REACTIONS OF CREATONE (2-METHYLAMINO-1H-IMIDAZOLE-4,5-DIONE)

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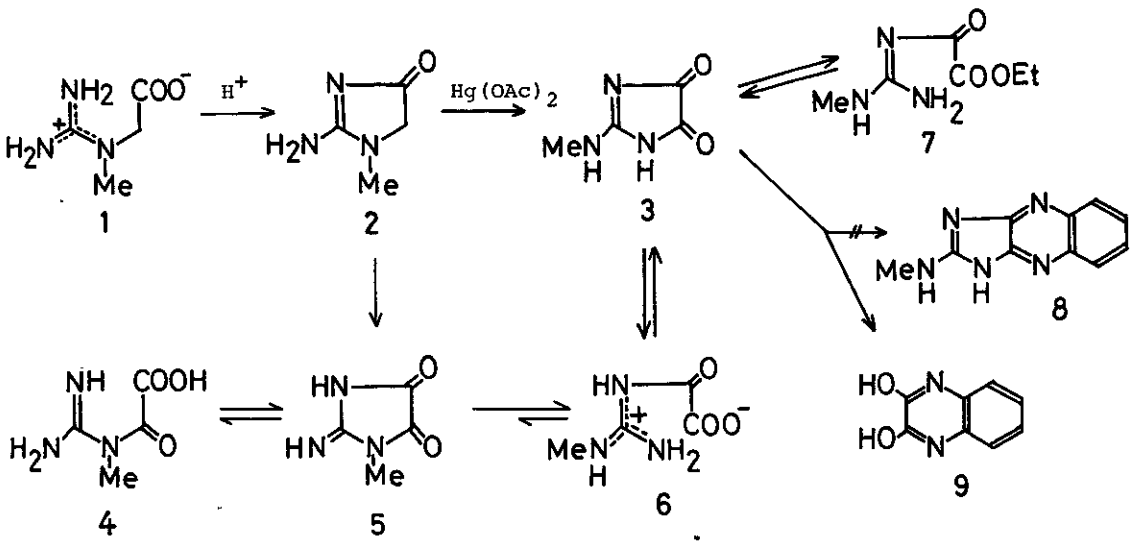
Abstract—— Creatone (3) reversibly gives (3-methylguanidino)-glyoxylic acid (6) and its ethyl ester (7) on heating with water and ethanol, respectively. These ring-opened compounds are important intermediates during the formation of creatone from creatine (1) and various other starting materials.

Creatine (1) and its cyclic form creatinine (2) are present in the muscular tissue of many vertebrates and play important roles in energy transfer and storage[1,2]. We reported[3] that the oxidation product (creatone) of 1 and 2 with $Hg(OAc)_2$ possessed the structure 3 (2-methylamino-1H-imidazole-4,5-dione), rather than the ring-opened formula (4)[4,5], on the basis of the spectra and pKa values. It was proposed[3] that the previous structures 5 and 6 (presented respectively for the condensation product[6] of methylguanidine and diethyl oxalate and for the peroxyacid oxidation product[7] of certain 2-amino-1-methyl-6-pyrimidones should also be replaced by the revised formulation 3. We describe in this paper some reactions of 3, which are closely related to the reaction pathways for the formation of 3 from various starting materials.

Creatone 3 (mp 204°C dec) is virtually insoluble in water, ethanol and other organic solvents at 20°C (except for trifluoroacetic acid, in which 3 dissolves as the monocation). However, when a suspension of 3 in ethanol was refluxed, it was gradually transformed into a clear solution, and the ethyl ester 7 (mp 123°C) was exclusively produced. The assignment of the (3-methylguanidino)-glyoxylate structure (7) was based on the elemental analysis and the spectroscopic data: The ^{1}H-nmr spectrum in DMSO-d_6 showed a doublet at δ 2.76 (3H, J = 5.0 Hz), which collapsed into a singlet after D_2O-exchange, indicating the presence of the N-CH_3 group at the γ-position (not α-position as in 4). The

same product 7 was obtained on treatment of methylguanidine with diethyl oxalate in t-butyl alcohol under high-dilution conditions at 15°C. When a concentrated solution of 7 in ethanol was stirred at 20°C, compound 3 was gradually regenerated, thus proving the interconversion of 3 and 7, depending upon the reaction temperature and concentration.



Similarly, creatone 3 afforded the ring-opened product 6 (mp 163-168°C) on heating with water; the Zwitter ion structure 6 was derived from the elemental analysis and the spectra as well as the high solubility of the product in water. This newly isolated compound, which can be regarded as a key intermediate in the formation of 3 from various starting materials, was found to be rather unstable and reproduce 3 by repeating recrystallization from ethanol or on standing its concentrated solution in water. No appreciable amount of the other isomers 4 and 5 appeared to have been produced in the above recyclization on the evidences of tlc and the nmr spectrum (see Experimenal part). Since various attempts to alternatively prepare compounds 4 and 5 always resulted in the exclusive formation of 3, these results leads to the conclusion that a Dimroth type of rearrangement[8] would proceed more favorably from 5 to 3 via 6 than to the reverse direction (3 to 5) as shown in the above Scheme, thus accounting for the exclusive formation of 3 from 1 and 2.

Treatment of 3 with o-phenylenediamine did not give the anticipated condensation product 8 but, instead, afforded 2,3-quinoxalinediol (9), as had been observed[9] in the case of parabanic acid.

Since creatone has been isolated[10] from beef and regarded as a constituent of muscle tissue, the above findings are considered to be of importance in view of the equilibrium scheme for the formation of 3 from various starting materials, and also believed to be of value in connection with a biological implication, such as the possibility of the reversible reaction between creatine and creatone, participating in oxido-reductive process of organism.

EXPERIMENTAL SECTION

The melting points were measured with a Yanagimoto MP-S3 instrument and are uncorrected. The ^{1}H-nmr spectra were recorded in D_2O or DMSO-d_6 with a Hitachi High-Resolution Nmr Spectrometer, R-20A (60 MHz) at 30°C. Substances stated to be identical were compared by means of their ir and ^{1}H-nmr spectra, and tlc (silica gel developed in 1:4 MeOH-$CHCl_3$).

Ethyl (3-Methylguanidino)glyoxylate (7). A) A suspension of 100 mg of 3 in 15 ml of absolute ethanol was refluxed under argon for 24 h, and then the solvent was evaporated in vacuo, to give 68 mg (60%) of 7. The analytical specimen was purified by chromatography on a column of silica gel using 1:9 MeOH-$CHCl_3$; colorless prisms, mp 123-124°C (from ethanol-ethyl acetate); ^{1}H-nmr (D_2O/TPS): δ 1.30 (3H, t, J = 7.0 Hz, C-CH_3), 2.87 (3H, s, N-CH_3), and 4.28 (2H, q, J = 7.0 Hz, O-CH_2), (DMSO-d_6/TMS): δ 1.20 (3H, t, J = 7.0 Hz), 2.76 (3H, bd, J = 5.0 Hz), 4.07 (2H, q, J = 7.0 Hz), 7.59 (2H, m, NH), and 8.15 (1H, bq, J = 5.0 Hz, NH-Me, exchangeable with D_2O); ir (KBr): 3350, 3100 (NH), 1705 (ester), and 1650 (amide) cm^{-1}; uv (EtOH): λ 230 nm (shoulder, ε 560). Anal. Calcd. for $C_6H_{11}N_3O_3 \cdot H_2O$: C, 37.69; H, 6.85; N, 21.98%. Found: C, 38.05; H, 7.13; N, 22.25%. B) Potassium t-butoxide (220 mg) was dissolved in 40 ml of dry t-butyl alcohol, then 264 mg of methyl guanidine hydrochloride and 350 mg of diethyl oxalate were added at 5°C. The mixture was stirred at 15°C for 2 days, then concentrated in vacuo, giving 160 mg (46%) of 7, mp 123-124°C, after the column chromatography.

(3-Methylguanidino)glyoxylic Acid (6). A suspension of 90 mg of 3 in 6 ml of water was refluxed under argon for 15 h, then the solvent was evaporated in vacuo, giving 42 mg (41%) of 6; a white powder, mp 163-168°C dec (from ethanol); ^{1}H-nmr (D_2O/PTS): δ 2.85 (3H, s, Me), (DMSO-d_6/TMS): δ 2.74 (3H, bd, J = 5 Hz, Me), 7.6 (3H, m, NH), and 8.3 (1H, bq, J = 5 Hz, NH); ir (KBr): 3300 and 1670-1600 cm^{-1}; uv (EtOH): end-absorption. Anal. Calcd. $C_4H_7N_3O_3$: C, 33.10; H,

4.86; N, 28.96%. Found: C, 33.31; H, 4.79; N, 28.79%.

Creatone (3). A) A solution of 20 mg of 7 in 1 ml of absolute ethanol was stirred at 20°C for 48 h, depositing 12 mg (46%) of 3, identical with the authentic specimen[3]. B) On stirring a solution of 6 in water, 3 was similarly obtained as a white powder (40% yield); ^{1}H-nmr spectrum (in TFA/TMS) of the crude product showed a very weak, singlet signal at δ 3.49 besides the intensive N-methyl signal of 3 and 6 at δ 3.31. The former was presumed to be due to either 4 or 5, but this minor product could not be isolated as a pure form.

2,3-Quinoxalinediol (9). A mixture of 30 mg of 3 and 31 mg of o-phenylenediamine was refluxed in 10 ml of dry t-butyl alcohol containing a drop of acetic acid for 48 h, depositing 28 mg (78%) of 9 as white prisms, which were identical with the specimen obtained (80% yield) from o-phenylenediamine and diethyl oxalate[11]; mp > 300°C; ^{1}H-nmr (TFA/TMS): δ 7.48 (s).

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