Dihydropyridazines. III [1,2]. Reactions with Oxygen

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The reactions of oxygen with a series of dihydropyridazines have been explored. The primary reaction other than aromatization appears to occur from the 1,4-dihydro tautomer. A single crystal x-ray structure has been determined on the product from the reaction of oxygen with 3,6-diphenyl-4,4-dimethyl-1,4-dihydropyridazine.

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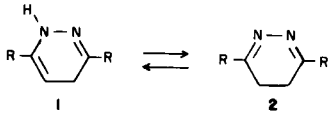
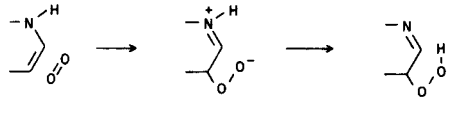
In our investigation of the use of dihydropyridazines as precursors to cyclic azo compounds we noted [3], as have others, [4,5] that these compounds are reactive toward molecular oxygen. The normal consequence of exposure to oxygen, particularly of dihydropyridazine solutions, is the formation of the corresponding aromatic pyridazine. However, in certain cases dihydropyridazines have been reported to give hydroperoxides and endoperoxides in lieu of, or in addition to, aromatic heterocycle [4,5]. We report here some additional observations on the reaction of dihydropyridazines with oxygen.

Dihydropyridazines having alkyl or aryl substituents in ring positions 3 and 6 exist in solution in an equilibrium

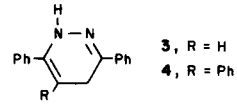


1 2

between the 1,4-dihydro tautomer **1** and a 4,5-dihydro tautomer **2** [6-14]. The reaction with oxygen appears to occur *via* the 1,4-dihydro tautomer and is mechanistically similar to reactions of the indole nucleus which lead to hydroperoxides [15]. Indeed, an *ab initio* calculation performed on the 1,4-dihydropyridazine nucleus using Gaussian 70 and an STO-3G basis set [16] (Figure 1) indicates that the ring system possesses considerable enamine character. Addition of oxygen can occur as shown in the scheme below. The "ene" reaction involving oxygen with enamines, unlike singlet oxygen ene reactions, cannot be concerted in a

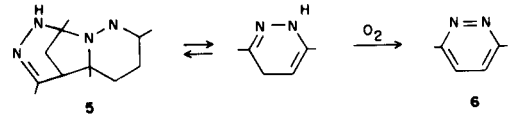


syn fashion as spin-inversion is necessary before hydrogen can be transferred from nitrogen to oxygen. However, only in one case has a dihydropyridazine hydroperoxide been isolated [5]. The normal course of reaction for 4,5-dihydropyridazines having substituents such as acetoxy [17], alkoxy [17], hydroxy [18], thioalkyl [19], dialkylamino [20,21], and sulphenyl [22] groups at ring positions 4 or 5 is a 1,2-elimination giving the aromatic pyridazine. It appears that the hydroperoxy group functions in the same manner and, in fact, hydrogen peroxide was observed as a product in the aromatization of **4** with oxygen.



3, R = H
4, R = Ph

We attempted to observe the hydroperoxide by proton nmr using dihydropyridazines **3** and **4**. In chloroform solution **3** exists in an 8:1 ratio of 1,4-dihydro to 4,5-dihydro forms, while the 4,5-dihydro tautomer of **4** is not even observable by nmr. The reaction of both compounds with oxygen to give their respective pyridazines is very fast but no intermediates could be observed, their lifetimes apparently being too short. Similar attempts to observe intermediates in the oxidation of 3,6-dimethyldihydropyridazine also failed. This compound, which is known to exist as a dimer [2,23] can dissociate to give small amounts of monomer which is susceptible to facile oxidation to pyridazine. Only dimer **5** and pyridazine **6** could be observed in the proton nmr.



5 6

When aromatization by elimination of hydrogen peroxide is not facile, endoperoxide formation may occur [4,5]. Thus it seemed reasonable that 4,4-dimethyl-3,6-diphenyl-1,4-dihydropyridazine **7** might give an isolable oxygen adduct.

Dihydropyridazines **7** and **8** were synthesized *via* the cycloaddition reaction of isobutylene with 3,6-diphenyl *sym*-tetrazine and they exist in chloroform solution as a 78:22% mixture of 1,4-dihydro tautomer **7** to 4,5-dihydro tautomer **8**.

Table 1A

Final Coordinates and Anisotropic Temperature Factors* [a]

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O1	0.5781(22)	0.1839(3)	0.1503(7)	1208(78)	6(2)	73(8)	−17(9)	−109(18)	3(3)
O2	0.7897(17)	−0.0588(3)	0.4906(6)	565(49)	12(2)	55(6)	−10(8)	−57(13)	6(3)
N1	0.6450(18)	0.0486(4)	0.2923(6)	401(49)	9(2)	37(6)	−13(8)	−2(13)	1(3)
N2	0.7365(18)	0.0269(4)	0.3891(6)	404(50)	8(2)	40(6)	−23(8)	−29(14)	3(3)
C1	0.6972(24)	0.1070(5)	0.2730(8)	429(67)	13(3)	36(8)	−4(11)	−10(18)	0(4)
C2	0.5869(24)	0.1273(5)	0.1660(9)	376(66)	17(3)	49(8)	−13(11)	−51(19)	−2(4)
C3	0.4866(27)	0.0825(5)	0.0824(8)	685(83)	11(3)	35(8)	31(12)	−47(21)	−4(4)
C4	0.5301(27)	0.1042(7)	−0.0224(10)	472(79)	35(5)	53(10)	34(15)	−19(22)	−6(5)
C5	0.2134(29)	0.0751(7)	0.0802(12)	525(86)	27(4)	109(14)	−32(15)	−32(28)	−2(6)
C6	0.8395(22)	0.1511(5)	0.3450(8)	359(62)	8(2)	48(8)	−20(10)	0(18)	−2(4)
C7	0.7702(27)	0.1663(5)	0.4395(9)	635(82)	9(3)	62(10)	−6(12)	−1(22)	−2(4)
C8	0.9055(31)	0.2092(6)	0.5064(10)	957(**)	14(3)	50(10)	29(15)	−34(26)	−11(5)
C9	1.1150(29)	0.2354(5)	0.4772(10)	787(95)	6(3)	81(11)	−38(12)	−66(26)	−1(4)
C10	1.1792(26)	0.2199(6)	0.3843(11)	429(75)	17(3)	100(12)	−20(12)	−20(25)	7(5)
C11	1.0426(26)	0.1790(5)	0.3181(10)	479(69)	11(3)	70(10)	−9(11)	9(20)	−2(4)
C12	0.6775(23)	−0.0362(5)	0.4115(9)	369(62)	11(3)	47(8)	−17(10)	−23(18)	3(4)
C13	0.4764(22)	−0.0657(5)	0.3445(9)	266(55)	9(2)	54(8)	−7(9)	−8(17)	1(4)
C14	0.2587(21)	−0.0398(5)	0.3085(9)	203(52)	14(3)	68(9)	0(10)	19(18)	−2(4)
C15	0.0710(23)	−0.0703(5)	0.2474(10)	284(64)	18(3)	75(10)	1(11)	−43(21)	1(5)
C16	0.1049(25)	−0.1333(6)	0.2253(10)	341(66)	20(3)	74(10)	−25(12)	3(21)	5(5)
C17	0.3186(26)	−0.1605(5)	0.2619(10)	581(77)	10(3)	73(10)	−37(12)	28(23)	−3(4)
C18	0.5145(24)	−0.1297(5)	0.3220(10)	326(63)	13(3)	65(9)	3(11)	−12(19)	6(4)

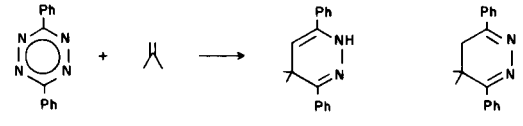
[a] Anisotropic temperature factors of the form EXP—[$\beta(11)h^2 + \beta(22)k^2 + \beta(33)l^2 + 2\beta(12)hk + 2S(13)hl + 2\beta(23)kl$]

Table IB

Calculated Hydrogen Positions

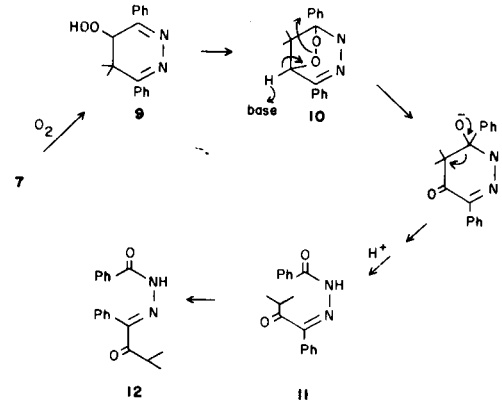
Atom [a]	X	Y	Z	β
HN2	0.9250(0)	0.0380(0)	0.4400(0)	5.8(0)
HC3	0.5642(0)	0.0406(0)	0.0997(0)	3.5(0)
HC4.1	0.7072(0)	0.1037(0)	−0.0246(0)	7.0 (0)
HC4.2	0.4431(0)	0.0758(0)	−0.0791(0)	7.0(0)
HC4.3	0.4648(0)	0.1480(0)	−0.0352(0)	7.0(0)
HC5.1	0.1480(0)	0..0419(0)	0.0288(0)	7.0(0)
HC5.2	0.1306(0)	0.1162(0)	0.0593(0)	7.0(0)
HC5.3	0.1886(0)	0.0633(0)	0.1530(0)	7.0(0)
HC7	0.6157(0)	0.1475(0)	0.4613(0)	6.8(0)
HC8	0.8642(0)	0.2226(0)	0.5744(0)	6.8(0)
HC9	1.2161(0)	0.2652(0)	0.5260(0)	6.8(0)
HC10	1.3395(0)	0.2386(0)	0.3671(0)	6.8(0)
HC11	1.0550(0)	0.1770(0)	0.2430(0)	6.8(0)
HC14	0.2140(0)	0.0000(0)	0.3400(0)	6.8(0)
HC15	−0.0923(0)	−0.0484(0)	0.2189(0)	6.8(0)
HC16	−0.0337(0)	−0.1589(0)	0.1848(0)	6.8(0)
HC17	0.3394(0)	−0.2059(0)	0.2448(0)	6.8(0)
HC18	0.6750(0)	−0.1518(0)	0.3483(0)	6.8(0)

[a] Identifying number refers to atom to which the hydrogen is bonded.



7 8

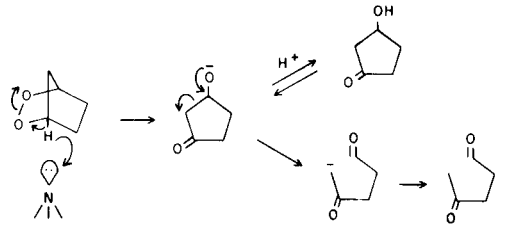
The reaction between **7** and oxygen was found to be rapid but neither hydroperoxide **9** nor endoperoxide **10** was obtained. These compounds are however, assumed to be intermediates in the pathway leading to the isolated product **12**, the structure of which was determined by single crystal x-ray diffraction and is displayed in Figure 2. It should be noted that the stereochemistry of **12** is not that expected from a simple ring opening of endo peroxide **10**. The existence of the intermediate **11** has not been



rigorously established but can be implied from nmr evidence. In the reaction between **7** and oxygen the doublet due to the isopropyl group in the product appears initially centered at δ 1.08. However, after isolation and recrystallization the doublet shifts to δ 1.21. The stereochemical change is accomplished simply by inversion of the imino nitrogen.

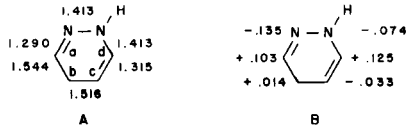
The base which catalyzes the opening of the endoperoxide **10** might be the dihydropyridazine itself. There is pre-

cedent for the amine catalyzed opening of endoperoxides to give products similar to **12**. Zagorski and Salomon [24] found that the amine catalyzed opening of 3,3-dioxabicyclo[2.2.1]heptane gives products best explained by the reaction scheme shown below.



It was thought that 3,4,4,5,5,6-hexamethyl 4,5-dihydropyridazine **13** might be stable to oxygen because it cannot form a 1,4-dihydro tautomer. However, **13** does undergo decompositon upon exposure to oxygen and forms small amounts of an unidentified crystalline product (mp ~ 70%). The reaction with oxygen may well occur *via* an exocyclic tautomer **14**, just as a similar intermediate **16** might be involved in the dimerization of diazanorcaradiene **15** [25]. Also, it may be noted that the analogous 3,6-diphenyl-4,4,5,5-tetramethyl-4,5-dihydropyridazine is stable to oxygen. In addition dihydropyridazines substituted in the 3 and 6 positions by alkoxy or dialkylamino groups are much more stable towards oxidation than the compounds studied in this work [26].

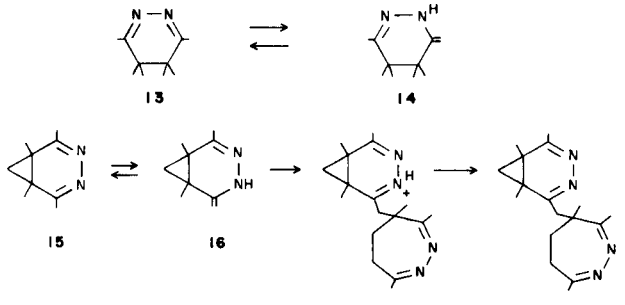
Figure 1.
A) Gaussian 70 geometry for 1,4-dihydropyridazine at the STO-3G level. Distances are in angstroms and the molecule is planar.
B) Net atomic charges ("condensed" to "heavy" atoms*) at the STO-6G level.



A B

$<a = 126.6°$
$<b = 110.6°$
$<c = 131.3°$
$<d = 121.7°$

*The atomic charges on the hydrogen atoms were summed into charges on the carbon or nitrogen atom to which they are bonded.



13 14 15 16

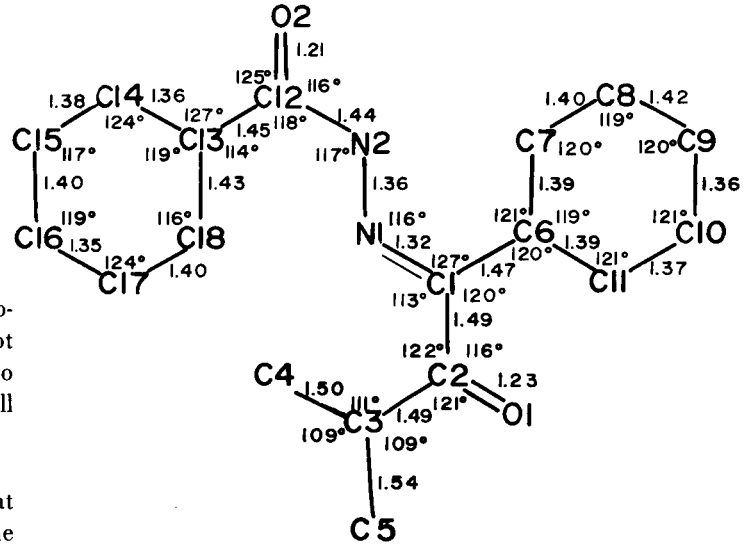


Figure 2. Bond lengths and bond angles from the x-ray structure of **12**.

EXPERIMENTAL

The molecular orbital calculations were performed on the University of New Orleans DEC system 10 computer. A complete geometry optimization was performed on 1,4-dihydropyridazine at the STO-3G level. The atomic charges were calculated at the STO-6G level.

X-Ray Structure of **12**.

Single crystals, cylindrical in shape, of usable dimensions were prepared by slow recrystallization from dichloromethane at −30°. A single crystal of diameter 0.15 mm and length 0.7 mm was chosen for analysis and cut to an appropriate length. Unfortunately, the poor quality of the crystals obtained affected the entire course of the data collection and resulted in a less than desirable ultimate refinement. However, the solution does provide an unambigous resolution of the molecular structure.

The symmetry of the unit cell was determined manually through polar plots of diffracted intensities with respect to the orientation axes of the diffractometer. The unit cell type was determined to be monoclinic by this method and systematically observed extinctions uniquely characterized the space group as $P2_1/c$. Accurate least squares lattice parameters were determined by careful measurement of 22 reflections all $>60°$ in 2θ, using CuKα radiation. Experimentally determined unit cell constants and their standard deviations are: a = 5.633(2) Å, b = 21.475(4) Å, c = 12.996(4) Å, β = 99.78(2).

Three dimensional intensities were collected within a sphere of enclosure bounded by a maximum 2θ of 140° yielding 2190 meausured reflections. Of these 984 (45%) were considered statistically significant based on the following criterion which was employed in the rejection of weak or unobserved data $[I_{Ni} - 2\sigma(I_{Ni})] - [I_{Co} + 2\sigma(I_{Co})] > N$. The sigmas are calculated solely on the basis of counting statistics and N is a constant for a given crystal. N, in turn, is established by the measurement of scattering intensity in the region of symmetry extinct reflections. The normal corrections were applied and the resultant intensities were then reduced to structure factor amplitudes in the usual manner.

The structure was solved by direct methods using the program FAZC [27]. The E-map from which the successful trial solution was obtained exhibited 21 peaks of reasonable structural geometry. Utilization of the coordinates obtained from the map in block diagonal least squares refinement with the full data set, arbitrarily assigning all atoms in the structure electronic scattering factors for carbon, converged to a value of R = 0.314. One additional atom was then observed on the subsequent Fourier electron density map and its coordinates appended to the original list. Atom type designation was then made on the basis of chemical information about the compound and interpretation of the defined isotropic thermal vibrational parameters. Incorporation of these modifications and subsequent isotropic least squares refinement led to a reduction in the reliablility factor to R = 0.174.

The various hydrogen atoms in the structure were located by difference Fourier synthesis or had positional coordinates calculated for them based upon the assumption of either trigonal or tetrahedral geometry. Full anisotropic refinement of all non-hydrogen atoms, fixing spatial and isotropic thermal vibrational parameters of all hydrogens converged to the final reliability factor of 0.094. The structure determination was terminated at this point. Observed shifts of atomic centers in the final cycles of refinement were less than 0.05 and examination of a difference Fourier electron density map revealed no peaks larger than 0.3e/Å.

Final refined atomic coordinates and temperature factors together with their estimated standard deviations (where appropriate) are listed in Table 1A for the non-hydrogens and Table 1B for the hydrogen atoms. A comparison of observed and calculated structure factor amplitudes are available as supplementary material. Estimated standard deviations are less than 0.02 Å for distances and 1° or less for all bond angles.

This compound dimerizes in the solid state as a result of the formation of complementary hydrogen bonds between the amide hydrogen in the structure and O2 in the adjacent molecule in the lattice to form a pseudocyclic structure in the unit cell.

Synthesis of 3,6-Diphenyl-1,4-dihydropyridazine (**3**).

The precursor to **3**, 1,4-diphenylbutane-1,4-dione, was prepared by the Friedel-Crafts acylation reaction between benzene and succinyl chloride in the presence of aluminum chloride. For instance, 10 g of aluminum chloride and 8.0 ml of succinyl chloride in benzene at 0° gave the diketone in 23% yield. This was converted to 3,6-diphenyl-1,4-dihydropyridazine as follows. To 50 ml of 95% ethanol was added 660 mg (2.68 mmoles) of 1,4-diphenylbutane-1,4-dione and 0.2 ml (6.2 mmoles) of hydrazine. The reaction was refluxed under nitrogen for 12 hours, cooled to room temperature, and the ethanol removed *in vacuo*. This gave a yellow solid which was recrystallized (toluene/hexane) under nitrogen to give yellow crystals, mp 147-150° in a sealed capillary (320 mg, 1.37 mmoles, 51% yield); ir (potassium bromide pellet): 3425, 3360, 3065, 1500, 1470, 1455, 1370, 1345, 760 (vs) and 705 cm^{-1} (vs); nmr (deuteriochloroform): 2.71 (s, methylene protons in 4,5-dihydro tautomer), 3.39 (d, methylene protons in 1,4-dihydro tautomer), 4.99 (m, vinylic protons of 1,4-dihydro split by the methylene protons and the proton on nitrogen), 7.2-7.65 and 7.7-8.0 (m, aromatic protons for both tautomers) and 8.0 (broad, 1,4-dihydro nitrogen proton).

Dihydropyridazine **3** was further characterized by its oxidative conversion to 3,6-diphenylpyridazine, mp 221-223° (lit mp 221°) [28].

Synthesis of 3,5,6-Triphenyl-1,4-dihydropyridazine (**4**).

3,6-Diphenyl-*sym*-tetrazine [29] (1.00 g, 4.27 mmoles) and 4.0 ml (34.8 mmoles) of styrene were dissolved in 15 ml of benzene and heated under nitrogen in a pressure tube to 80° for 12 hours. Removal of the benzene *in vacuo* and recrystallization of the residue from toluene/hexane under nitrogen gave 0.26 g (0.83 mmole, 20% yield) of **4** as yellow crystals, mp 182-184° (lit mp 182-186°) [30]; ir (potassium bromide pellet): 3340, 3060, 1600, 1485, 785 (very strong), and 710 cm^{-1} (very strong); nmr (deuteriochloroform): 3.61 (s, 2H), 7.10 (s, 5H), 7.30 (s, on top of m), and 7.2-8.0 (m, 11 H).

Dihydropyridazine **4** was further characterized by its oxidative conversion to 3,4,6-triphenylpyridazine, mp 173-175° (lit mp 176-177.5°) [30].

Synthesis of the Dimer **5** of 3,6-Dimethyl-4,5-dihydropyridazine.

The dimer was synthesized by the method of Overberger, *et al.* [23b] mp 49-51° (lit mp 52-53°).

Synthesis of 4,4-Dimethyl-3,6-diphenyl-1,4-dihydropyridazine (**7**).

3,6-Diphenyl-*sym*-tetrazine [29] (320 mg, 1.37 mmoles) and 5 ml of isobutylene were dissolved in 40 ml of benzene and heated in a pressure tube under nitrogen at 75° for 12 hours. As the red color of the tetrazine was still present, the temporature was raised to 110° for 24 hours after which the reaction mixture was yellow. The removal of solvent left an orange solid wihich was recrystallized (toluene/hexane) under an argon flow yielding white crystals, mp 118.5-124°; ir (potassium bromide pellet): 3433, 3403, 3056, 2961, 1949, 1881, 1805, 1753, 1659 (impurity from oxygen addition), 1600, 1494, and 1451 cm^{-1}; nmr (deuteriochloroform): δ 1.26 (, 4,5- and 1,4-dihydro), 2.54 (s, 4,5-dihydro), 4.73 (d, 1,4-dihydro), 7.2-7.5 (m, 4,5- and 1,4-dihydro), and 8.0 (broad, 1,4-dihydro).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.44; H, 6.87; N, 10.68. Found: C, 82.35; H, 6.86; N, 10.61.

Reaction of **7** with Oxygen to Give the 1-Benzoylhydrazone of 1-Phenyl-3-methylbutane-1,2-dione (**12**).

Attempted recrystallization of **7** from hexane, ether/hexane, and finally 95% ethanol in the presence of atmospheric oxygen gave white needles of **12** mp 155-157°; ir (potassium bromide pellet): 3141, 3072, 2961, 1665, and 1568 cm^{-1}; nmr (deuteriochloroform): δ 1.21 (d, 6H), 3.91 (heptet, 1 H), 7.0-8.0 (m, 10 H) and 9.25 (broad, 1 H); ^{13} C nmr (deuteriochloroform): decoupled, 18.79, 34.27, 128.24, 128.43, 130.25, 132.21, 132.34, 202.96 and one week signal at 152. One carbon signal was not observed in the routine cmr scan; ms: Calcd. molecular weight, 294.5. The largest observed ion at ionization energies of 12, 20 and 70 eV was 223. This is due to cleavage of the nitrogen-nitrogen bond.

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.47; H, 6.12; N, 9.25. Found: C, 73.48; H, 6.06; N, 9.45.

The structure was determined by x-ray crystallography.

Synthesis of 3,4,4,5,5,6-Hexamethyl-4,5-dihydropyridazine (**13**).

3-Methyl-2-butanone was prepared *via* the sodium dichromate/sulfuric acid/water oxidation [31] of 3-methyl-2-butanol, which was prepared by the reaction between methylmagnesium iodide and isobutyraldehyde. 3-Methyl-2-butanone (96 g, 1.12 moles) and 20 ml (0.108 mole) of di-*t*-butyl peroxide were heated in a 1 liter Parr autoclave for 10 hours at 145°. Distillation of the resulting mixture gave 14.36 g (83.9 mmoles, 77% yield) of diketone, bp 85-89° (1 mm); ir (neat): 2960, 2920, 2860 and 1695 cm^{-1}; nmr (deuteriochloroform): δ 1.20 (s, 6 H), 2.16 (s, 3 H) [32].

In a glass pressure tube were placed 3.87 g (22.8 mmoles) of 3,3,4,4-tetramethylhexane-2,5-dione, 4 ml of 2-propanol, and 2 ml (62.5 mmoles) of hydrazine. After 20 hours at 140° the reaction was poured into water and extracted with ether (3 × 25 ml). The combined extracts were dried over magnesium sulfate, the ether removed, and the residue distilled, giving 2.5 g (15 mmoles, 66% yield) of **13**, bp 88° (1 mm). The product is an oil which crystallizes on standing under nitrogen at 0° to a solid, mp 30-34°; ir (carbon tetrachloride): 2970, 2910, 2865, 1595 and 1560 cm^{-1}; nmr (deuteriochloroform): 0.96 (s, 12 H) and 2.05 (s, 6 H).

The product was further characterized as the *p*-toluenesulfonyl derivative of its tetrahydro sodium borohydride reduction product.

Anal. Calcd. for $C_{17}H_{26}N_2O_2S$: C, 63.31; H, 8.14; N, 8.69. Found: C, 63.20; H, 7.94; N, 8.55.

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