of N,N′-dimethyl-N,N′-dinitrosoterrephthalamide) in 20 ml of methanol–ether (1:2). The reaction was allowed to stand for *ca.* 36 hr. Evaporation and purification through the hydrochloride (prepared with HCl in ethanol) gave **5h** in *ca.* 95% yield from both compounds.

4-Phenyl-1,2,3,4-tetrahydroisoquinolines. General Procedure.—Crude substituted N-benzylaminoacetaldehyde diethyl acetals[9,13] (**3**, 0.01 mol) were allowed to stand with 0.011 mol of the appropriate phenols in 20 ml of 6 *N* HCl at room temperature for 12–15 hr. The product (**7**) precipitated. Concentration of the reaction mixtures yielded additional amounts of product. They were combined and recrystallized from ethanol or ethanol–ether.

Registry No.—**5a**, 23230-67-3; **5b**, 23282-29-3; **5c**, 23230-68-4; **5d**, 23230-69-5; **5e**, 23230-70-8; **5f**, 23230-71-9; **5g**, 23230-72-0; **5h**, 23230-73-1; **7a**, 23230-74-2; **7b**, 23263-77-6; **7c**, 23263-78-7; **7d**, 23230-75-3; **7e**, 23230-76-4; **7f**, 23230-77-5; **7g**, 23230-78-6.

Rearrangement of a 2,3-Alkylene-2,3-dihydro-1,5-benzoxazepine into a 2-Substituted Benzoxazole

FRANCIS J. MCEVOY AND GEORGE R. ALLEN, JR.

Process and Preparations Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York 10965

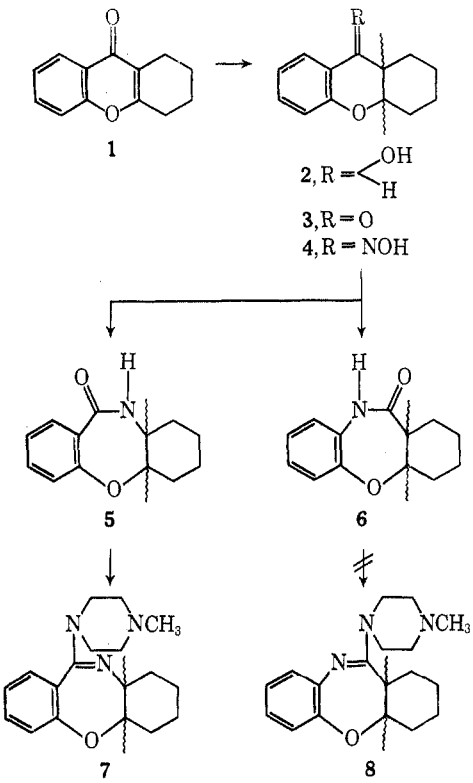
Received October 10, 1969

Discussion

Laboratory[1] studies have suggested that 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b,f*][1,4]oxazepine[1c,2] possesses potential psychotropic utility. In view of the interest of our laboratories in this agent,[1b–d] we undertook the preparation of partially saturated congeners of this compound. During this study we observed a facile rearrangement of a 2,3-alkylene-2,3-dihydro-1,5-benzoxazepine into a 2-substituted benzoxazole, which is the subject of this report.

1,2,3,4-Tetrahydroxanthone (**1**)[3] served as the starting material for this investigation (see Scheme I). Catalytic reduction of **1** gave the hexahydro alcohol **2**, which afforded ketone **3** on treatment with chromium trioxide–pyridine.[4] Beckmann rearrangement of the derived oxime **4** furnished a separable mixture of lactams **5** and **6**. Consonant with earlier studies,[5] lactam **6**, the product of aryl migration, predominated. Treatment of **5** with phosphorus oxychloride gave a chloroimidate, which reacted with 1-methylpiperazine to give 5a,6,7,8,9,9a-hexahydrodibenz[*b,f*][1,4]oxazepine (**7**).

SCHEME I



Application of this sequence to the isomeric lactam **6** failed to afford hexahydrodibenz[*b,f*][1,4]oxazepine (**8**); instead a product with composition $C_{13}H_{13}NO$ was isolated. This material appeared to result from a skeletal rearrangement in view of its distinctive ultraviolet spectrum (λ_{max} 265, 285, and 290 mμ). In contrast, the spectrum of **7** shows only weak end-absorption. The identity of the ring system present in the $C_{13}H_{13}NO$ substance was indicated by dehydrogenation in boiling decalin with palladium on carbon, which afforded the known 2-phenylbenzoxazole.[6] Although thermally induced rearrangement under the stringent conditions of dehydrogenation could not yet be eliminated from consideration, this observation suggested that the $C_{13}H_{13}NO$ substance was 2-(1-cyclohexenyl) benzoxazole (**11**). Thus the formation of **11** from the intermediate chloroimidate **9** could be interpreted as proceeding *via* a base-induced elimination to give phenoxide **10**, which then undergoes intramolecular displacement of chloride to afford **11** (see Scheme II). The well-known intermolecular reaction of phenoxides with chloroimidates constitutes ample precedent for this last stage.[7]

The 2-substituted benzoxazole **11** was synthesized independently by ring closure of anilide **12** with phosphorus pentachloride.[8] The identity of **11** prepared in this manner with the $C_{13}H_{13}NO$ product established the structure of the latter material and confirmed that base treatment of chloroimidate **9** results in rearrangement of the 2,3-dihydro-1,5-benzoxazepine system into a benzoxazole.

(1) (a) G. Stille, H. Lauener, E. Eichenberger, F. Hunziker, and J. Schmutz, *Arzneim.-Forsch.*, **15**, 841 (1965); (b) C. N. Latimer and L. C. Malone, *Fed. Proc.*, **27**, 438 (1968); (c) C. F. Howell, N. Q. Quinones, E. N. Greenblatt, A. C. Osterberg, and R. A. Hardy, Jr., Abstracts of Papers, 1st Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968; (d) C. N. Latimer, *J. Pharmacol. Exp. Ther.*, **166**, 151 (1969).

(2) J. Schmutz, F. Künzle, F. Hunziker, and R. Gauch, *Helv. Chim. Acta*, **50**, 245 (1967).

(3) Prepared by the procedure of L. A. Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).

(4) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

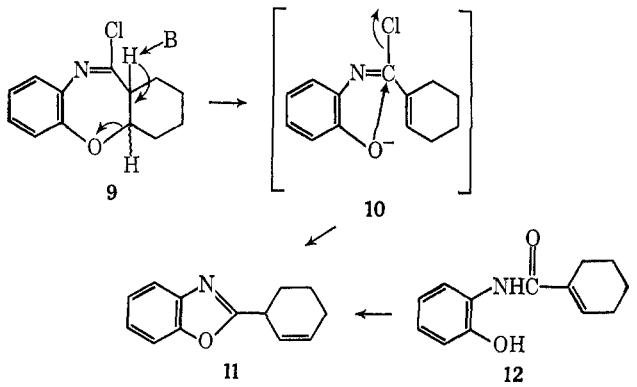
(5) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 17 (1960).

(6) H. L. Wheeler, *Amer. Chem. J.*, **17**, 400 (1895).

(7) J. W. Schulenberg and S. Archer, *Org. React.*, **15**, 38 (1965).

(8) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 420.

SCHEME II



Experimental Section

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined in potassium bromide discs on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were measured with a Cary recording spectrophotometer. Nmr spectra were determined in the indicated solvent on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectrum was determined on an AEI MS-9 spectrometer. All evaporations were carried out at reduced pressure.

1,2,3,4,4a,9a-Hexahydro-9-xanthenol (2).—To a solution of 10.3 g of 1,2,3,4-tetrahydroxanthone (1)[3] in 150 ml of absolute ethanol was added 20 g of wet commercial Raney nickel catalyst.[9] The mixture was shaken under hydrogen for 2 hr, during which time 2 equiv of hydrogen were absorbed and crystals separated from solution. The mixture was filtered through diatomaceous earth and the filter cake was washed with 100 ml of acetone. The combined filtrate and washes were evaporated and the residue was crystallized from acetone–hexane, affording in two crops 7.4 g of white needles, mp 161–165°. A similar preparation, twice recrystallized from acetone–hexane, melted at 165–167°, ν 3350 and 3290 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.67; H, 8.24.

1,2,3,4,4a,9a-Hexahydro-9-xanthone (3).—To a stirred, ice-cooled slurry of 1.0 g of chromium trioxide in 10 ml of pyridine was added a solution of 500 mg of 1,2,3,4,4a,9a-hexahydro-9-xanthenol (2) in 2 ml of pyridine. The mixture was stirred at 25° for 18 hr and then poured into 100 ml of water. The aqueous solution was extracted with ethyl acetate, and this extract was washed with water and dried with magnesium sulfate and the solvent was removed to give 480 mg of pale yellow oil which absorbed at 1680 cm^{-1} in its infrared spectrum. This material was utilized for preparation of the oxime without further purification.

1,2,3,4,4a,9a-Hexahydro-9-xanthenone Oxime (4).—A solution of 480 mg (2.38 mmol) of 1,2,3,4,4a,9a-hexahydro-9-xanthenone (3) and 480 mg (6.9 mmol) of hydroxylamine hydrochloride in 5 ml of pyridine was heated at reflux temperature for 18 hr. The mixture was cooled and poured into 50 ml of water. The resulting gum was rubbed to a solid and collected to afford 380 mg of oxime: mp 164–166° (two recrystallizations from methanol–water raised the melting point to 165–167°); λ_{max} 254 mμ (ϵ 9765), 305 (5425), and 317 (4665); ν 3250, 992, 968, and 948 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.17; H, 7.12; N, 6.71.

Beckmann Rearrangement of Oxime 4.—A suspension of 3.75 g (17.3 mmol) of 1,2,3,4,4a,9a-hexahydro-9-xanthenone oxime (4) in 60 g of polyphosphoric acid was placed in an oil bath preheated to 135° and stirred with a glass rod until solution was complete (*ca.* 5 min). The heating was continued for an additional 15 min. The reaction mixture was cooled, and 200 ml of water was added slowly with stirring and cooling. The resulting mixture of lactams was collected as 3.40 g of tan crystals, mp 117–120°. The lactams were separated by chromatography on 60–100 mesh magnesia–silica adsorbent. Elution with 1.5% acetone–methylene chloride and crystallization from acetone–water afforded 2.02 g of **1,2,3,4,4a,11a-hexahydrodibenz[*b*,*f*]-[1,4]oxazepine-11(10H)-one (6)**, mp 149–150°. A similar preparation gave the following data: λ_{max} 244 mμ (ϵ 9114) and 275 (2821); ν 3180 and 1675 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.64; H, 6.66; N, 6.68.

Elution was continued with 5% acetone–methylene chloride to give a mixture of the lactams, as determined by thin layer chromatography; *ca.* 80 mg of mixture was eluted. The column was then washed with 30% acetone–methylene chloride to afford 0.97 g of 5a,6,7,8,9,9a-hexahydrodibenz[*b*,*f*][1,4]oxazepine-11-(10H)-one (5). Crystallization from acetone–hexane gave shiny plates, mp 196–198°. A similar preparation gave the following data: λ_{max} 225 mμ (ϵ 8140) and 282 (1410); ν 3175 and 1660 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.84; H, 6.56; N, 6.68.

5a,6,7,8,9,9a-Hexahydro-11-(4-methyl-1-piperazinyl)dibenz-[*b*,*f*][1,4]oxazepine (7).—To a solution of 280 mg (1.29 mmol) of 5a,6,7,8,9,9a-hexahydrodibenz[*b*,*f*][1,4]oxazepin-11(10H)one (5) in 10 ml of benzene was added 300 mg (1.44 mmol) of phosphorus pentachloride. The solution was heated at reflux temperature for 2 hr and then evaporated. The residual gum was dissolved in 5 ml of N-methylpiperazine and the solution was heated at reflux for 2 hr. The cooled solution was diluted with water and extracted with ethyl acetate. The organic solution was extracted with three 15-ml portions of 1 *N* hydrochloric acid. The acid extract was washed with ethyl acetate and then made alkaline with 10% sodium hydroxide solution to give 220 mg of tan crystals: mp 114–116° (two recrystallizations from methanol–water raised the melting point to 117–119°); λ_{max} 233 mμ (ϵ 7775); ν 1608 and 1592 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.04. Found: C, 72.61; H, 8.74; N, 14.26.

2-(1-Cyclohexenyl)benzoxazole (11). A.—A suspension of 110 mg (0.53 mmol) of phosphorus pentachloride and 100 mg (0.46 mmol) of 1,2,3,4,4a,11a-hexahydro[*b*,*f*][1,4]oxazepin-11(10H)-one (6) in 5 ml of dry benzene was stirred and heated at reflux temperature for 2 hr and then evaporated. The residual gum was dissolved in 5 ml of benzene, and a solution of 0.3 ml (*ca.* 3 mmol) of N-methylpiperazine in 2 ml of benzene was added. The solution was heated at reflux temperature for 90 min and then evaporated. The resultant gum was crystallized from acetone–water to give 30 mg of white crystals: mp 55–57°; λ_{max} 230 mμ (ϵ 7450), 265 (13,000), 285 (16,400), and 290 (17,400); ν 2525, 2840, 1640, 1535, 1450, 1240, and 747 cm^{-1}; mass spectrum *m/e* 199.

A similar preparation, recrystallized twice from acetone–water, melted at 62–63°.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.09; H, 6.86; N, 6.93.

B.—A solution of 300 mg (1.39 mmol) of 2′-hydroxy-1-cyclohexene-1-carboxanilide (12) and 0.30 ml (3.37 mmol) of phosphorus oxychloride in 7.5 ml of benzene was stirred at reflux temperature for 90 min and then evaporated. The residue was treated with 15 ml of ice–water and extracted with ethyl acetate. The extract was washed with 10 ml of 10% sodium hydroxide solution and water, dried with magnesium sulfate, and evaporated. The residue was dissolved in methylene chloride and passed through a magnesia–silica column. The product was collected by evaporation of the first five 50-ml fractions of eluate and crystallized from acetone–water to give 60 mg of white needles, mp 63–64°. Admixture with the previously described product from 1,2,3,4,4a,11a-hexahydrodibenz[*b*,*f*][1,4]-oxazepine-11(10H)-one showed no depression of melting point.

2-Phenylbenzoxazole.—A soluion of 50 mg (0.25 mmol) of 2-(1-cyclohexenyl)benzoxazole in 2 ml of decalin and 50 mg of 10% palladium on charcoal was stirred at reflux temperature for 18 hr. The cooled solution was diluted with methylene chloride, filtered, and evaporated. The residue was dissolved in a water–ethanol mixture and this solution was evaporated. This process was repeated and the residue was crystallized from acetone–water to give 7.5 mg of 2-phenylbenzoxazole, mp 100°. The identity of this material with an authentic specimen[6] was shown by mixture melting point and comparison of infrared spectra.

(9) Raney active nickel catalyst (No. 28) as supplied by W. R. Grace and Co.

2'-Hydroxy-1-cyclohexene-1-carboxanilide (12).—To a solution of 1.26 g (10 mmol) of 1-cyclohexenecarboxylic acid in 5 ml of benzene was added dropwise 0.87 ml (12 mmol) of thionyl chloride. The mixture was allowed to stand at room temperature for 1 hr, heated on the steam bath for 30 min, and evaporated. The evaporation was repeated several times with toluene, leaving the 1-cyclohexenecarboxylic acid chloride as an oil. The acid chloride was added dropwise to a stirred, ice-cooled solution of 545 mg (0.5 mmol) of *o*-aminophenol in 2 ml of pyridine. The solution was stirred at room temperature for 2 hr and then poured into 30 ml of ice–water. The resulting oil was rubbed to a solid, which was collected and washed successively with 1 *N* hydrochloric acid, water, and saturated sodium bicarbonate solution to afford 1.05 g of a brown solid. The solid was dissolved in 20 ml of 10% sodium hydroxide solution, treated with activated charcoal, and filtered. The filtrate was acidified with acetic acid to afford 700 mg of white solid, mp 158–160°. A sample of this material, twice recrystallized from acetone–hexane, melted at 163–164°: λ_{max} 215 mμ (ε 20,600), 256 (8250), and 292 (8470); ν 3400, 3030, 2670, 1665, 1630, 1615, 1590, and 1538 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.07; N, 6.35.

Registry No.—**2**, 23386-10-9; **4**, 23386-11-0; **5**, 23386-12-1; **6**, 23386-13-2; **7**, 23386-14-3; **11**, 23386-15-4; **12**, 23386-16-5.

Acknowledgment.—We wish to thank Mr. L. Brancone and his staff for the microanalyses and Mr. W. Fulmor and his associates for the spectral data.

Oxazoline Formation from N-Acylaziridines. Isolation of an Intermediate in an Octahydrophenanthrene System

WENDEL L. NELSON AND DUANE D. MILLER[1]

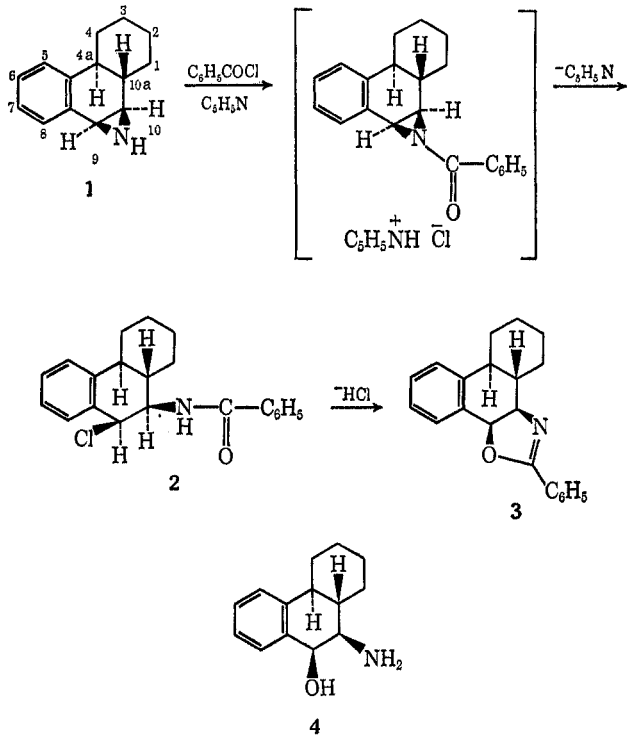
College of Pharmacy, University of Washington, Seattle, Washington 98105

Received July 22, 1969

Opening of styrylaziridines and -aziridinium ions has been shown to afford products characteristic of both carbonium ion and displacement mechanisms,[2-4] while the isomerization of N-acylaziridines to oxazolines has been reported to occur under the influences of nucleophilic catalysis or heat.[5] The latter process is thought to involve formation of an intermediate β-halobenzamide in which carbonyl oxygen displacement of the halide occurs.[6] We wish to report a case of opening of an N-acylaziridine capable of forming an intermediate carbonium ion which affords a *cis*-β-halobenzamide stereoselectively, and which is readily converted into the corresponding oxazoline, probably through a solvolytic process.

In a study of amino alcohols in the octahydrophenanthrene system, we attempted the N-benzoylation of *syn*-aziridine 1.[7,8] Aziridine **1** was prepared by the addition of iodoisocyanate (INCO) to 1,2,3,4,4a,10a-(*trans*-4a,10a)-hexahydrophenanthrene, followed by methanolysis, and aqueous potassium hydroxide treatment of the resulting β-iodocarbamate.

Attempted N-benzoylation of **1** with benzoyl chloride in pyridine at 60° afforded only small amounts of the oxazoline **3**. However, when the reaction was performed using a single equivalent of the acyl halide, and of the pyridine in ether, below 10°, an intermediate, 9(*a*)-chloro-10(*e*)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene[9] (**2**), was readily isolated.



1 2 3 4

Structural assignment of **2** is based primarily on infrared and nmr data.[10] The infrared spectrum showed an NH stretching band at 3330 cm^{-1} and amide I and II carbonyl bands at 1630 and 1520 cm^{-1}. The nmr spectrum (60 MHz) showed a broadened NH doublet at δ 6.65 for NH ($J_{10,NH}$ = 9 Hz), a doublet at 5.46 for H_9 ($J_{9,10}$ = 4 Hz) and a sextet at 4.67 for H_{10} ($J_{10,10a}$ = 9 Hz) (Figure 1). The nmr spectrum is consistent with the *cis* disposition of substituents.

When a chloroform solution of **2** was warmed at 75° for 10–20 min, formation of oxazoline **3** hydrochloride was noted by following the course of the reaction by observing the nmr spectrum of the reaction mixture (Figure 1). The nmr spectrum of **3** hydrochloride showed a doublet for H_9 at δ 6.18 ($J_{9,10}$ = 9 Hz) and a triplet for H_{10} at 4.52 ($J_{10,10a} \simeq$ 9 Hz), consistent with *cis*-oxazoline **3**. Cyclization of **2** was more readily accomplished in refluxing acetone in the presence of

(1) Public Health Service Predoctoral Fellowship 1-F1-GM-33,942, 1966–1969.

(2) (a) K. Kotera, M. Motomura, S. Miyazaki, T. Okada, and Y. Matsukawa, *Tetrahedron*, **24**, 1727 (1968); (b) K. Kotera, T. Okada, and S. Miyazaki, *ibid.*, **24**, 5677 (1968).

(3) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1385 (1963).

(4) (a) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963); (b) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, **84**, 4806 (1962).

(5) (a) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962); (b) H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967), and references cited therein; (c) H. W. Heine, D. C. King, and L. A. Portland, *ibid.*, **31**, 2662 (1966).

(6) P. E. Fanta and E. N. Walsh, *ibid.*, **30**, 3574 (1965).

(7) We have chosen to designate the epoxides and aziridines in this system as *syn* or *anti* to indicate the relative geometry of the heterocyclic three-membered ring and the hydrogen atom at C-10a.

(8) All materials are racemic, although only a single isomer is drawn.

(9) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (*e*) and axial (*a*) substituents at C-9 are in fact pseudo-equatorial and pseudoaxial, respectively.

(10) Elemental analysis does not distinguish between **2** and the hydrochloride salt of **3**.