Investigations in Heterocycles. VII.[1] Oxazolin-2-ones

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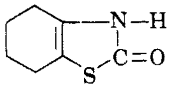
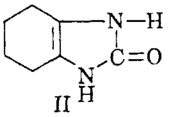
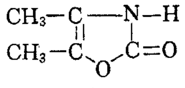
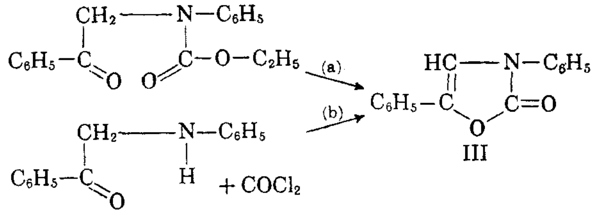
Previous papers[2] in this series have demonstrated that some thiazolin-2-ones [*e.g.*, 2,3,4,5,6,7-hexahydrobenzothiazolin-2-one (I) and various derivatives] exert a marked analgetic effect when tested in laboratory animals. In connection with this program, it appeared that a modification of the hetero atoms in this type of molecule would shed some light on the cause or causes of this pharmacological effect. Replacement of the sulfur for nitrogen leading to 4,5,6,7-tetrahydrobenzimidazolin-2-one (II)[3] did not offer any advantages over I.


I


II


IV

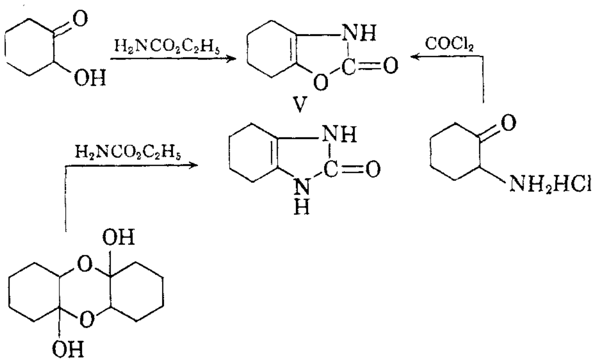
Another likely modification of this type of heterocycle was the exchange of sulfur for oxygen. At the time this investigation was begun, the only oxazolin-2-one reported[4] was 3,5-diphenyloxazolin-2-one (III) which was prepared from *N*-phenylphenacylurethan or from phenacylaniline and phosgene.

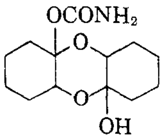


Thus, it appeared that the most direct routes to the synthesis of these compounds were (Synthesis a) through the urethan derivative of an α-hydroxyketone and (Synthesis b) treatment of an α-aminoketone with phosgene. Acetoin was thus treated with ethyl carbamate in boiling toluene. However, only a low yield of 4,5-dimethyloxazolin-2-one (IV) was obtained.

During the course of this investigation there appeared a report by Gompper[5] in which he outlined the preparation of several 4,5-disubstituted oxazolin-2-ones by this same method, although he employed dimethylformamide as a solvent. However, this preparation of IV was not described. We utilized the higher boiling solvent, dimethylformamide, in our acetoinethyl carbamate reaction leading to 75% conversion. Several 3-substituted derivatives of IV were prepared through alkylation of the sodium salt of the parent compound followed by condensation with an alkyl or aralkyl halide.

In the synthesis of the desired 2,3,4,5,6,7-hexahydrobenzoxazolin-2-one (V), several difficulties were encountered. α-Hydroxycyclohexanone, when freshly distilled exists indeed as a true monomer.[6] This was demonstrated by its strong infrared absorption bands at 3480 cm.$^{-1}$ and at 1715 cm.$^{-1}$ However, as outlined by Sheehan, this acyloin on standing for several hours dimerizes to a hemiacetal (m.p. 111–120°)[7] and exhibits very little absorption at 1715 cm.$^{-1}$ This point is emphasized since, in our hands, condensation of the monomer with ethyl carbamate gave only V as a product, whereas the dimer condenses with the ester to yield II plus an oil which analyzes for the carbamate of the dimer




VI

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(1) For part VI of this series see: G. deStevens, A. Halamandaris, and L. Dorfman, *J. Am. Chem. Soc.*, in press.

(2) (a) G. deStevens, H. A. Luts, J. A. Schneider, *J. Am. Chem. Soc.*. **79**, 1516 (1957); (b) G. deStevens, A. Frutchey, A. Halamandaris, H. A. Luts, *J. Am. Chem. Soc.*, **79**, 5263 (1957); (c) G. deStevens and A. Halamandaris, *J. Am. Chem. Soc.*, **79**, 5710 (1957); (d) G. deStevens, A. F. Hopkinson, M. A. Connolly, P. Oke, and D. C. Schroeder, *J. Am. Chem. Soc.*, **80**, 2201 (1958); (e) G. deStevens, A. Halamandaris, and H. A. Luts, *J. Org. Chem.*, **23**, 114 (1958).

(3) This compound, described in Part III (Ref. 2c) of this series, was prepared in 80% yield by isocyanation of 2-aminocyclohexanone hydrochloride.

(4) H. McCombie and H. A. Scarborough, *J. Chem. Soc.*, **103**, 56 (1913).

(5) R. Gompper, *Chem. Ber.*, **89**, 1762 (1956).

(6) J. C. Sheehan, R. C. O'Neill, and M. A. White, *J. Am. Chem. Soc.*, **72**, 3376 (1950).

(7) R. A. Raphael, *Chemistry of Carbon Compounds* Vol. IIa, Elsevier Publishing Co., Amsterdam, The Netherlands, 1953, p. 200.

(VI). As yet, the structure of VI is not fully elucidated.

Finally, the alternate approach through α-aminocyclohexanone hydrochloride and phosgene gave a small amount of product which was identical with V in all chemical and physical properties.

2,3,4,5,6,7-Hexahydrobenzoxazolin-2-one (V) was tested for analgesia according to the rat-tail burn technique. It was found to be comparable to I in activity. Subcutaneous doses of 50 mg./kg. in mice produced analgesic action of the same order as pyramidon. However, V was found to be more toxic than I. Further work in this series is underway.

EXPERIMENTAL[8]

4,5-Dimethyloxazolin-2-one (IV). A mixture of 44 g. (0.5 mole) of acetoin, 125 g. (1.5 moles) of ethyl carbamate, and 250 ml. of dimethylformamide was refluxed for 25 hr. after which time the solvent and the excess urethane were distilled off at the water pump. The residue was distilled *in vacuo* to give a 75% yield of a yellow oil, b.p. 125–130° (0.3 mm.); it solidified on standing, m.p. 108–111°. Two recrystallizations from ethyl alcohol:hexane (1:1) gave analytically pure substance, m.p. 112–113°.

Anal. Calcd. for $C_5H_7NO_2$: C, 53.09; H, 6.24, N, 12.37. Found: C, 53.23; H, 6.47; N, 12.32.

3,4,5-Trimethyloxazolin-2-one. A sodium methoxide solution was made by the addition of 0.23 g. (0.01 gram-atom) of sodium to 50 ml. of methyl alcohol. To this solution there was added 1.2 g. (.01 mole) of 4,5-dimethyl-oxazolin-2-one and the solution was heated at reflux for 15 min. An excess of methyl iodide (20 ml.) was added and heating was continued for 24 hr. The clear solution was evaporated to dryness *in vacuo* whereupon the light brown residue was extracted with anhydrous benzene. Removal of the benzene and distillation of the residue under vacuum gave rise to a 55% yield of product, b.p. 76° (0.12 mm.). The oil became crystalline on standing. It was washed with a small amount of ether to remove the yellow impurities and finally recrystallized from water as fine white needles, m.p. 62°.

Anal. Calcd. for $C_6H_9NO_2$: C, 56.70; H, 7.13. Found: C, 56.76; H, 6.90.

3-Benzyl-4,5-dimethyloxazalin-2-one. Six grams (0.53 moles) of IV was added to a solution of 1.24 g. of sodium dissolved in 200 ml. of isopropyl alcohol and the mixture was heated at reflux for 15 min. Benzyl chloride (6.7 g.) was added and heating was continued for 16 hr. After chilling, the sodium chloride was collected on a filter, the alcohol was stripped from the filtrate and the residue distilled, b.p. 140° (0.06 mm.). One recrystallization from benzene, gave 3.2 g. of pure material, m.p. 90–91°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.20; H, 6.41; N, 6.96.

3-(p-Acetamidophenoxyethyl)-4,5-dimethyloxazolin-2-one. This compound was prepared in the same manner as the previous example. After recrystallization from benzene stubby crystals of pure substance was obtained, m.p. 150–151°.

Anal. Calcd. for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.20; N, 9.65. Found: C, 62.08; H, 6.25; N, 9.66.

3-(3-Dimethylaminopropyl)-4,5-dimethyloxazolin-2-one hydrochloride. Compound IV (6.8 g.; 0.06 mole) was added to a solution of 1.38 g. of sodium dissolved in 200 ml. of isopropyl alcohol. After a 10 minute reflux period, a molar equivalent of 3-dimethylaminopropyl chloride was added and heating at reflux was continued for 24 hr. The alcohol was removed at reduced pressure and the residue was extracted with 10% hydrochloric acid. The aqueous acid extract was made slightly alkaline with 10% sodium hydroxide solution, and extracted with ether. After drying the ether extract over anhydrous potassium carbonate, it was filtered and dry hydrogen chloride was added to the extract. The resulting white flocculent precipitate was recrystallized from ethyl alcohol to yield analytically pure material, m.p. 222–223°.

Anal. Calcd. for $C_{10}H_{19}ClN_2O_2$: Cl, 15.10. Found: Cl, 15.11.

3-(2-Piperidinoethyl)-4,5-dimethyloxazolin-2-one hydrochloride was prepared as in the previous example. The melting point of this substance after two recrystallizations from ethyl alcohol was 226°.

Anal. Calcd. for $C_{12}H_{21}ClNO_2$: Cl, 13.60. Found: Cl, 13.69.

The *methiodide* of the free base was prepared by treating an ether solution of the free base with methyl iodide and allowing it to stand at room temperature for three days. After recrystallization from ethyl alcohol, the product melted at 216–218° dec.

Anal. Calcd. for $C_{12}H_{23}IN_2O_2$: I, 34.74. Found: I, 34.66.

3-Acetyl-4,5-dimethyloxazolin-2-one. A mixture of 0.5 g. of IV and 6 ml. of acetic anhydride was heated at reflux for 3 hr. After removal of the anhydride, the residue was distilled over at 67–69° (0.08 mm.) and solidified on standing, m.p. 45–50°. The material was recrystallized from water, m.p. 50°.

Anal. Calcd. for $C_7H_9NO_5$: N, 9.03. Found: N, 8.70.

2,3,4,5,6,7-Hexahydrobenzoxazolin-2-one. (V). Seventeen grams (0.15 mole) of freshly distilled α-hydroxcyclohexanone, 32 g. (0.36 mole) of ethyl carbamate, 350 ml. of dimethylformamide, and one ml. of pyridine were heated at reflux temperature for 20 hr. The solvent and the excess ethylcarbamate were then removed at the water pump and the residue distilled *in vacuo*. A yellow oil was collected at 160° (0.6 mm.). This was taken up in 2 ml. of ethyl alcohol followed by 2 ml. of hexane. Upon the addition of 2 ml. of ether, crystals were formed. After chilling overnight the crystals were collected on a filter and washed with a small amount of ether. After two recrystallizations from ethyl alcohol:ether (1:1), pure compound, m.p. 130–131°, was obtained.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.11. Found: C, 60.37; H, 6.54; N, 10.22.

Employing identical reaction conditions but using the dimer of α-hydroxycyclohexanone (m.p. 111–120°) resulted in 90% formation of 4,5,6,7-tetrahydrobenzimidazolin-2-one, (II), m.p. 340°. (See ref. 2e), and a small amount of yellow oil, b.p. 94° (0.1 mm.) which may be the monocarbamate of the dimer.

Anal. Calcd. for $C_{13}H_{21}NO_5$: N, 5.14. Found: N, 5.16.

α-Aminocyclohexanone hydrochloride (14.8 g., 0.1 mole) in toluene was saturated with phosgene and then heated at reflux for 2 hr. The solution turned dark brown in color. It was chilled, filtered, and the filtrate was evaporated to dryness. The residue was worked up to give 0.5 g. of product, m.p. 129–130°. Mixture melting point with V (see above) gave no depression. The infrared absorption spectra of the two samples were superimposable.

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(8) All melting points reported herein are uncorrected.