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Reactions of 2,2,4,4-Tetramethyl-1,3-Cyclobutanedione with Aziridines and Other Nucleophiles

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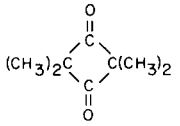
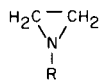
2,2,4,4-Tetramethyl-1,3-cyclobutanedione (I) has been shown to participate in ring opening reactions with a variety of bases. Alkyl amines and ammonia react to form their respective 2,2,4-trimethyl-3-oxovaleramides in yields up to 80% (2,3). Hydrazine reacts with the dione to give ring opening, followed by condensation to yield 4,4-dimethyl-3-isopropyl-2-pyrazolin-5-one (2). With acid catalysis, weaker bases such as aniline condense to form Schiff bases (2).

The basicity of aziridines, with *p*Ka values of approximately 8.0, is intermediate between the *p*Ka values of amines which cause ring opening reactions (i.e. ethyl amine, *p*Ka = 10.75) and amines which yield carbonyl condensation products (i.e. aniline, *p*Ka = 4.58) with tetramethyl-1,3-cyclobutanedione. By virtue of their strained three membered ring aziridines are known to readily undergo ring opening reactions. In this investigation the reactions of tetramethyl-1,3-cyclobutanedione with various *N*-substituted aziridines (II) were studied in benzene solution or neat with varying conditions such as high temperature and acid catalysts (PTSA and stannic chloride) to promote aziridinium ring opening. The acid catalysts were either ineffective or produced considerable polymerization of the aziridine. Other organic bases and nucleophiles such as N-cyclohexyl-3-azetidinol (III), styrene oxide (IV) and the carbon disulfide anion were also allowed to react with the 1,3-cyclobutanedione nucleus in order to determine under what conditions ring cleavage occurred.

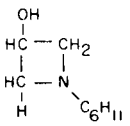
Ethyleneimine and *N*-(2-hydroxyethyl)aziridine gave ring opening products (V, VI). The structure elucidation of the products was based on infrared, nmr and mass spectral data. The infrared spectrum of *N*-2′-(1″-aziridinyl)-ethyl-2,2,4-trimethyl-3-oxovaleramide (V) shows λ max C=O = 1655 cm^{-1} for the amide carbonyl and λ max C=O = 1710 cm^{-1} for the keto group. The nmr spectrum shows a doublet at 1.01 ppm and a heptet at 3.00 ppm for the isopropyl group, a singlet at 1.31 ppm for the 2-C methyl groups, a triplet at 2.25 ppm (1′-CH_2), a multiplet at 3.30 ppm (2′-CH_2), a broad singlet (N-H) at 6.50 ppm,



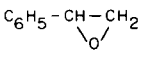
I



II



III



IV

II-a, R = H

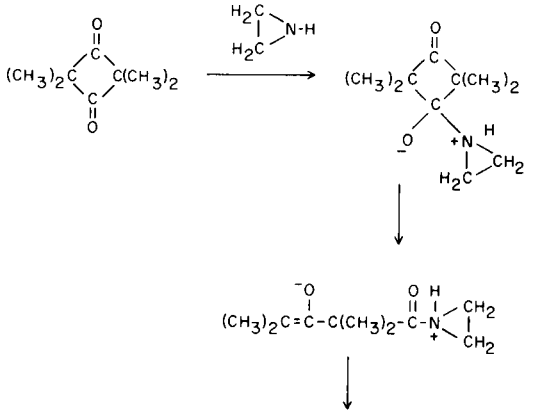
II-b, R = CH_2CH_2OH

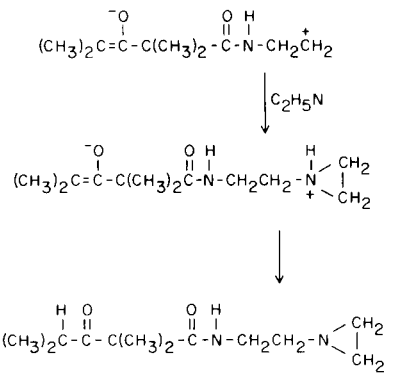
II-c, R = n-C_4H_9

II-d, R = C_6H_5

and peaks at 1.14 and 1.67 for the four aziridinyl methylene protons. The mass spectrum showed a parent peak at mass equal 226.

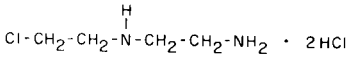
The formation of *N*-2′-(1″-aziridinyl)ethyl-2,2,4-trimethyl-3-oxovaleramide may proceed by the following mechanism:





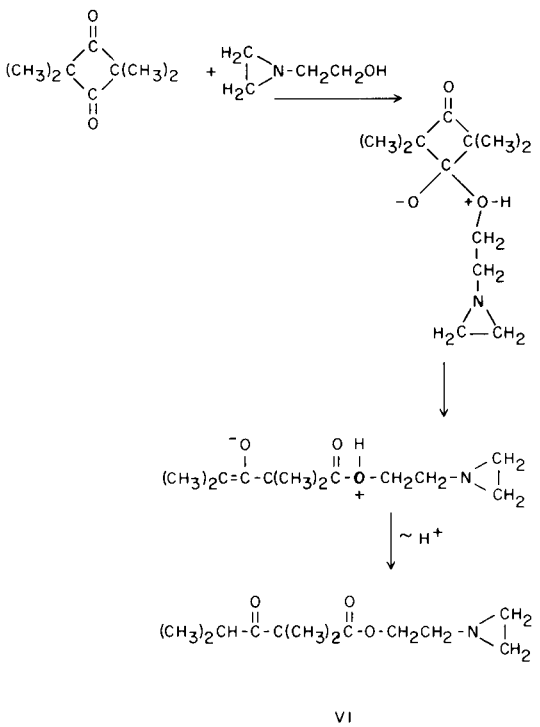
V

Hydrolysis of V with 10% hydrochloric acid hydrolysed the amide and opened the aziridine ring to give *N*-2-chloroethyl-1,2-diaminoethane dihydrochloride (VII).



VII

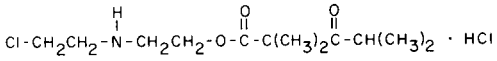
When *N*-(2-hydroxyethyl)aziridine was allowed to react with the dione the strongest nucleophile appeared to be the hydroxyl oxygen as only the ester was isolated. A plausible mechanism for the formation of this ester is given below.



VI

The infrared spectrum for 2′-(1″-aziridinyl)ethyl-2,2,4-trimethyl-3-oxovalerate (VI) shows λ max C=O = 1740 cm^{-1} for the ester carbonyl and λ max C=O = 1710 cm^{-1} for the keto group. The nmr spectrum showed a doublet at 1.10 ppm and a heptet at 2.83 ppm for the isopropyl group, a singlet at 1.30 ppm for the six methyl group protons at C-2, triplets centered at 2.37 for (CH_2N) and 4.20 for (CH_2-O) and 2 peaks at 1.13 and 1.64 for the aziridinyl methylene protons. The mass spectrum shows the molecular weight to be 227.

Hydrolysis of VI with hydrochloric acid caused cleavage of the aziridine ring and gave the expected *N*-(β-chloroethyl)-2′-aminoethyl-2,2,4-trimethyl-3-oxovalerate hydrochloride (VIII).



VIII

This product was identified by its infrared spectrum λ max C=O = 1700 cm^{-1} (3-C=O), λ max C=O = 1740 cm^{-1} (ester C=O) and a quaternary ammonium absorption at 2460 cm^{-1}.

The nmr spectrum in deuteriochloroform showed a doublet at 1.10 ppm and a heptet at 3.00 ppm for the isopropyl group, a singlet at 1.44 ppm (2-C methyl protons), triplets at 4.03 (CH_2-O) and 4.63 (CH_2-Cl) and a broad singlet at 3.47 ppm (CH_2-N), the ammonium protons exchanged with the solvent.

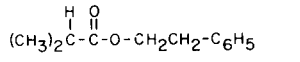
Basic hydrolysis of the ester (VIII) followed by neutralization gave 2,2,4-trimethyl-3-oxovaleric acid, which spontaneously lost carbon dioxide to give diisopropyl ketone (4).

N-phenylaziridine (II-d), in addition to being sterically hindered is a very weak base due to electron delocalization by the phenyl ring and did not react with the dione under a wide variety of conditions.

N-Butylaziridine (II-c) also suffers from steric hindrance in its reaction as a nucleophile. In the reactions studied with this compound and the dione the only compound isolated, *N,N′*-dibutylpiperazine, resulted from dimerization of the aziridine nucleus.

1-Cyclohexyl-3-azetidinol (6), which is a much stronger base than the aziridines, did not react with tetramethyl-1,3-cyclobutanedione. This shows that base strength is not the only prerequisite for a successful nucleophilic attack on the dione ring. The steric effect of the large cyclohexyl group is very evident and apparently prevented the nucleophilic reaction. The nucleophilicity of the hydroxyl group is possibly decreased by association of the electrons on oxygen with the four membered ring as 1-cyclohexyl-3-azetidenol does not react similarly to *N*-(2-hydroxyethyl)-aziridine to give an ester.

The reaction of tetramethyl-1,3-cyclobutanedione with 2-epoxyethylbenzene at high temperature gave a ring fragmentation product, phenethyl isobutyrate (IX). This product was identified by its infrared (λ max C=O = 1735 cm^{-1}) and nmr spectra [doublet at 1.10 ppm and heptet at 2.44 ppm for the isopropyl group, singlet for the aromatic protons at 7.12, and triplets at 4.20 (CH_2-O) and 2.85 (CH_2-C_6H_5)]. Independent synthesis of phenethyl isobutyrate from phenethyl alcohol and isobutyric acid gave an identical product.



IX

The anion formed from carbon disulfide and potassium hydroxide did not participate in nucleophilic attack on the cyclobutane ring, which was shown by quantitative recovery of the carbon disulfide. The product, diisopropyl ketone, was formed as a result of a basic attack on the ring by potassium hydroxide to give the acid salt, which upon neutralization gave 2,2,4-trimethyl-3-oxovaleric acid. This acid has been shown to lose carbon dioxide and yield diisopropyl ketone (4).

EXPERIMENTAL

Melting points and boiling points are uncorrected. All infrared spectra were obtained on a Perkin-Elmer Infracord, Model 137B, Spectrophotometer. Nmr spectra were run on a Varian Assoc. Model A-60 spectrophotometer as 10% solutions in carbon tetrachloride or neat, with respect to TMS as an internal standard. Elemental analyses were determined by Galbraith Laboratories, Knoxville, Tennessee and Alfred Beinhardt, Mikroanalytisches Laboratorium, Ruhr, West Germany. Mass spectral analyses were supplied by Mr. Al Struck of the Perkin-Elmer Corporation, Norwalk, Connecticut.

Aziridines.

Ethyleneimine, *N*-butylaziridine and *N*-(2-hydroxyethyl)aziridine were obtained commercially. *N*-phenylaziridine [b.p. 70-75° (13 mm), lit. (5) b.p. 70° (13 mm)] was prepared from 2-anilinoethanol according to a known procedure. All were stored in a refrigerator over sodium hydroxide and used without further purification.

N-2′-(1-Aziridinyl)-ethyl-2,2,4-trimethyl-3-oxovaleramide (V).

A mixture of 70.0 g. (0.50 mole) of 2,2,4,4-tetramethyl-1,3-cyclobutanedione and 50 g. (1.16 mole) of ethyleneimine were refluxed for 24 hours in 150 ml. of dry benzene. After cooling the solution was filtered to remove unreacted dione. Distillation at reduced pressure gave 22.2 g. (19.7%) of a clear liquid product (V), b.p. 104° (0.25 mm), n_D^{20} = 1.4770.

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.6; H, 9.80; N, 12.4; mol. wt. 226. Found: C, 63.2; H, 9.56; N, 12.1; mol. wt. 226 (mass spectograph).

N-2-Chloroethyl-1,2-diaminoethane Dihydrochloride (VII).

A solution of 5 g. of V and 15 ml. of 6 *N* hydrochloric acid was refluxed for 5 hours. The water and excess hydrochloric acid was removed under reduced pressure leaving an oil, which upon cooling solidified to a white gum. This gum was refluxed with 10 ml. of chloroform and refrigerated. The white crystals which formed were filtered and dried under reduced pressure to give 1.3 g. of a hygroscopic solid (VII), m.p. 170-171°, (lit. (7) m.p. 167° (MeOH)).

Anal. Calcd. for $C_4H_{13}N_2Cl_3$: N, 14.3. Found: N, 13.9.

The nmr spectrum shows a peak at 3.41 ppm for the four CH_2-NH protons and triplets at 3.48 (CH_2NH_2) and 3.89 (CH_2Cl) for the remaining protons.

2′-(1″-Aziridinyl)ethyl 2,2,4-Trimethyl-3-oxovalerate (VI).

A mixture of 45 g. (0.52 mole) of *N*-(2-hydroxyethyl)aziridine and 70 g. (0.50 mole) of 2,2,4,4-tetramethyl-1,3-cyclobutanedione were refluxed for 24 hours in 150 ml. of dry benzene. The benzene was removed leaving a clear oil. The oil was distilled and trace amounts of a volatile liquid identified as diisopropyl ketone were separated; 80.5 g. (71%) of VI was collected, b.p. 92-94° (1.0 mm), n_D^{20} = 1.4495.

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.4; H, 9.31; N, 6.17; mol. wt. 227. Found: C, 63.3; H, 9.23; N, 6.34; mol. wt. 227 (mass spectograph).

A solution of 25 g. of VI and 50 ml. of 6 *N* sodium hydroxide was refluxed for 10 hours. The mixture was neutralized with 10% hydrochloric acid and extracted with ether. After drying over magnesium sulfate the ether was removed leaving an oil which was distilled and gave 16 g. of diisopropyl ketone, b.p. 121° (atm.), 2,4-dinitrophenylhydrazone derivative, m.p. 91-93°, (lit. (8) b.p. 123.7°), 2,4-DNP derivative, m.p. 94°.

N-(2″-Chloroethyl)-2′-aminoethyl 2,2,4-Trimethyl-3-oxovalerate Hydrochloride (VIII).

A mixture of 25 g. of VII and 40 ml. of 6 *N* hydrochloric acid was refluxed for four hours. Partial evaporation of the resulting liquid under reduced pressure and cooling gave 31.6 g. of a crude solid which was recrystallized from chloroform-carbon tetrachloride to give 24.1 g. of a white, water soluble solid (VIII), m.p. 96-98°

Anal. Calcd. for $C_{12}H_{23}Cl_2NO_3$: C, 48.0; H, 7.72; N, 4.67; Cl, 23.7. Found: C, 48.3; H, 7.75; N, 4.41; Cl, 22.7.

Reaction of 2,2,4,4-Tetramethyl-1,3-cyclobutanedione with *N*-*n*-Butylaziridine.

A mixture of 50 g. of *N*-*n*-butylaziridine and 35 g. of tetramethyl-1,3-cyclobutanedione in 150 ml. of dry benzene were placed in a Parr bomb and heated at 200° for 24 hours. The cooled reaction mixture was filtered, the benzene removed and sublimed (50°, 5 mm) to remove any residual dione. Distillation of the residue at reduced pressure gave 6.6 g. of a yellow oil, *N*,*N*-dibutylpiperazine, b.p. 99° (4.5 mm), picrate m.p. 268-269° dec.; (Lit. (9) b.p. 126-128° 12 mm), picrate, m.p. 270-271° dec.

Reaction of I with 2-Epoxyethylbenzene.

A mixture of 35 g. of I and 35 g. of 2-epoxyethylbenzene in 150 ml. of dry benzene were placed in a Parr bomb and heated at 220° for 24 hours. The cooled reaction mixture was filtered, the benzene removed and sublimed (50°, 5 mm) to remove any residual dione. Distillation of the residue gave 1.1 g. of a sweet smelling oil identified as β-phenylethyl isobutyrate, b.p. 77° (4.6 mm), n^{25} = 1.4862; (Lit. (10) b.p. 124°, 30 mm, n_D^{20} = 1.4871).

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.0; H, 8.39. Found: C, 75.1; H, 8.62.

Refluxing an equimolar mixture of phenethyl alcohol and isobutyric acid with 5 ml. of concentrated sulfuric acid gave a product, b.p. 95°, 8 mm, whose infrared spectrum was identical to the oil described above.

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