Heterocycles from Ketenimines. VII. 3,4-Dihydroquinazolines through Thermolysis (1a,b)

Marvin W. Barker and James D. Rosamond

Department of Chemistry, Mississippi State University
Mississippi State, Mississippi 39762

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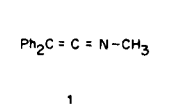
Ketenimines have been shown to dimerize and trimerize during thermolysis to yield heterocycles whose structures depend on the ketenimine substitution pattern. For example, if **1** (a diaryl *N*-alkyl substituted ketenimine) is heated for one week at 125°, the azetidine **2** results (2). Similar treatment of **3** (a totally alkyl substituted ketenimine) results in the production of the hexahydrotriazine **4** (1a). This report concerns the dimer obtained when dialkyl *N*-aryl ketenimines are subjected to thermolysis.



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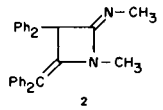

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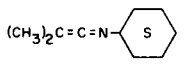

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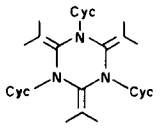

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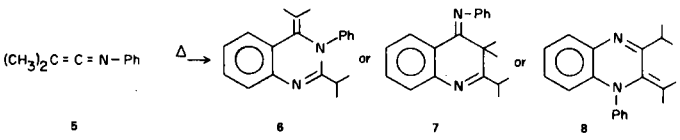
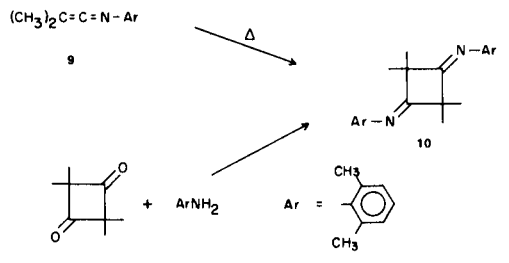
Thermolysis of a sample of dimethylketene *N*-phenylimine (**5**) at 125° for one week gave an amber residue that was found by gc/ms analysis to be 76% dimer, 20% trimer, and 4% higher molecular weight material. The dimer, which could be isolated by acid extraction of the reaction mixture, exhibited a strong absorption in the ir at 1580 cm^{-1}, absorptions in the nmr at δ 1.33 (d, 6H), δ 2.89 (m, 1H), δ 1.89 (s, 3H), δ 1.99 (s, 3H), and in the aromatic region; and principle mass spectrum peaks at 290 (parent ion, 52%) 275 (M^+-15, 85%), 91 (23%), and 43 (100%). This spectroscopy data eliminates all but three structures for the dimer for the following reasons: (a) the strength of the ir absorption in the unsaturated region at 1580 cm^{-1} strongly suggests this absorption is due to C=N. (b) The doublet in the nmr at δ 1.33 of 6H coupled with a multiplet of 1H at δ 2.89 is characteristic of the isopropyl function while the two singlets of 3H each at δ 1.89 and 1.99 must be due to two methyl groups which are deshielded and in slightly different environments. (c) The ms data suggests a dimeric structure which can easily lose



5 6 7 8

a methyl group and which has the isopropyl ion as the most abundant ion. If one simply puts two molecules of **5** together in all possible ways, only **6**, **7**, and **8** can satisfy all the spectroscopic data. Each of these structures contain the C=N to satisfy the ir and the isopropyl function to match the nmr spectrum. Furthermore, both **6** and **8** contain the deshielded methyl groups in different environments which the nmr demands. Structure **7** only satisfies this requirment with the ring *gem* dimethyls if one assumes an equimolar amount of the *syn* and *anti* exocyclic imine is formed. Furthermore, nothing in **7** accounts for the chemical shifts of the methyls observed in the nmr; thus, **7** must be viewed with skepticism.

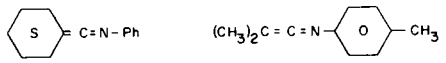
Each of the possible structures represents the cyclization of one monomer unit into the *o*-position of the other monomer. Thus, if the *o*-positions on a compound similar to **5** were blocked, dimerization of it should produce a product totally different from the dimer of **5** and hence serve as a test of the feasibility of the cyclized structures. Compound **9** was prepared and subjected to the same conditions of thermolysis as were employed for **5**. The dimer (**10**) proved to be a cyclobutadione diimine as shown by its unequivocal synthesis from tetramethylcyclobutadione (3). Therefore, the proposed structures based on *o*-cyclization do seem reasonable.



9 10

In the process of deducing the actual structure for the dimer of **5** from **6**, **7**, and **8**, **8** was the first to be eliminated from consideration. The reaction of 2-aminodiphenylamine with 2,5-dimethyl-3,4-hexandione (4) provides an unequivocal synthesis of **8**, and the product obtained by this reaction has physical and spectroscopic properties quite different from the dimer of **5**.

The differentiation between **6** and **7** was made on the basis of hydrogenation. Although the dimer of **5** was not hydrogenated at atmospheric pressure with hydrogen and a catalyst, the dimer reacted smoothly when treated with PMHS and catalyst (5) to yield an adduct which contained no methyl singlets in the nmr but only a complex series of absorptions from δ 0.7 to 1.3. Structure **7** if hydrogenated, should be expected to show a different chemical shift for the methyls, but they should still be observable in the nmr. However, if **6** is hydrogenated, two similar but not identical isopropyl groups should result. This is in agreement with the observed nmr of the hydrogenated dimer and, thus, **6**, a 3,4-dihydroquinazoline, is the dimer of **5**. Thermolysis of **11** and **12** (both dialkyl *N*-alkyl ketenimines) also yielded 3,4-dihydroquinazolines indicating that in general ketenimines with this substitution pattern dimerize through thermolysis to produce dihydroquinazolines.



11 12

EXPERIMENTAL

Infrared spectra were determined with a Perkin-Elmer Model 137 or 137G spectrometer. Nuclear magnetic resonance spectra were taken on a Varian A-60 instrument in carbon tetrachloride solvent and peak positions are reported in ppm from internal tetramethylsilane. Mass spectrum were obtained on a Perkin-Elmer Model 270 gc/ms instrument. Analyses were performed by Galbraith Laboratories, Incorporated, Knoxville, Tennessee. 2-Isopropyl-4-isopropylidene-3-phenyl-3,4-dihydroquinazoline (**6**).

In an ampoule was placed 5.95 g. (41 mmoles) of dimethylketene *N*-phenylimine (6). The sealed ampoule was heated in an oil bath at 125° for one week. After cooling, the reaction mixture was analyzed by vpc-ms and found to contain a dimer (76%) as the major product and a trimer (20%) as the minor product. The contents of the ampoule (amber in color) were dissolved in a mixture of 100 ml. of acetone and 50 ml. of 1 *N* hydrochloric acid and refluxed for 4 hours. The solution assumed an emerald green color. The acetone was removed by distillation to afford a yellow aqueous solution containing an oily green precipitate. The aqueous solution (containing oily precipitate) was extracted with ether (oily precipitate dissolved and both layers became yellow in color). Concentration of the ether extract afforded 0.22 g. of a semisolid material that could not be identified.

The aqueous layer was made alkaline with 5% sodium carbonate and extracted with ether. The ether extract was dried over magnesium sulfate and evaporated to dryness. There was obtained an amber semisolid material which was distilled to give 3.1 g. (52%) of **6** a pale yellow material that slowly solidified in the receiver, b.p. 157-160° (0.2 mm). Recrystallization from ethanol-water gave a white solid, m.p. 93.2-94.0°; ir 1600 (w), 1580 (s), 1495 (m), 1455 (m), 1380 (m), 760 (s), and 750 cm^{-1} (s); nmr (carbon tetrachloride): δ 1.33 (d, 6H, $CH(CH_3)_2$), δ 1.89 (s, 3H, $C=CCH_3$), δ 1.99 (s, 3H, $C=CCH_3$), δ 2,89 (m, 1H, $CH(CH_3)_2$), δ 6.80-7.35 (m, 9H, ArH); ms (70 eV) m/e (relative intensity) 43 (100), 77 (55), 91 (23), 119 (15), 129 (27), 186 (21), 213 (15), 275 (85), 276 (29), 289 (26), 290 (52) parent ion, and 291 (17).

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64: N, 9.65. Found: C, 82.94; H, 7.60; N, 9.77.

Dimethylketene *N*-(2,6-Dimethylphenyl)imine (**9**).

The procedure of Stevens and French (7) was followed in the synthesis of dimethylketene *N*-(2,6-dimethylphenyl)imine from *N*-(2,6-dimethylphenyl)isobutyrimino chloride and triethylamine in 89% yield. The product was found by gc to be contaminated with some imino chloride. Redistillation from sodium afforded pure ketenimine, b.p. 68-69° (0.6 mm) (61% yield overall); ir 2020 (s), 1600 (w), 1480 (m), and 1380 cm^{-1} (m); nmr δ 1.07 (6H, $ArCH_3$), 1.72 (6H, $C=CCH_3$), 6.38 (3H, ArH), all singlets.

Anal. Calcd. for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.13; H, 8.68; N, 8.20.

Tetramethyl-*N*,*N*′-bis(2,6-dimethylphenyl)cyclobutane-1,3-diimine, (**10**).

Into an ampoule was placed 3.92 g. (22.7 mmoles) of dimethylketene N-(2,6-dimethylphenyl)imine. The sealed ampoule was heated at 125° for two weeks. After cooling, the amber liquid deposited crystals upon scratching the walls of the ampoule with a glass rod. The supernatant liquid was removed with an eye dropper and sealed in an ampoule for further heating; while the precipitate was collected and recrystallized from acetone-water. There was obtained 0.85 g. (22%) of **10** white solid, m.p. 178-179°; ir 1695 (s), 1680 (s), 1595 (m), 1470 (m), 1455 (m), 1380 (m), 1360 (m), 1220 (m), 1060 (m), and 765 cm^{-1} (s); nmr (carbon tetrachloride): δ 1.27 (broad singlet, 12H, 2 $C(CH_3)_2$), 2.08 (s, 12H, 2 $Ar(CH_3)_2$), 6.5-7.2 (m, 6H, ArH); ms (70eV) m/e (relative intensity) 77 (20), 79 (17), 105 (18), 131 (17), 158 (36), 172 (17), 173 (100), 174 (30), 150 (40), 251 (18), 346 (33) parent ion, and 347 (22).

Anal. Calcd. for $C_{24}H_{30}N_2$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.25; H, 8.63; N, 8.16.

There was subsequently obtained 1.81 additional grams of **10** (68% total yield) from the supernatent liquid after heating for an additional 4 weeks.

The reaction of tetramethylcyclobutadione with 2,6-dimethylaniline using *p*-toluenesulfonic acid as catalyst yielded a product identical to **10** (3,8).

3-Isopropyl-2-isopropylidene-1-phenyl-1,2-dihydroquinoxaline (**8**).

In a 100 ml. flask equipped with a reflux condenser, a magnetic stirrer, and a nitrogen atmosphere were placed 4.38 g. (23.8 mmoles) of 2-aminodiphenylamine, 3.38 g. (23.8 mmoles) of 2,5-dimethyl-3,4-hexandione, and 50 ml. of absolute ethanol. The stirred solution was refluxed under nitrogen for 24 hours. After the solution had cooled, it was concentrated on the rotatory evaporator. The heated ethanol solution was diluted with water to induce crystallization. Recrystallization of the resultant precipitate from ethanol-water afforded 1.90 g. (41%) of **8** light tan solid, m.p. 147-148°. The product was found to fluoresce yellow upon irradiation with ultraviolet light. Two recrystallizations from ethanol-water afforded the analytical sample, m.p. 147.5-148.0°; ir 1595 (s), 1555 (m), 1495 (s), 1473 (s), 1385 (m), 1375 (m), 1290 (s), and 1030 cm^{-1} (m); nmr (carbon tetrachloride): δ 1.04 (d, 6H,

$CH(CH_3)_2$), 1.92 (s, 6H, $C=C(CH_3)_2$), 2.99 (m, 1H, $CH(CH_3)_2$), 6.7-7.5 (m, 9H, ArH); ms (70 eV) m/e (relative intensity) 77 (45), 91 (35), 105 (36), 119 (50), 129 (23), 186 (55), 199 (17), 213 (12), 247 (17), 275 (40), 289 (22), 290 (100), parent ion, and 291 (40).

Anal. Calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.53; H, 7.57; N, 9.73.

Hydrogenation of **6**.

To 40 ml. of 95% ethanol were added 132 mg. of **6**, 1 drop of concentrated hydrochloric acid and 50 mg. of 5% Pd on C. To this solution was slowly added 1 ml. of PMHS and the solution was maintained between 40 and 60° for 2 hours. The solution was filtered, diluted with 80 ml. of water and extracted with hexane (1 x 30 ml.) and ether (3 x 30 ml.). The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure (aspirator) to leave a liquid which possessed nmr absorptions from δ 0.7-1.3 and in the aromatic region.

Pentamethyleneketene *N*-Phenylimine (**11**).

An adaptation of the Stevens and Singhal (9) procedure for the dehydration of amides was used. Into a 1-l. flask equipped with a reflux condenser, a nitrogen inlet tube, and a stirrer, was placed 20.3 g. (0.1 mole) of cyclohexanecarboxanilide followed by 50 g. each of phosphorus pentoxide and oven-dried Florisil and then 400 ml. of dry triethylamine. The system was flushed with nitrogen and then vigorously stirred and refluxed under nitrogen for 24 hours. After the mixture had cooled to room temperature, the triethylamine solution was decanted from the solid residue and the residue washed with 100 ml. of triethylamine. Concentration of the triethylamine solutions under reduced pressure gave an amber oily residue. Distillation afforded 4.0 g. (21%) of a pale yellow liquid, b.p. 80-82° (0.15 mm): ir 2010 (s), 1595 (m), 1490 (m), and 1410 cm^{-1} (m); nmr δ 1.4-1.8 (m, 6H), 2.0-2.3 (m, 4H), 7.1 (s, 5H, ArH). The analytical sample was obtained upon redistillation, b.p. 79-80° (0.1 mm).

Anal. Calcd. for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.03; H, 8.23; N, 7.62.

2-Cyclohexyl-4-cyclohexylidene-3-phenyl-3,4-dihydroquinazoline.

Into an ampoule was placed 2.31 g. (7.1 mmoles) of pentamethyleneketene *N*-phenylimine. The sealed ampoule was heated at 125° for one week. After cooling, the amber contents of the ampoule were dissolved in carbon tetrachloride. Analysis by vpc-ms showed a major product (73%, dimeric) and a minor product (23%, dimeric). The carbon tetrachloride solution was placed on an alumina column and eluted with carbon tetrachloride. A yellow solid recrystallized from acetone-water. After three recrystallizations there was obtained 1.06 g. (46%) white solid, m.p. 144-145°; ir 1580 (s), 1565 (m), 1495 (m), 1470 (m), 1450 (m), 1215 cm^{-1} (m); nmr (carbon tetrachloride): δ 1.1-2.2 (m, 16H), 2.25-2.80 (m, 5H), 6.6-7.3 (m, 9H, ArH); ms (70 eV) (relative intensity) 77 (40), 91 (13), 239 (33), 240 (20), 315 (60), 316 (54), 340 (23), 341 (20), 369 (54), 370 (100) parent ion, 371 (68), and 372 (20).

Anal. Calcd. for $C_{26}H_{30}N_2$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.44; H, 8.14; N, 7.77.

2-Isopropyl-4-isopropylidene-6-methyl-3-*p*-tolyl-3,4-dihydroquinazoline.

In an ampoule was placed 4.83 g. (30.4 mmoles) of dimethylketene *N*-*p*-tolylimine (6). The ampoule was sealed and heated in an oil bath at 125° for one week. After cooling, the amber colored contents were dissolved in methylene chloride for analysis by vpc. The chromatogram showed a major product (58%) and a minor product (17%) as well as numerous low percentage products. Preparative vpc resulted in the isolation of the major and minor products. Repeated attempts to recrystallize either product from various solvent systems met with failure.

An ir of the major product (in dichloromethane) showed absorption bands at 1620 cm^{-1} (m), 1570 (s), 1510 (m), 1480 (m), 1385 (m), 1225 (m), and 832 cm^{-1} (m). Vpc-ms revealed it to be a dimer of molecular weight 318 with m/e values of 91 (35), 119 (30), 132 (38), 143 (25), 200 (33), 303 (100), 304 (70), 317 (30), and 318 (78) parent ion.

Acknowledgment.

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