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Identification of the So-called[2] Triacetonehydroxylamine as Hexahydro-3,3,7,7-tetramethyl-1,2-oxazepine-5-one.

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For work in progress in our laboratory, a supply of 1-hydroxy-2,2,6,6-tetramethyl-4-piperidone (1) was required. A compound, $C_9H_{17}NO_2$, mp. 50-51°, formulated as 1, has been prepared in 1897 by Harries and Lehmann,[1] in 10% yield, through reaction of phorone (2) with hydroxylamine in methanolic sodium methoxide. We readily obtained this compound by the published procedure in 14% yield; it had the expected molecular weight (171, mass spec.) and showed the melting point given by Harries and Lehmann, as did its hydriodide and benzoyl derivative. However, the substance does not have the structure assigned to it. It can not be a hydroxylamine, since we find that it does not reduce Tollens' reagent at room temperature (contrary to a statement in the literature[2]) and that it is not oxidized to the nitroxyl (3) by silver oxide in ether. Furthermore, the NMR spectrum is quite incompatible with a symmetrical structure such as 1. This spectrum (which will be discussed in more detail below) at room temperature shows signals (singlets, 3H) from four different quaternary methyl groups and two AB systems ascribable to the protons of two different methylene groups.

Authentic 1, mp. 90-91°, has actually been prepared through reduction of 3 with phenylhydrazine by Rosantzeff and Golubev[3] who, however, did not comment on the fact that their substance is different from the one of Harries and Lehmann.[1] We have found that this compound gives a positive Tollens test at room temperature; it is re-oxidized to 3 by silver oxide in ether.[4]

A non-symmetrical structure isomeric with 1 and not containing the group $\rangle$N-OH could result from a double Michael-type addition of the OH and NH of hydroxylamine across the double bonds of 2 to give hexahydro-3,3,7,7-tetramethyl-1,2-oxazepine-5-one (4). Formula 4 perfectly fits the available evidence. Bands at ν = 1705 and 950 cm^{-1} are consistent with the carbonyl and N-O [5] groups. The NMR spectrum at room temperature is complex, indicating a marked conformational preference. On heating to about 150°, it coalesces to the simpler

one expected for structure 4 if no conformation preference exists: 60 MHz, 150°, DMF-d_7, δ 1.12 (S, 6H), 1.19 (S, 6H), 2.43 (S, 2H) 2.63 (S, 2H) and 3.70 (S, 1H, broad). The spectrum at room temperature shows the following signals: 220 MHz, $DCCl_3$, δ, 1.09 (S, 3H), 1.17 (S, 3H), 1.20 (S, 3H), 1.30 (S, 3H), 2.24 d, d, 1H, J = 10.8, 1.17), 2.30 (d, d, 1H, J = 11.1, 1.7), 2.56 (d, 1H, J = 11.1), 3.13 (d, 1H, J = 10.8) and 4.80 (S, 1H, exchanges with D_2O). The assignments for the four non-equivalent methylene protons were confirmed by the satisfactory agreement between a computed curve and the observed one. The small splitting (J = 1.7 Hz) observed for two of the four methylene protons is likely to be due to long-range coupling through the carbonyl group[6] and implies that the spatial relationship of these two protons is close to pseudo-1,3-diequatorial. A detailed study of the conformation of 4 and certain of its derivatives is now in progress in our laboratory.

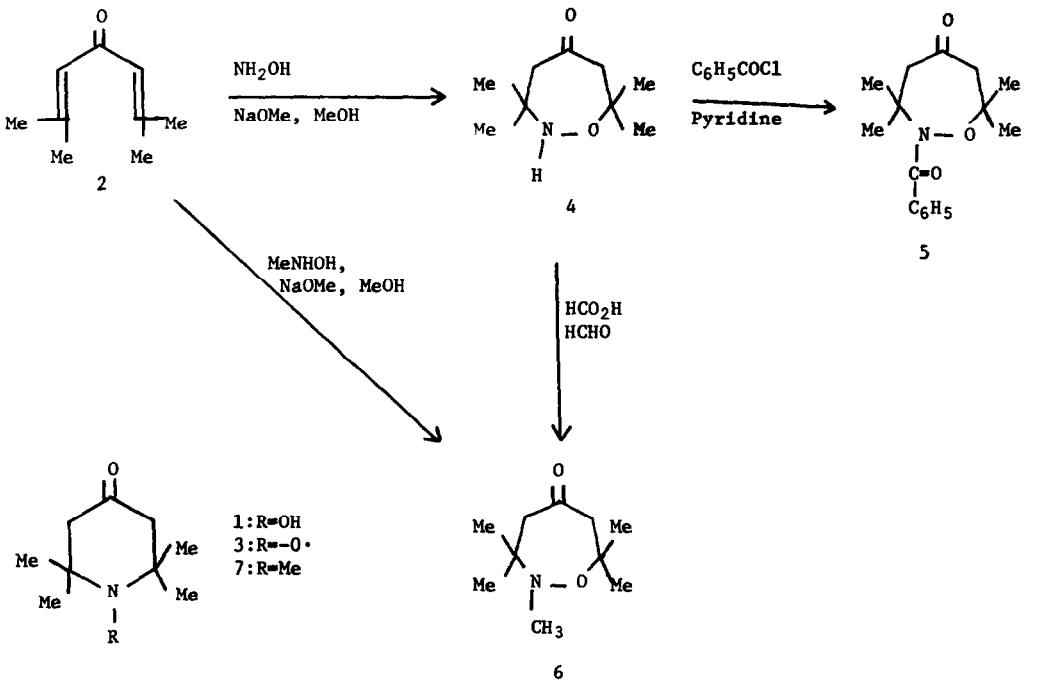
The benzoyl derivative (5) of 4, described by Harries and Lehmann,[1] is shown by its IR spectrum to be an amide, as expected: ν (C = O) 1720 cm^{-1}, ν (amide) 1645 cm^{-1}, ν (N - O) 910 cm^{-1}.[5] The NMR spectrum (220 MHz, $DCCl_3$) showed absorptions at 0.69 (S, 3H), 1.10 (S, 3H), 1.59 (S, 3H) 1.78 (S, 3H), 2.31 (d, 1H, J = 16.0), 2.34 (d, 1H, J = 15.0), 2.85 (d, 1H, J = 15.0), 3.16 (d, 1H, J = 16.0) 7.35 (m, 3H) and 7.65 δ (M, 2H).

Additional proof for structure 4 was obtained by preparation of the corresponding N-methyl derivative (6) (liquid, bp 92-94/9 mm) in low yield[7] (3%) through reaction of 2 and N-methylhydroxylamine in methanolic sodium methoxide. The compound was isolated by chromatography over silica gel, and characterized as the crystalline oxime,[8] mp. 100-102°, identical (mmp, IR, NMR, TLC) with a sample prepared from 4 by Clarke-Eschweiler methylation (75% yield) followed by oximation. Clearly, N-methylhydroxylamine on reaction with 2 could only give a hexahydro-1,2-oxazepine derivative and not a piperidone related to 1.

Since N-alkylated hexahydro-1,2-oxazepins and tetrahydro-1,2-oxazines have been obtained[9,10] by pyrolytic ring-enlargement of the N-oxides of N-alkylpiperidines and pyrrolidines, 1,2,2,6,6-pentamethyl-4-piperidone[11] (7) was treated with 30% hydrogen peroxide at room temperature. However, the expected N-oxide of 7 was not obtained, but 6, characterized as the crystalline oxime, was isolated from the complex reaction mixture by chromatography over silica gel.

Analogous hexahydro-1,2-oxazepine-5-ones should be generally obtainable through reaction of cross-conjugated ketones other than II with hydroxylamine or its N-substituted derivatives. The preparation of 6 from 4 should be capable of similar extension. These methods may thus

provide convenient entry into a little-known series of compounds so far accessible only through more involved reaction sequences.[9,10,12]



2 4 5 6

References and Footnotes

1. C. Harries and F. Lehmann, Ber., 30, 2736 (1897).
2. C. Harries and F. Lehmann, Ber., 30, 230 (1897).
3. E. G. Rozantsev and V. A. Golubev, Bull. Acad. Sci. USSR, Div. Chem. Sci., 1966, 852. [C.A., 65, 10559e (1966).]
4. E. G. Rozantsev and M. B. Neiman, Tetrahedron, 20, 131 (1964).
5. L. D. Quin and G. L. Roof, J. Org. Chem., 27, 4451 (1962).
6. N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, pp. 121-123.
7. The low yield in this reaction is not surprising in view of the multiple possibilities for interaction of the starting materials.

8. Correct analytical and spectroscopic data were obtained for the oxime.

9. L. D. Quin and F. A. Shelburn, J. Org. Chem., 30, 3135 (1965).

10. W. Carruthers and R. W. A. Johnstone, J. Chem. Soc., 1965, 1653.

11. W. B. Lutz, S. Lazarus, and R. I. Meltzer, J. Org. Chem., 27, 1695 (1962).

12. Hexahydro-1,2-oxazepine and its N-methyl derivative have been prepared through a multistep sequence in 12 and 10% overall yield, respectively. G. Pifferi and P. Consonni, J. Heterocyclic. Chem., 6, 111 (1969).