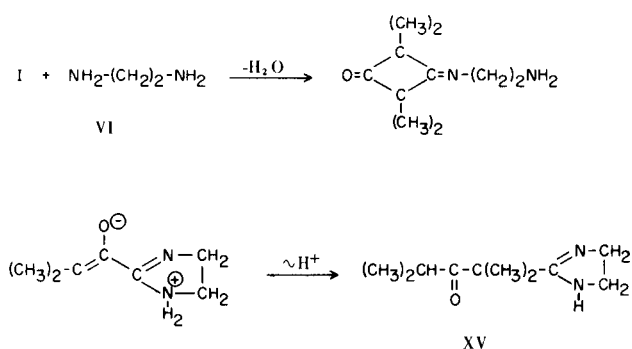


pentyl)]imidazoline (XV), resulting from an imine formation followed by an intramolecular nucleophilic attack of the β -amino group upon the imine. The structure for this compound was substantiated by the following spectral data.

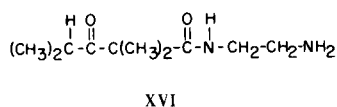
The infrared spectrum shows λ max, 3250 cm^{-1} for the amino group, λ max, 1725 cm^{-1} for the keto carbonyl and λ max, 1610 cm^{-1} for the cyclic imine. The nmr spectrum shows a doublet at 0.92 ppm for the six isopropyl methyl protons, a singlet at 1.27 ppm for the six 2-C methyl protons, a multiplet at 3.07 ppm for the isopropyl proton and a singlet for the four imidazoliny methylene protons. Integration of the nmr was consistent with the product XV. Mass spectral analysis gave a parent peak at $m/e = 182$ and large fragmentation at $m-71$ and $m-113$ due to a loss of $\text{C}_4\text{H}_7\text{O}$ and $\text{C}_7\text{H}_{13}\text{O}$, respectively.

The formation of XV provides mechanistic evidence regarding the pathway by which primary amines react with the dione nucleus. The reactants are refluxed in benzene with azeotropic removal of water which forms immediately. The primary amino group can then intramolecularly attack the imine to give the imidazoline according to the following outline:



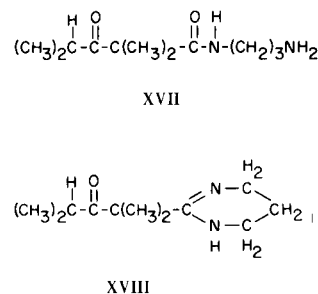
If it is postulated that the dione ring opening occurs first, then the condensation step must occur on an amide carbonyl group, which is not consistent with the reaction product. The production of amides must be a secondary reaction step due to the hydrolysis of the imine by water.

When ethylenediamine is refluxed with I in benzene and the liberated water is not isolated the corresponding amide, *N*-(2-aminoethyl)-2,2,4-trimethyl-3-oxopentanamide (XVI) is isolated.



The structure for this compound was elucidated from spectral studies. The infrared spectrum shows λ max, 3400 cm^{-1} (broad) for the amino and amide N-H, λ max, 1720 cm^{-1} for the keto carbonyl, λ max, 1655 cm^{-1} for the amide carbonyl and λ max, 1540 cm^{-1} for the amino and amide N-H. The nmr spectrum contained a doublet at 1.0 ppm for the six isopropyl methyl protons, a singlet at 1.27 ppm for the six 2-C methyl protons, a broad singlet at 1.67 ppm for the two amino protons, multiplets centered on 3.0 ppm for the four ethylene and one isopropyl proton and a broad singlet at 7.05 ppm for the amide proton. The mass spectrograph showed a parent peak at $m/e = 200$.

The reaction of 1,3-diaminopropane (VII) with the dione resulted in the formation of *N*-(3-aminopropyl)-2,2,4-trimethyl-3-oxopentanamide (XVII) and 1*H*-4,5-dihydro-2-[2-(2,4-dimethyl-3-keto-pentyl)]pyrimidine (XVIII).



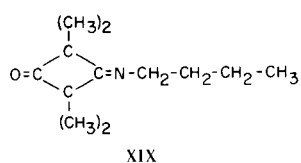
The structure for (XVII) was determined by infrared, nmr and mass spectral data. The infrared spectrum showed λ max, 3400 cm^{-1} for the amino and amide N-H, λ max, 1720 cm^{-1} for the carbonyl carbon and λ max, 1655 cm^{-1} for the amide carbonyl. The nmr spectrum contained a doublet at 0.91 ppm for the six isopropyl methyl protons, a singlet at 1.24 ppm for the six 2-C methyl protons, a broad singlet at 7.89 ppm for the amide proton, multiplets centered at 2.63 and 3.17 for the α - and γ -methylene protons and the 4-C methylenide proton, a multiplet at 1.50 ppm for the β -methylene protons and a singlet at 1.81 for the primary amino protons. The mass spectrograph showed a parent peak at $m/e = 214$ and a large fragmentation peak at $m-43$ for loss of C_3H_7 .

The structure for (XVIII) was also elucidated from spectral studies. The infrared shows λ max, 3300 cm^{-1} for the imine and λ max, 1705 cm^{-1} for the keto carbonyl group, λ max, 1620 cm^{-1} for the imine and λ max, 1505 cm^{-1} for the amino group. The nmr spectrum contained a doublet at 0.90 ppm for the six isopropyl protons, a singlet at 1.15 ppm for the six 2-C methyl protons, a multiplet at 1.61 ppm for the two

5-pyrimidyl methylene protons, a multiplet centered at 3.11 ppm for the four 4- and 6-pyrimidyl methylene protons and the isopropyl proton and a broad peak at 4.58 ppm for the amine proton. The mass spectrograph shows a parent peak at $m/e=196$ and a large fragmentation at $m-43$ for the loss of C_3H_7 .

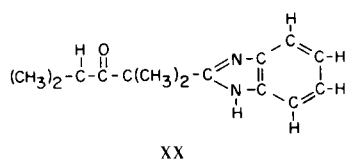
The initial reaction of 1,3-diaminopropane (VII) and I was carried out in refluxing benzene using a Dean-Stark trap. The major product isolated was XVII but little water was collected in the Dean-Stark trap. When the reaction was carried out under the same conditions, with the addition of a molecular sieve to the reaction vessel, XVIII was isolated with little collection of water in the Dean-Stark trap. This indicates that the rate at which the water is removed from the reaction also determined the product isolated.

The reaction of *n*-butylamine (XXXIII) with I resulted in the formation of 2,2,4,4-tetramethyl-3-*n*-butylimino-cyclobutanone (XIX).



The structure was determined from spectral data. The infrared spectrum shows λ max, 1805 cm^{-1} for the $C=O$ and λ max, 1700 cm^{-1} for the $C=N$. The nmr spectrum contains a triplet at 0.58 ppm for the three butyl methyl protons, singlets at 0.82 ppm and 0.97 ppm for the twelve cyclobutyl methyl protons, a multiplet centered at 1.17 ppm for the four β - and γ -methylene protons and a triplet at 3.08 ppm for the two α -methylene protons. Mass spectral data gives a parent peak at $m/e = 195$. The formation of XIX as the only isolated product again illustrates the imine formation in the absence of water. The formation of *N*-butyl-2,2,4-trimethyl-3-oxo-pentanamide has been reported (4) when butyl amine is refluxed with I in the presence of water.

The reaction of *o*-phenylenediamine (IX) with I resulted in the formation of 2-[2-(2,4-dimethyl-3-ketopentyl)]-benzimidazole (XX).



The structure for this compound was determined by nmr and mass spectral data. The nmr spectrum shows a doublet at 0.67 ppm for the six isopropyl methyl protons, a singlet at 1.43 ppm for the six 2-C methyl protons, a multiplet at 2.79 ppm for the isopropyl hydrogen, a broad peak at 3.08 ppm for the N-H hydrogen and a multiplet centered at 7.17 ppm for the four aromatic protons. Mass spectral analysis shows a parent peak at $m/e = 230$ and a large fragmentation at $m-71$ for the loss of C_4H_7O .

A monocondensation product has been reported (5) for the reaction of I with *o*-phenylenediamine. The melting point of XX and the reported product are within 1° , but the structure of the reported product violates Bretd's rule in that it contains a double bond to a bridge-head carbon atom.

The reactions of the dione with carbon disulfide using either acidic or basic catalysts (XII-A, B, C) resulted in a quantitative recovery of the tetramethyl-1,3-cyclobutanedione. Apparently the expected sulfide anion was not formed to any appreciable extent and therefore, no nucleophilic attack occurred. The reaction of carbon disulfide in potassium hydroxide has been reported (2) to give products resulting from the nucleophilic attack of the hydroxide ion, which when hydrolyzed gave diisopropyl ketone.

Potassium xanthate (X) also failed to give any product when reacted with I in a wide variety of solvents and at various temperatures. The general lack of reactivity may again be attributed to the insufficient nucleophilic strength of the xanthate or instability of the resulting intermediate.

Tetramethyl-1,3-cyclobutanedione also failed to react with thietane (XI). In this case the nucleophilicity of thietane is very poor. The basicity of the cyclic sulfides was reported (6) during the course of this research as being reversed from the cyclic oxides and the order being 5-membered ring $> 6 > 4 > 3$.

Tertiary amines such as *N*-methylmorpholine (V) and *N*-benzylazetidine (IV) when treated with tetramethyl-1,3-cyclobutanedione resulted only in the quantitative recovery of the dione. The steric effect of the tertiary nucleophile was undoubtedly a factor in this reaction. The relative difficulty in the stabilization of any intermediate would also prevent the reaction from proceeding to completion. However, no polymerization of the dione was noted and this indicates that direct ring cleavage by the nucleophile does not occur.

EXPERIMENTAL

Melting points and boiling points are uncorrected. All infrared spectra were obtained on a Perkin-Elmer Infracord, Model 157B, Spectrophotometer. Nmr spectra were run on a Varian Associates Model A-60 Spectrometer as 10% solutions in carbon tetrachloride, dimethyl sulfoxide- d_6 or neat, with respect to TMS as an

internal standard. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tennessee. Mass spectral analysis were run on an RMU-6E Hitachi Mass Spectrograph.

Amines.

Azetidine, pyrrolidine, *N*-methylmorpholine, ethylenediamine, 1,3-diaminopropane and butylamine were obtained commercially, distilled over potassium hydroxide and stored over Linde Molecular Sieve type 4A. The *o*-phenylenediamine was recrystallized prior to its use.

N-Benzylazetidine (IV).

This synthesis is a modification of a previously reported (7) method.

N-Benzyl-3-amino-1-propanol.

A solution of 53 g. (0.5 mole) of benzaldehyde and 38 g. (0.5 mole) of 3-amino-1-propanol were placed into a 500 ml. Parr hydrogenation bottle and diluted to 250 ml. with ethanol. To this solution was added 0.5 g. of platinum oxide and the mixture was hydrogenated on a Parr Hydrogenation Apparatus, Model A, for 6-7 hours at 50 psi. The ethanolic solution was then filtered and the ethanol removed on a rotary evaporator. The oily residue was vacuum distilled to give 54 g. (72%) of the amino alcohol, b.p. 87-90° (0.2 mm) [Lit. (8), 125-130°, (2 mm)], $n_D^{21} = 1.5384$. The hydrogen chloride salt was prepared by adding 1 g. of the amino alcohol to ether and bubbling hydrogen chloride gas into the solution. The solid was filtered and recrystallized from ethanol/ether, m.p. 83-85° (Lit. (8) 83.5-85°).

Ethyl *N*-benzyl-*N*-(3-hydroxypropyl)-3-aminopropanoate.

In 100 ml. of ethyl acrylate which contained 0.1 g. of *m*-dinitrobenzene was placed 50 g. of *N*-benzyl-3-amino-1-propanol. The solution was refluxed for one day. The excess ethyl acrylate was removed on a rotary evaporator to give 79 g. (98%) of ethyl *N*-benzyl-*N*-(3-hydroxypropyl)-3-aminopropanoate. This was used without further purification in the next step.

Ethyl *N*-benzyl-*N*-(3-chloropropyl)-3-aminopropanoate.

To a solution of 160 g. of ethyl *N*-benzyl-*N*-(3-hydroxypropyl)-3-aminopropanoate in 640 ml. of chloroform and 17 ml. of dimethylformamide was added a solution of 77 g. of thionyl chloride in 80 ml. of chloroform at a temperature of 20-25°. After the addition of thionyl chloride was complete the solution was stirred for thirty minutes and then poured into a saturated solution of sodium bicarbonate. The chloroform layer was separated and dried over anhydrous magnesium sulfate. After filtration, the chloroform was removed on a rotary evaporator to give 171 g. (99%) of ethyl *N*-benzyl-*N*-(3-chloropropyl)-3-aminopropanoate, which was used without further purification.

N-Benzylazetidine.

1. A mixture of 30 g. of ethyl *N*-benzyl-*N*-(3-chloropropyl)-3-aminopropanoate, 15 g. of triethanolamine and 60 g. of powdered anhydrous sodium carbonate was heated in a short path distillation system to 215° under 15 mm. of pressure and hot air was used to warm the neck of the flask. The colorless liquid which distilled over was re-distilled to give 3.9 g. (25%) of *N*-benzylazetidine.

2. A mixture of 45 g. of ethyl *N*-benzyl-*N*-(3-chloropropyl)-3-aminopropanoate, 25 g. of triethanolamine, 1.5 g. of silver carbonate and 90 g. of sodium carbonate was treated as described above. Redistillation gave 9.1 g. (39%) of *N*-benzylazetidine. Nmr showed a quintet at 1.45 ppm for the two 3-azetidyl

methylene protons, a triplet at 2.64 ppm for the four 2- and 4-azetidyl methylene protons, a singlet at 3.02 ppm for the two benzyl methylene protons and a singlet at 6.82 ppm for the five aromatic protons.

N-Azetidiny-2,2,4-trimethyl-3-oxopentanamide (XIII).

A solution of 5 g. (0.088 mole) of azetidine and 12.3 g. (0.088 mole) of dione were refluxed in 100 ml. of dry benzene for 16 hours. The benzene was then removed at atmospheric pressure to give 2.9 g. of a solid and an oil residue. The solid was sublimed to give 2.32 g. of unreacted dione. The oil was vacuum distilled to give 7.5 g. (43%) of *N*-azetidiny-2,2,4-trimethyl-3-oxopentanamide (XIII), b.p. 86-88°, (0.5-0.6 mm), $n_D^{21} = 1.4759$.

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 67.0; H, 9.71; N, 7.10; mol. wt. 197. Found: C, 67.1; H, 9.84; N, 7.11; mol. wt. 197.

A solution of 5 g. (0.088 mole) of azetidine and 12.3 g. (0.088 mole) of dione were refluxed in benzene for 42 hours. The benzene was removed at atmospheric pressure and the residue sublimed to remove the last traces of dione. The oil remaining after sublimation was distilled to give 10.4 g. (61.4%) of XIII.

N-Pyrrolidiny-2,2,4-trimethyl-3-oxopentanamide (XIV).

A solution of 14 g. (0.1 mole) of dione and 7.1 g. (0.1 mole) of pyrrolidine were refluxed in 200 ml. xylene for 22 hours. The xylene was removed at reduced pressure and the residual oil distilled to give 2.69 g. (13%) of XIV as a yellow oil, b.p. 89° (0.7 mm), $n_D^{21} = 1.4767$; [Lit. (3), b.p. 118° (1.8 mm)], $n_D^{21} = 1.4802$.

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.2; H, 10.0; N, 6.63; mol. wt. 211. Found: C, 68.2; H, 10.0; N, 6.72; mol. wt. 211.

2-[2-(2,4-dimethyl-3-ketopentyl)]imidazoline (XV).

A solution of 15 g. (0.25 mole) of ethylenediamine and 200 ml. of benzene were added dropwise to a solution of 35 g. (0.25 mole) of dione in 400 ml. of benzene. The resulting solution was refluxed for 43 hours using a Dean-Stark trap. During this time 3.5 ml. of water was collected. The benzene was removed at atmospheric pressure and the residue sublimed under vacuum. The solid was recrystallized from hexane to give 11.07 g. (24.6%) of the imidazoline (XV), m.p. 80-82°. No other condensation products were isolated.

Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.9; H, 9.95; N, 15.4; mol. wt. 182. Found: C, 65.9; H, 9.81; N, 15.3; mol. wt. 182.

N-(2-aminoethyl)-2,2,4-trimethyl-3-oxopentanamide (XVI).

A solution of 14 g. (0.1 mole) of dione, 6 g. of ethylenediamine and 200 ml. of benzene was refluxed for 43 hours. The benzene was removed at atmospheric pressure and the residue sublimed to give 2.5 g. (13%) of the imidazoline (XV). The sublimation residue was distilled on a platinum spinning band column to give 4.17 g. (21%) of the oxopentanamide (XVI), b.p. 86-90°, (0.15 mm-0.2 mm). Excessive pot decomposition was noted during the distillation of various runs.

Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 60.0; H, 10.1; N, 14.0; mol. wt. 200. Found: C, 59.8; H, 10.1; N, 13.8; mol. wt. 200.

N-(3-aminopropyl)-2,2,4-trimethyl-3-oxopentanamide (XVII).

A solution of 7.4 g. (0.1 mole) of 1,3-diaminopropane and 100 ml. of benzene was added dropwise to a solution of 14 g. (0.1 mole) of dione in 200 ml. of benzene. The resulting solution was refluxed using a Dean-Stark trap for 43 hours and less than 0.5 ml. of water was collected during this time. The benzene was removed at atmospheric pressure and the residue was distilled using short path distillation methods to give two fractions. The first

fraction (2.1 g.) distilled at 114°, (0.4 mm), and solidified, m.p. 43-46°. The second fraction (2 g.) distilled at 104°, (0.3 mm). The infrared spectra of these fractions were identical, giving 19.4% of the oxopentanamide (XVII).

Anal. Calcd. for C₁₁H₂₂N₂O₂: C, 61.7; H, 10.4; N, 13.1; mol. wt. 214. Found: C, 61.4; H, 10.4; N, 13.0; mol. wt. 214.

1*H*-4,5-dihydro-2-[2-(2,4-dimethyl-3-ketopentyl)]pyrimidine (XVIII).

A solution of 14.8 g. (0.2 mole) of 1,3-diaminopropane and 200 ml. of benzene was added to a solution of 28 g. (0.2 mole) of I in 400 ml. of benzene to which 100 cc. of molecular sieve (Type 4A) had been added. The resulting solution was refluxed for 43 hours using a Dean-Stark trap. During this time 0.4 ml. of water was collected. After filtering the solution the benzene was removed at atmospheric pressure. The residue was sublimed to give 1.7 g. (8.7%) of the pyrimidine (XVIII). The solid was recrystallized from hexane to give a white solid, m.p. 93-95°. Distillation of the dark viscous residue gave no additional products.

Anal. Calcd. for C₁₁H₂₀N₂O: C, 67.3; H, 10.3; N, 14.3; mol. wt. 196. Found: C, 67.1; H, 10.2; N, 14.2; mol. wt. 196.

2,2,4,4-Tetramethyl-3-butyliminocyclobutanone (XIX).

A solution of 7.3 g. (0.2 mole) of butylamine and 100 ml. of benzene was added dropwise to a solution of 14 g. (0.2 mole) of dione in 200 ml. of benzene to which 100 cc. molecular sieve had been added. The resulting solution was refluxed using a Dean-Stark trap for 43 hours, filtered, and the benzene was removed on a rotary evaporator. The residue was distilled on a spinning band column to give 7.8 g. (40%) of XIX, b.p. 92°, (10.6 mm), $n_D^{21} = 1.4472$. No other product could be isolated from the viscous distillation residue.

Anal. Calcd. for C₁₂H₂₁NO: C, 73.8; H, 10.8; N, 7.17; mol. wt. 195. Found: C, 73.7; H, 11.0; N, 7.34; mol. wt. 195.

2-(2-(2,4-dimethyl-3-ketopentyl)]benzimidazole (XX).

A solution of 8 g. (0.074 mole) of *o*-phenylenediamine in 100 ml. of *m*-xylene was refluxed for 30 minutes using a Dean-Stark trap to remove any water. To the hot xylene solution 10.4 g.

(0.074 mole) of dione and 0.07 g. of *p*-TSA were added and the solution was again refluxed using a Dean-Stark trap. After one hour a violet colored solid had precipitated from solution. The solution was refluxed for an additional nine hours, then cooled and filtered. The resulting solid was sublimed under vacuum (185°, 2.5-3 mm.) to give 12.3 g. (67%) of the benzimidazole (XX). Distillation of the xylene resulted in recovery of additional small amounts of crude benzimidazole and unreacted *o*-phenylenediamine.

Anal. Calcd. for C₁₄H₁₈N₂O: C, 73.0; H, 7.88; N, 12.2; mol. wt. 230. Found: C, 72.8; H, 7.86; N, 12.1; mol. wt. 230.

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