Tetrahedron. Vol. 24, pp. 6735 to 6739. Pergamon Press 1968. Printed in Great Britain

STUDIES IN THE ENAMINE FIELD—XXIX[1]

AUTOCONDENSATION OF 2-(N-METHYLANILINO)-PROPENE: 2,2,8,8-TETRAMETHYL-SPIRO-[5.5]-UNDECANE-4,10-DIONE

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(*Received in the UK* 9 *May* 1968; *accepted for publication* 20 *June* 1968)

Abstract—The reaction between acetone diethyl ketal and N-methylaniline yields as the main product a cyclic diketone which has been assigned the structure of 2,2,8,8-tetramethyl-spiro-[5,5]-undecane-4,10-dione on chemical and spectroscopic evidence.

THE reaction between acetone diethyl ketal and morpholine was the subject of previous papers on the autocondensation of acetone morpholino-enamine.[2]

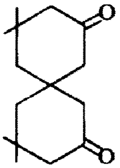
This reaction afforded a complex mixture of enamine compounds which, upon hydrolysis, yielded: mesityl oxide; isophorone; 2,6,8,8-tetramethyl-bicyclo-[4.2.0]-octene-2-one-4; 2-(2-methyl-1-propenyl)-6,8,8-trimethyl-bicyclo-[4.2.0]-octene-2-one-4 and 3,3,5,5-tetramethyl-cyclooctadiene-2,7-one-1. A diketone (I) of molecular formula $C_{15}H_{24}O_2$, m.p. 122–123°, was also isolated but the investigation of this substance was discontinued since only very poor yields were obtained.

In order to investigate the autocondensation reactions of the acetone-enamines, the behaviour of acetone N-methylanilino-enamine was studied since previous experiments showed that in general N-methylanilino-enamines behave differently from the morpholino-enamines.

Acetone diethyl ketal reacted with an equimolecular amount of N-methylaniline with continuous distillation of the ethanol formed during the reaction. The theoretical amount of alcohol was collected after a few hours, while the analogous reaction using morpholine takes two or three days. This observation is consistent with the reactions of morpholine and N-methylaniline with ketals of other aliphatic ketones to yield simple enamines which do not undergo subsequent autocondensation. After completion of the reaction, the enamine II (mol formula $C_{29}H_{38}N_2$) was isolated with great difficulty. Upon hydrolysis, this enamine yielded the same ketone I, which had been previously obtained by autocondensation of acetone morpholino-enamine. Considering the difficulties related to the isolation of II, it was found advisable to obtain I by direct acid hydrolysis of the crude reaction mixture. It was thus possible to isolate the diketone I in a satisfactory yield (20–30%).

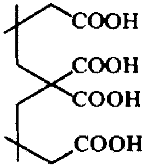
Compound I does not contain ethylenic bonds conjugated with the carbonyl group as is evidenced by the lack of corresponding absorptions in the UV spectrum. The IR spectrum shows a carbonyl band at 1710 cm^{-1} which can be associated with CO groups in linear chains or in 6- or higher-membered rings. The NMR spectrum shows two singlets (12 H) at 8·98 and 8·92 τ, corresponding to four very similar Me groups; moreover it contains a singlet (4 H) at 8·30 τ associated with two equivalent methylene groupings and two singlets (8 H) at 7·81 and 7·67 τ, each evidencing the presence of two identical methylenes adjacent to the CO groups. The whole spectrum is characterized by lack of any coupling.

The above spectroscopic data are strongly in favour of a 2,2,8,8-tetramethyl-spiro-[5.5]-undecane-4,10-dione structure:

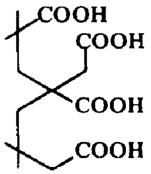


I

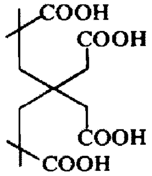
Chemical confirmation of this structure (I) was obtained by nitric acid degradation which yielded a mixture of two tetracarboxylic acids isolated as the free acids and as the corresponding methyl esters. This result is evidence that the two carbonyl groups belong to two different rings. Theoretically, the oxidation of I should yield three isomeric tetracarboxylic acids (IIIa, b, c) but as the isolation of one isomer was sufficient to demonstrate the presence of two cyclanonic systems the degradation was not studied in greater detail.



IIIa



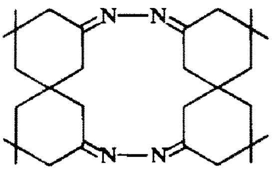
IIIb



IIIc

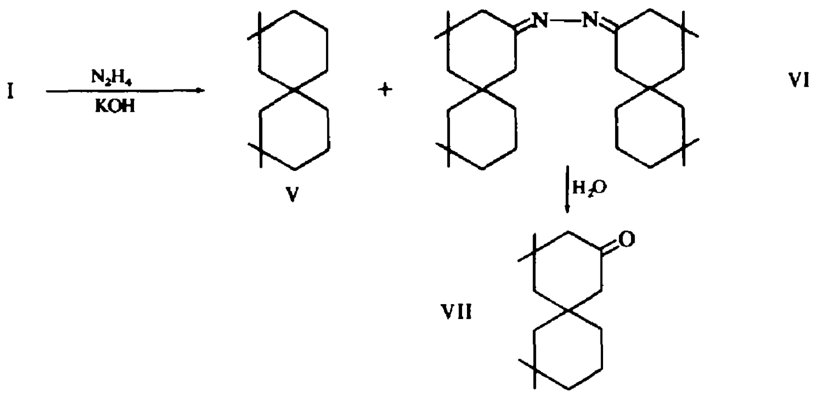
In order to demonstrate the symmetric nature of the proposed structure, the two rings were degraded independently.

Wolff-Kishner reduction of only one of the ketone groups to a methylene failed to yield the desired product since the reaction of I with hydrazine yielded a high-melting oxygen-free derivative (IV) which showed a very slight solubility in the usual solvents and the desired monohydrazone could not be isolated. The mol wt, analytical values and spectroscopic data of IV strongly support the following structure:



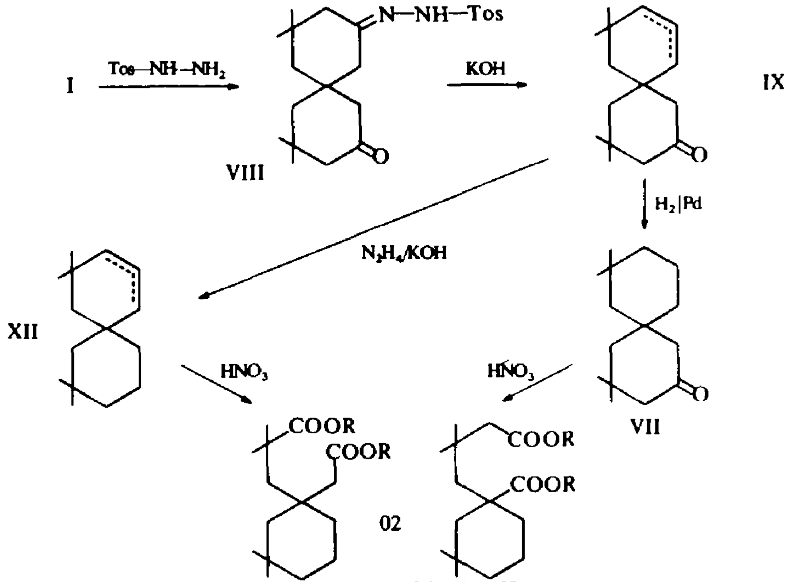
IV

Huang Minlon reduction of I gave a mixture of two products the main component being a saturated hydrocarbon (V; $C_{15}H_{18}$) corresponding to I. Compound V was accompanied by a small amount of a N-containing compound identified as the azine (VI) of the expected monoketone (VII) which could be obtained by hydrolysis of VI. Unfortunately this method could not be used for the preparation of VII in view of the low yield of VI:



Finally, the monoketone VII was obtained in satisfactory yield starting from the monotosylhydrazone of I (VIII). This derivative was prepared in excellent yields from equimolar amounts of the two reactants. It was then degraded with potassium hydroxide to the corresponding unsaturated ketone IX* which was catalytically reduced to VII. The nitric acid oxidation of VII afforded a dicarboxylic acid (X; $C_{15}H_{26}O_4$) which was isolated as the dimethyl ester (XI). These compounds correspond to one of the two possible structures Xa and Xb (respectively, XIa and XIb).

Degradation of the second ring in I was brought about by reducing first the unsaturated ketone IX to the corresponding unsaturated hydrocarbon (XII) $C_{15}H_{26}$.† This was also oxidized with nitric acid to the dicarboxylic acid (X) identical with the product produced by degradation of VII. The above reactions are outlined in the following scheme:



Xa : R = H Xb : R = H

XIa : R = CH_3 XIb : R = CH_3

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* As expected, this product was a mixture of two isomers which were not separated.

† This compound appeared homogeneous by VPC but, the position of the double bond was not determined.

These results indicate the importance of the secondary amine in enamine formation from the corresponding ketals and, in this case, the influence the amine has on the course of the autocondensation of the acetone enamines. The main product of the autocondensation of acetone morpholino-enamine is a bicyclic monoketone, namely 2,6,8,8-tetramethyl-bicyclo-[4.2.0]-octene-2-one-4 while autocondensation of acetone N-methylanilino-enamine yields the spiranic diketone I. The difference is reactivity of the two enamines and the higher formation rate of N-methylanilino-enamine accounts for the differences observed in the ratios of the autocondensation products.

EXPERIMENTAL

The m.ps are uncorrected. The NMR spectra were recorded on a Varian A-60 spectrometer at 60 Mc/s with TMS as internal standard (τ = 10·00 ppm).

N-Methylanilino-enamine of 2,2,8,8-*tetramethyl-spiro-*[5.5]-*undecane*-4,10-*dione* (II). To 2,2-diethoxypropane (92 g, 0·7 moles) and N-methylaniline (75 g, 0·7 moles), 0·2 g of *p*-toluenesulphonic acid was added and the mixture refluxed for 12–16 hr. EtOH was distilled off slowly and the residue was rectified at 0·5 torr. After N-methylaniline had distilled over at 65°, the temp was raised to 180° and II was distilled as a yellow viscous oil. This was redistilled at 180–185°/0·5 torr and a 20% yield based on the 2,2-diethoxypropane was obtained as a pale yellow viscous oil which darkened upon exposure to air. (Found: C, 84·32; H, 9·27; N, 6·76. $C_{29}H_{38}N_2$ requires: C, 84·00; H, 9·24; N, 6·67%).

2,2,8,8-*Tetramethyl-spiro-*[5,5]-*undecane*-4,10-*dione* (I). In the reaction of 2,2-diethoxypropane and N-methylaniline, after removal of the EtOH, the residue was directly hydrolysed with 15% HCl (300 ml) by heating under reflux for 5 hr. The organic products were then extracted several times with benzene and after drying (Na_2SO_4) the solvent was evaporated under reduced press. The brown residue was washed with cold ligroin, filtered and recrystallized from ligroin (b.p. 80–120°) yielding 20% of I as white plates, m.p. 122–123°. (Found: C, 76·30; H, 10·24. $C_{15}H_{24}O_2$ requires: C, 76·50; H, 10·20%).

Bis-4-nitrophenylhydrazone of I. This was obtained in MeOH and recrystallized from AcOH, m.p. 221°. (Found: C, 63·85; H, 6·60; N, 16·73. $C_{27}H_{34}N_6O_4$ requires: C, 64·01; H, 6·77; N, 16·59%).

Bis-tosylhydrazone of I. This was obtained in EtOH and thoroughly washed with warm EtOH, m.p. 201°. (Found: C, 60·85; H, 7·24; N, 9·94. $C_{29}H_{40}N_4O_4S_2$ requires: C, 60·82; H, 7·04; N, 9·78%).

Nitric acid degradation of I. Compound I (10 g; 42 mmoles) was dissolved in 40 ml conc HNO_3 and the mixture cautiously heated on an oil bath until a vigorous reaction set in. The heating was continued for 2 hr at 130°. After 24 hr at room temp a white microcrystalline ppt formed which was filtered off, washed with a little ether and recrystallized from diisopropyl ether, m.p. 180° (35% yield). (Found: C, 54·13; H, 7·48. $C_{15}H_{24}O_8$ requires: C, 54·21; H, 7·28%). This acid was suspended in ether and reacted with an ethereal soln of diazomethane. After evaporating the solvent, the residue was distilled at 0·1 torr. The ester was obtained as a highly viscous oil, b.p. 160°/0·1 torr. (Found: C, 59·19; H, 8·23. $C_{19}H_{32}O_8$ requires: C, 58·74; H, 8·30%). Mol wt (osmometric): Found 387, required 388. Gaschromatographic analysis showed that this product was a nearly equimolecular mixture of the two isomers.

Reaction of I *with a mole of hydrazine.* To a soln of I in EtOH (2 g), 0·5 g of 85% hydrazine hydrate was added together with a drop of 98% H_2SO_4. After heating under reflux for 12 hr, the reaction mixture was cooled and filtered. The product was isolated as white crystals (1·2 g), m.p. 280–285° (dec). (Found: C, 76·99; H, 10·49; N, 12·08. $C_{30}H_{48}N_4$ requires: C, 77·53; H, 10·41; N, 12·06%); IR spectrum: 1640 cm^{-1} (C=N). Mol wt (mass spectroscopy): 465; required: 464·7.

Huang Minlon reduction of I. Compound I (5 g; 21 mmoles) was suspended in 20 ml diethylene glycol and treated with 5 ml 85% hydrazine hydrate and 8·5 g KOH dissolved in 50 ml glycol. The mixture was then slowly distilled over a direct flame during 1·5 hr. Together with water, a small amount of the product distilled over. After cooling, the distillate was added to the distillation residue and the reaction product isolated by steam-distillation. The distillate was extracted with ether, washed with dil HCl, then with a sat $NaHCO_3$ aq. After drying over Na_2SO_4 the solvent was evaporated and the residue distilled at 60–65°/0·1 torr yielding V (85%) as a colourless product. (Found: C, 86·37; H, 13·61. $C_{15}H_{28}$ requires: C, 86·46; H, 13·54%). The residue from the distillation was further distilled at 180°/0·1 torr. The product solidified on cooling and was recrystallized from acetone yielding VI as white crystals, m.p. 120°, 10% yield. (Found: C, 81·16; H, 12·11; N, 6·01. $C_{30}H_{52}N_2$ requires: C, 81·75; H, 11·89; N, 6·36%); IR spectrum: 1640 cm^{-1} (C=N).

Monotosylhydrazone of I (VIII). A soln of 15·6 g (85 mmoles) of tosylhydrazine in 300 ml EtOH was added dropwise during 4 hr to a stirred boiling soln of I (20 g; 85 mmoles) in 500 ml EtOH. The mixture was refluxed while stirring for 12 hr. EtOH was then distilled off until the volume was about 60 ml. This mixture was kept at 0° for 24 hr and the ppt formed was filtered off and washed with a little EtOH. After recrystallization from EtOH VIII was obtained in 65% yield as colourless needles, m.p. 142°. (Found: C, 65·32; H, 7·90; N, 7·02. $C_{22}H_{32}N_2O_3S$ requires: C, 65·32; H, 7·97; N, 6·93%).

Degradation of VIII. Compound VIII (10 g; 25 mmoles) was suspended in a soln of 20 g KOH in 100 ml diethylene glycol. The mixture was then heated on an oil bath to 140° until N_2 began to evolve and then maintained at the same, or slight higher, temp for 1 hr. After cooling, the soln was subjected to steam-distillation. The distillate was extracted with ether, dried over Na_2SO_4 and evaporated. A crystal of hydroquinone was added to the residue and the unsaturated ketone IX was vacuum distilled. It was obtained in 50% yield as a colourless liquid, b.p. 90–100°/0·1 torr. (Found: C, 81·84; H, 10·96. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

2,2,8,8-*Tetramethyl-spiro-*[5.5]*-undecane-*4*-one* (VII)

(a) The unsaturated ketone IX (4 g) was dissolved in 40 ml MeOH. After adding 0·1 g 5% Pd-C, the compound was hydrogenated at room temp and press. The theoretical amount of H_2 was consumed in about 0·75 hr. The catalyst was filtered off and the solvent evaporated. The residue was distilled and the product isolated as a colourless liquid, b.p. 100–105°/0·2 torr. (Found: C, 81·02; H, 11·75. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·79%).

(b) The azine VI (0·2 g) was hydrolysed with 30% HCl (5 ml) by heating under reflux for 0·5 hr. The hydrolysis product was extracted with ether and the ketone VII obtained in the usual manner (90% yield).

Nitric acid oxidation of VII. Compound VII (4·0 g) was mixed with 10 ml conc HNO_3 and heated on an oil bath until a vigorous reaction with evolution of nitrous fumes set in. The mixture was then heated at 150° for 45 min. After cooling a dense oil separated which was decanted from the supernatant liquid and dissolved in 5% NaOH. The alkaline soln was washed with ether and acidified with 10% H_2SO_4. The organic phase was then extracted with ether and dried over Na_2SO_4. After evaporation, the residue was crystallized by the addition of a small amount of diisopropyl ether and filtered. After thorough washing with diisopropyl ether the acid X was obtained as colourless crystals, m.p. 210° in 20% yield. (Found: C, 66·34; H, 9·46. $C_{15}H_{26}O_4$ requires: C, 66·63; H, 9·69%). This acid was esterified with an ethereal soln of diazomethane, whereby the methyl ester was obtained in 95% yield as a colourless liquid, b.p. 110°/0·1 torr; IR spectrum: 1740 cm^{-1} (C═O). (Found: C, 68·17; H, 10·27. $C_{17}H_{30}O_4$ requires: C, 68·42; H, 10·13%).

Huang Minlon reduction of ketone IX. The unsaturated ketone IX (10 g) was mixed with 8 ml 85% hydrazine hydrate and 13 g KOH in 100 ml diethylene glycol. The mixture was heated on an oil bath at 180° for 1·5 hr. Some distillate was collected. After cooling this distillate was returned to the reaction flask. The mixture was then steam-distilled. The ether extract of the distillate was dried over Na_2SO_4 and vacuum distilled. The olefin XII was isolated in 50% yield as a colourless liquid, b.p. 60–70°/0·5 torr. (Found: C, 87·57; H, 12·52. $C_{15}H_{26}$ requires: C, 87·30; H, 12·70%).

Nitric acid oxidation of XII. The olefin XII (0·1 g) was mixed with 0·8 ml conc HNO_3 and the reaction started with evolution of nitrous gases and heating at 100° was continued for 1 hr. After cooling, a heavy oil separated. After decantation of the exhausted acid, the product was dissolved in a few ml 5% NaOH. The alkaline soln was washed with ether and acidified with 10% H_2SO_4. The organic layer was extracted with ether and the soln obtained reacted with diazomethane. After evaporation, the residue was analyzed by gas chromatography (Perkin–Elmer 800 Apparatus, column P, col. temp 190°, vap temp 250°, 30 ml/min) and found to be identical with the diester obtained by the degradation of VII.

Acknowledgement—We gratefully thank Dr. T. Salvatori, Prof. G. G. Gallo and Dr. A. Vigevani for the NMR spectra. We are indebted to the Italian C. N. R. for financial aid.

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