acid, having several reactive sites, is very susceptible to attack by the nucleophilic reagents at the carbonyl of the acetyl group, carbon atom terminating the conjugated carbon chain at 6-position, the lactone carbonyl and the carbonyl of the 4-position. A study of the tautomerism of dehydroacetic acid using H, C (solution and CPMAS), gated H-decoupling techniques, deuterium-induced isotope effects on C chemical shifts, fully coupled C, H correlation (FUCOUP) and molecular modeling with AM1 has established that the compound exists as the 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one in solution and also in the solid state.

Dehydroacetic acid can be obtained from ethylacetoacetate, t-buty lacetoacetate, acetyl acetic acid and oxo-ketone. It continues to remain the most inexpensive starting material for the synthesis of a variety of compounds e.g. natural products, benzodiazepines, metal chelates of Schiff bases for biological properties such as antitumor, antibacterial and antiviral and a host of compounds with diverse chemical structures. In view of growing interest in the reactions of significance available in the literature, we herein report a detailed account of the structure of the products resulting from the reaction of dehydroacetic acid with alkyl, aryl and heteroaryl hydrazines under various experimental conditions.

Discussion
Perkin and Bernhart described the first reaction involving DHAA and phenylhydrazine in 1884. However, the authors failed to propose the correct structure for the product. Later, Stolle in 1905 and subsequently Benary in 1910 reinvestigated this reaction and isolated two products, which were characterized as 1,1'-diphenyl-3,3'-dimethyl-(4,5'-bipyrazol)-5-ol (4) and 3,6-dimethyl-1-phenylpyrano[4,3-c]pyrazol-4(2H)-one (3). The exclusive formation of 4 was also described under different conditions. The formation of these products were proposed via the intermediacy of phenylhydrazone of 1 (2) (Scheme 1).

Russian group reported the reaction between methyl ether of 1 (5) and phenylhydrazine affording 3,6-
of pyrone ring of 8. It was reported that reaction of 1 with phenylhydrazine in methanol followed by refluxing in xylene in presence of p-toluenesulphonic acid resulted in the formation of 3 along with a compound identified as 11 (discussed later). The structure assignment was unambiguously made by homonuclear $^{13}$C-$^1H$ NOE measurements, including long-range selective heteronuclear $^{13}$C-$^1H$ NOE enhancement measurements.

The reaction of 1 with phenylhydrazine was investigated (Scheme 4) and the product was incorrectly characterized as 5-anilino-3,6-dimethyl-1-pyrazolo[4,3-c]pyridine-4-one (9, also called pyridinopyrazole) on the basis of elemental analysis, IR and mass spectral data. Probably, the authors were not aware of the earlier work of Stolle and Benary and did not even consider the isomeric structure 4 (bipyrazole). It was explained that hydrazone 2 underwent cyclization to the corresponding pyranopyrazole (3) as well as the hydrolysed to generate the starting materials (dehydroacetic acid and phenylhydrazine) (path a). Compound 3 on reaction with phenylhydrazine (generated in situ via path a) resulted in the formation of 9 (path b). The formation of pyridinopyrazole (9) and other derivatives was also subsequently reported by Hassan et al.

Gelin et al. in 1983 studied the reaction of 1 with phenylhydrazine and established as 4,5'-bipyrazole structure (4) instead of the previously reported pyridinopyrazole (9). The structure revision was based on the isolation of the key intermediate 1-(5-hydroxy-3-methyl-1-phenylpyrazol-4-yl)-1,3-butanedione (10, also called 4-

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Diagram 1

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Diagram 2

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Diagram 3
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(acetylacetyl)-1-phenyl-2-pyrazolin-5-one) and its subsequent transformation to 3,6-dimethyl-1-phenylpyrano[2,3-c]pyrazol-4-(1H)-one (11) and 4 under different reaction conditions. The key intermediate 10 was obtained by refluxing 2 in acetic acid in good yields. This procedure did not in fact provide pyridinopyrazole (9) as erroneously claimed. Attempts to generate the product 10 without the isolation of 2 were unsuccessful.

A significant aspect of this work was the treatment of 13 with 2-hydrazino-6-methoxy-4-methylquinoline under different reaction conditions (ethanol-hydrochloric acid or ethanol-sodium acetate-acetic acid), which resulted in the formation of either 4,5'-bipyrazole (14) (path a) or the product of C-C bond cleavage generating two molecules of 1-(6-methoxy-4-methyl-2-quinolyl)-3-methylpyrazol-5-ol (15) (path b), respectively (Scheme 7). For the confirmation of structure of compound 15, it was prepared by the reaction of quinolylhydrazine (13) and ethyl acetoacetate. The physical data (m.p. 179-180 °C, TLC) and $^1$H spectroscopic data ($^1$H NMR) of 15 were in consonance with that obtained from C-C bond cleavage.

Singh et al. working independently, reported the formation of some novel products in the reaction of 1 with 2-hydrazino-6-methoxy-4-methylquinoline (Scheme 6) in a separate communication. Quinolylhydrazone of 1 (12) underwent skeletal rearrangement to 1-[5-hydroxy-3-methyl-1-(6-methoxy-4-methyl-2-quinolyl)pyrazol-4-yl]-1,3-butanedione (13) which is analogous to compound 10. The mechanism proposed for its formation consists of a rearrangement of 12 involving a nitrogen nucleophilic attack at the C2 lactone carbonyl with ring opening, thus generating 13. The mechanism was also supported by deuterium labeling studies experiments and $^1$H NMR spectroscopy.
using electron-impact mass spectrometry and the major process were interpreted. The common features were the loss of ketene, acetonyl radical, acetone and two molecules of ketenes from the molecular ion (Scheme 8). All the processes were substantiated with the help of accurate mass measurements of the fragment ion and by a study of the 1st field-free region (FFR) metastable ions which were obtained by linked scans.

The reaction of 1-(5-hydroxy-3-methyl-1-substitutedpyrazol-4-yl)-1,3-butanediones (10, 13 and 16) were carried out with hydrazine, alkylhydrazines and arylhydrazines under different experimental conditions. It was found that the reaction leads to the formation of one compound 17 instead of a mixture of isomers (17, 18).

Although the reaction led to the formation of only one compound (17) and not to a mixture of isomers (17, 18), its structure assignment appeared to be a complex problem. This structure may present isomerism, tautomerism (OH/NH) and rotational isomerism (atropisomerism) thereby generating sixteen possible structures for discussion.

The structure, 17d (NH-Z), was eventually established by a combined use of X-ray crystallography, NMR (\(^1H\) and \(^13C\)) spectroscopy, AM1 calculations and the solid state cross polarisation magic angle spinning (CPMAS-NMR) spectrum of the compound. The 4,5'-bipyrazole (4) crystallizes in the space group \(P2_1/a\) [C\(_{20}\)H\(_{18}\)N\(_4\)O, \(a = 11.801(2)\), \(b = 7.911(1)\), \(c = 18.363(2)\) Å, \(\alpha = 90.00^\circ\), \(\beta = 100.04^\circ\), \(\gamma = 90.00^\circ\), \(z = 4\)]. The structure
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between OH tautomer probably in the Z conformation and the NH tautomer probably in the E conformation. The structure of the type 17a, was also reported in the case of hydrazine itself (R = H)\textsuperscript{33} and phenylhydrazine (R = C\textsubscript{6}H\textsubscript{5})\textsuperscript{27}. Nevertheless, these two works lacked a convincing spectroscopic support. Surprisingly, Djerrari et al.\textsuperscript{34} proposed structure 19a in solution (NMR) and 19c in gas phase (mass spectrometry).

It is noteworthy that in the \textsuperscript{1}H NMR spectrum of 17 (Ar and R = phenyl, 4), the 3-methyl signal (\(\delta = 1.791\) ppm) was clearly shielded as compared to the one in simple pyrazolinones (\(\sim 2.1\) ppm). This shielding was assigned to the proximity of the 1'-phenyl ring which was confirmed by the NOE experiments as summarized below.

It was found that if 1'-phenyl ring is replaced by some other moiety such a signal of 3-methyl jumps to about \(\delta = 2.4\) ppm which provided another proof that the methyl protons are shielded by the phenyl group. The fact that the signal at 1.791 ppm shows both NOE's with phenyl protons and H\textsubscript{4}, further indicated that 17 exists in two conformations\textsuperscript{32}.

While treating 10/13/16 with a variety of hydrazines and employing different reaction conditions, an interest-
ing observation concerning the mechanism of formation of bipyrazoles became known. Whereas all the hydrazines provided the expected bipyrazole on treatment with 10 in the presence of strong acid; unexpected formation of pyrazol-5-ols was observed with some hydrazines on performing the reaction in ethanol-acetic acid/sodium acetate (Scheme 9). The hydrazine attacked on the terminal carbonyl carbon of the side chain giving rise to the corresponding hydrazone (20) followed by ring closure to produce an intermediate. This intermediate then underwent (i) dehydration in the presence of strong acid yielding 4,5'-bipyrazole (21) and/or (ii) C-C bond cleavage resulting in the formation of pyrazol-5-ols (22, 23) in ethanol-acetic acid/sodium acetate. Formation of pyrazol-5-ols (22, 23) clearly indicated the cleavage of C-C bond in the proposed intermediate. The mechanism for these processes has been postulated in Scheme 9.

It was also observed that the above results depend on the nature of hydrazines employed. The available data (Table 1) indicate that electronic effects of bulky group in RNHNH₂ play a significant role in directing the course of the reaction³⁵. The conformational behaviour of 4,5'-bipyrazole is still under investigation using NMR spectroscopy and AM1 and PM3 calculations.

However, in a typical experiment when the reaction of 10 was performed in ethanol with 1-hydrazinophthalazine hydrochloride (24, a biologically important compound), there was formation of two products identified as 3-methyl-s-triazolo[3,4-a]phthalazine (25) and 4-acetyl-1-phenylpyrazol-5-ol (26) instead of the expected 4,5'-bipyrazole³⁶ (Scheme 10) based on elemental analysis, NMR (¹H and ¹³C) spectroscopy and mass spectrometry. The ¹H NMR spectrum of 26 displayed signals at δ 2.40 for both C₃-CH₃ and C₄-COCH₃ besides aromatic protons at δ 7.15–8.00 (5H). 4-Acetyl-1-phenylpyrazol-5-ol (26) type of compounds found applications in agrochemicals and extraction of metal ions³⁷ and can also be used for conversion to pyranopyrazole (11)³⁸. Moreover, reaction of 10 with hydroxylamine also generated pyrazolylloxazoles³⁹.
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With a view to extend the scope of this reaction, DHAA was converted to thiosemicarbazone 27 which on reaction with α-haloketones afforded the hydrazone (28) followed by its smooth conversion to 1-[5-hydroxy-3-methyl-1-(4-aryltiazol-2-yl)pyrazol-4-yl]-1,3-butanedione (29) (Scheme 11). The reaction of 29 with various hydrazines generated 4,5′-bipyrazoles (30). The thiosemicarbazone 27 was also found to form nickel(II) and palladium(II) chelates which were confirmed through spectroscopic techniques.

![Scheme 11](image)

**Scheme 11**

Synthesis and distinction between four isomeric pyranopyrazoles (31-34) and their pyridine analogues have been made by NMR (1H and 13C) spectroscopy. Complete analyses of the structural features of these compounds were achieved employing homonuclear 1H{1H} and two-bond heteronuclear 13C{1H} nuclear Overhauser effects techniques. The chemical shift of each carbon was confirmed by selective decoupling of the corresponding protons.

**Conclusions**

Presence of several electrophilic site in the molecule of dehydroacetic acid (3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one) makes it an attractive target for nucleophilic attack. In particular, reactions of DHAA with hydrazines provide useful synthesis involving rearrangements. These compounds undergo a wide variety of reactions leading to the formation of products, which display interesting structural features.

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