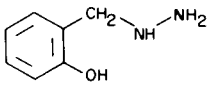
3,3a-Dihydro-2,3,3,3a-tetramethyl-9*H*-pyrazolo[3,2-*b*] [1,3] benzoxazine. A Novel Heterocyclic System Resulting from Intramolecular Alcohol-Enamine Addition

David T. Manning

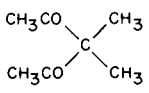
Research and Development Department, Union Carbide Corporation

Earlier in our study of heterocycles derived from 3,3-disubstituted 2,4-pentanediones we noted the formation of 3,3a,5,6-tetrahydropyrazolo[3,2-*b*]oxazoles by condensation of these diketones with 2-hydroxyethylhydrazines (1). Given this concept of an intramolecular enamine-alcohol cyclization, the possibility of preparing analogous systems with fused phenyl rings was apparent and seemed particularly attractive in view of the well-known pharmacological activity of such classes as the diuretic and vasoactive benzothiadiazines (2) and the benzodiazepine tranquilizers (3). Accordingly, preparation of the previously undescribed *o*-hydroxybenzylhydrazine (I) was undertaken. Sodium borohydride reduction of salicylaldehyde hydrazone afforded I which, however, could not be purified to the degree of conventionally-acceptable combustion analyses. Further confirmation of the structure of I was given by its NMR data and by a mass spectrogram which showed the parent mass along with an *o*-hydroxybenzyl ion resulting from loss of $NHNH_2$ as indicated by a definitive metastable 82.96 species. Condensation of I with 3,3-dimethyl-2,4-pentanedione (II) in refluxing butanol containing aqueous sodium hydroxide gave 3,3a-dihydro-2,3,3,3a-tetramethyl-9*H*-pyrazolo[3,2-*b*][1,3]-benzoxazine (III), representing a novel heterocyclic system, in 13% yield. Compound III, purified by column chromatography, gave confirmatory combustion and mass spectrometric data and its identify was further established by its simple NMR spectrum consisting of four sharp methyl singlets, an AB coupling pattern for the nonequivalent C-9 methylene protons and an ABCD phenyl multiplet. A strong infrared band at 9.4μ may be attributed to asymmetric C-O-C stretching in the central ring (4). Preliminary pharmacological evaluation of III by a modification of Irwin's method (5) revealed only mild, general CNS depressant properties.

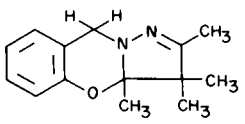


I

+



II



III

EXPERIMENTAL

Melting points are corrected. Mass spectrometric data for compound I were obtained with an AEI MS 902 spectrometer while data for III were obtained with a Bendix Model 14-101 time-of-flight instrument. NMR spectra were determined with a Varian HA-100 instrument employing TMS as the internal reference. 3,3-Dimethyl-2,4-pentanedione (II) was prepared by the method of Bloomfield (6).

Salicylaldehyde Hydrazone.

To a stirred solution of 165.0 g. (5.0 mole) of anhydrous hydrazine (97%) in 200 ml. of ethanol was added 122.1 g. (1.00 mole) of salicylaldehyde, dropwise, over a 1-hour period. The reaction solution was heated under reflux for 6 hours, cooled to room temperature and diluted with 180 ml. of water after which the mixture was concentrated to *ca.* 400 ml., causing a yellow solid to separate. The latter was collected and crystallized from ethanol giving 103.5 g. (76.0%) of salicylaldehyde hydrazone, m.p. 94-95.5° (reported (7) m.p. 96°).

o-Hydroxybenzylhydrazine (I).

A mixture of salicylaldehyde hydrazone (13.6 g., 1.0 mole), sodium borohydride (13.3 g., 0.3 mole) and 2-propanol (500 ml.) was refluxed with stirring for 6 hours under a dry nitrogen atmosphere. Solvent was removed under reduced pressure and the resulting residue then dissolved in water, adjusting the *p*H to 10 with hydrochloric acid. Continuous liquid-liquid extraction of the solution with chloroform gave 11.9 g. of an oil which was dissolved in 70 ml. of tetrahydrofuran. The solution was filtered and refrigerated at 0-5° for two days after which *o*-hydroxybenzylhydrazine (2.0 g., 14.5%) separated as a solid: m.p. 73-76°; NMR spectrum (deuteriochloroform), δ 3.98 (CH_2, singlet), δ 5.21 (4H exchangeable, singlet), δ 6.68-7.25 (C_6H_4, multiplet); infrared (potassium bromide), 3.0 (NH_2) 3.9, 5.5 (broad, H bonded OH), 6.22 (NH_2), 6.3 (phenyl unsaturated), 8.05 (phenyl OH), 13.2μ (*o*-disubstituted phenyl). The mass spectrum indicated the presence of impurities but verified the structure of I as follows; m/e 138 (parent), 107 (loss of $NHNH_2$) metastable 82.96 (loss of $NHNH_2$ from parent 138), 32 (NH_2NH_2).

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.32; N, 20.27. Found: C, 61.32; H, 7.05; N, 19.24.

3,3a-Dihydro-2,3,3,3a-tetramethyl-9*H*-pyrazolo[3,2-*b*][1,3]benzoxazine (III).

o-Hydroxybenzylhydrazine (8.28 g., 0.06 mole) and 3,3-dimethyl-2,4-pentanedione (8.22 g., 0.063 mole) were dissolved in 100 ml. of warm butanol and *ca.* 3 ml. of 6*N* sodium hydroxide added to bring the *p*H to 8.5. The mixture was then refluxed for *ca.* 6 hours and evaporated free of solvent under reduced pressure. The residue was taken up in ethyl ether, filtered to remove solids and the filtrate chromatographed on a 1" x 12" alumina column, giving an ether eluate from which 4.3 g. of oil was recovered by evaporation. A second alumina chromatography and ether elution gave 1.7 g. (13.1%) of III as a colorless syrup found, by tlc, to be essentially a single product; NMR spectrum (deuteriochloroform), δ 0.96 and 1.18 (CH_3-C-CH_3, two singlets), δ 1.35 (CH_3-CO, singlet), δ 1.75 (CH_3-C=N, singlet), δ 4.35 and 4.53 (-CH_2-, AB coupling pattern, J = 18), δ 6.55-7.20 (C_6H_4, multiplet); infrared (sodium chloride) 6.3, 6.4 (C=C, C=N), 7.8 (C-CH_3), 7.95, 8.1 (C-N, phenyl O?), 9.4 (C-O-C), 11.05, 11.6 (O-C-N?), 13.3μ (ortho disubstituted phenyl); mass spectrum m/e 230 (parent), 124 (3,4,4,5-tetramethyl-4*H*-pyrazole ion).

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.83; H, 8.03; N, 11.95.

Acknowledgement.

The author is indebted to C. B. Strow, Jr., and H. L. Joyce for the NMR and infrared studies performed and to B. E. Wilkes and H. R. Harless for the mass spectrometric data obtained.

REFERENCES

(1) David T. Manning and Harold A. Colemen, *J. Org. Chem.*, **34**, 2746 (1969).

(2) J. M. Sprague in "Molecular Modifications in Drug Design," Advances in Chemistry Series 45, American Chemical Society, Washington, D. C. 1964, Chapter 8.

(3) Leo H. Sternbach, L. O. Randall and S. R. Gustafson in "Psychopharmacological Agents," Vol. I, Maxwell Gordon, Ed., Academic Press, New York and London, 1964, Chapter 5.

(4) N. B. Colthrup, L. H. Daly and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York and London, 1964, page 272.

(5) S. Irwin in "Animal and Clinical Pharmacologic Techniques in Drug Evaluation," J. H. Nodine and P. E. Siegler, Ed., Year Book Medical Publishers, Inc., Chicago, Illinois, 1964.

(6) J. J. Bloomfield, *J. Org. Chem.*, **26**, 4112 (1961).

(7) T. Curtius and H. Franzen, *Ber.*, **35**, 3234 (1902).

Received September 29, 1969 South Charleston, West Virginia 25303