[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Investigations in the Retene Field. XII. The Synthesis of 10-Phenanthr[2,3-b]-azepine Derivatives by the Beckmann Rearrangement of a Tetrahydrobenzoretene Ketoxime*

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Our original plan was to prepare a retopyridine by a Beckmann rearrangement of the 3′-methyl-2,3-cyclopentenoretene-1′-ketoxime, first described by Adelson and Bogert[1] as a 5,6-cyclopentenoretene derivative, but which has since been shown, by the work of Fieser and Clapp,[2] to be in all probability the 2,3-cyclopentenoretene isomer. But difficulties encountered in the synthesis of the desired oxime in sufficient quantities and, in particular, in the cyclization of the β-3-retylbutanoic acid to the requisite ketone, caused us to turn our attention, temporarily at least, to the more easily accessible oxime (I) of the ketotetrahydrobenzoretene, which latter was readily synthesized by the procedure of Adelson and Bogert,[1] with slight modifications, via β-3-retoylpropionic acid and γ-3-retylbutanoic acid.

The possibility that the oxime obtained might be a mixture of *syn* and *anti* forms caused us some concern at first, although in the case of the acetylphenanthrene oximes it has been shown that only small amounts of a second isomer are formed when the oximation is carried out by the method we used, and that this second isomer is removed in the crystallization.[3] On the other hand, in the case of certain phenyl diphenyl oximes, repeated fractional crystallization proved necessary to separate the two isomers.[4]

Ray and Rieveschl[5] separated 9-benzoylfluorenone oxime into two isomers; but Huntress and Moore[6] could isolate only one in the case of the oxime of 2-nitrofluorenone. Therefore, our oxime (I) was first examined microscopically under a powerful lens, then fractionally recrystallized, and its picrate prepared, and in no case was there any evidence of the presence of an isomer. For further proof of its identity, the oxime was hydrolyzed back to the initial ketone, which was accomplished only with some difficulty and in poor yield, and a hydrochloride of the oxime was obtained by the action of hydrogen chloride upon its ether solution.

The Beckmann rearrangement of the oxime was attempted first with phosphorus pentachloride, in cold anhydrous ether or benzene solution, and a mixture of products resulted from which no pure compounds could be isolated. But when a benzene solution of the oxime was refluxed with phosphorus pentachloride, a white crystalline compound, $C_{22}H_{24}Cl_3N$, was obtained which proved to be an H_2Cl_2 addition compound of a chlorotrihydroazeporetene (II). When this product was hydrolyzed by 50% sulfuric acid, or dilute acetic acid, another white crystalline compound resulted, whose analysis indicated its formula to be $C_{22}H_{25}OCl_2N$, and its structure that of a ketotetrahydroazeporetene (III) to which two molecules of hydrogen chloride had been added. The lactam itself (III) was in turn converted into the trichloride (II) by the action of phosphorus pentachloride.

When the oxime (I) was treated with very dilute sulfuric acid, it was unaltered, but the concentrated acid decomposed it. With 50% sulfuric acid, however, a Beckmann rearrangement was achieved, through an unidentified S-containing intermediate, with formation of the expected lactam (III), which was hydrolyzed by concentrated hydrochloric acid to an aminoretylbutanoic acid (IV), which could be diazotized, thus establishing the constitution of the azepine ring in the lactam (III), as well as in the trichloride (II), and showing also the direction in which the rearrangement had taken place. If we accept the *trans* shift mechanism of Meisenheimer[7] postulated for the Beckmann rearrangement, the stereoconfiguration of the original oxime (I) follows.

The indications therefore are that the above dihydrochloro addition products are post-phases of the Beckmann reaction in which two molecules of hydrochloric acid have been added to the primary product. Attempts to remove or replace these chlorine atoms all failed to give identi-

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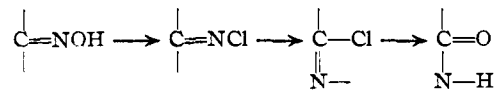
(1) Adelson and Bogert, THIS JOURNAL, **59**, 399 (1937).
(2) Fieser and Clapp, *ibid.*, **63**, 319 (1941).
(3) Bachmann and Boatner, *ibid.*, **58**, 2097 (1936).
(4) Bachmann and Barton, *J. Org. Chem.*, **3**, 300 (1938).
(5) Ray and Rieveschl, THIS JOURNAL, **60**, 2675 (1938).
(6) Huntress and Moore, *ibid.*, **49**, 2621 (1927).
(7) Meisenheimer, *Ber.*, **54**, 3206 (1921).

fiable products, presumably because of the instability of the azepine cycle.

As to the probable constitution of these di- and trichloro compounds, we think it likely that two mols of hydrochloric acid have attached themselves directly to the nucleus.

In support of this hypothesis, the lactam (III) contains an atom of oxygen, so that the two chlorine atoms present in its H_2Cl_2 addition product are not due to a replacement of oxygen by chlorine. Further, hydrochloric acid is always evolved in a Beckmann rearrangement with phosphorus pentachloride[8]; and a case is on record[9] in which two molecules of hydrochloric acid so liberated attached themselves to the benzene nucleus. Not many halogenated retenes have been described, and in most of them the location of the halogen is still unknown. They were prepared by the direct action of the free halogen, and we have been unable to chlorinate retene itself by the action of phosphorus pentachloride. Ekstrand[10] has reported a dichloro derivative which was convertible into a monochloro derivative. Komppa and Wahlforss[11] prepared a monochlororetene carrying its chlorine in either the 9 or 10 position.

Removal of a chlorine atom in the conversion of (II) into (III) recalls the hydrolysis observed by Huntress and Moore,[6] when they subjected their fluorenone oximes to a Beckmann rearrangement with phosphorus pentachloride, and formulated the mechanism of the reaction as follows



The S-containing intermediate, formed by the action of 50% sulfuric acid upon the oxime (I), can be explained on a similar basis, if we assume it to have consisted of a mixture of compounds possessing such linkages as $\begin{matrix}|\\C{=}NSO_3H\\|\end{matrix}$ and $\begin{matrix}|\\C{-}SO_3H\\\|\\N{-}\end{matrix}$, whose ready hydrolysis would account for the presence of traces of the lactam (III).

Stephen and Bleloch[8] have observed that amidines of the type RC(NHR)=NR are often found as products of the Beckmann reaction, and that they can be formed by the interaction of an imide chloride RCCl=NR and an amide dichloride, $RCCl_2NHR$. They suggested also that the latter two were post-phases of the Beckmann rearrangement. As (II) was obtained from the lactam (III), as well as from the oxime (I), it also probably represents a post-phase of the reaction. The trichloride (II) cannot be an amide dichloride hydrochloride, because it can be dissolved in acetic acid and reprecipitated by alkali unaltered. The assumption that during the rearrangement by phosphorus pentachloride the azepine cycle is opened, with formation of an acid chloride and an amino group on the retene nucleus, is untenable because the trichloride (II) contains no oxygen and forms no hydrochloride.

The production of these azepine, or ϵ-caprolactam, derivatives is of interest not only because of Wallach's synthesis of ϵ-caprolactams by the action of phosphorus pentachloride, or sulfuric acid, upon cyclohexanone oximes,[12] but also because ϵ-caprolactam is stated to be a nerve poison, and the free ϵ-aminocaproic acid is also known as ϵ-norleucine.

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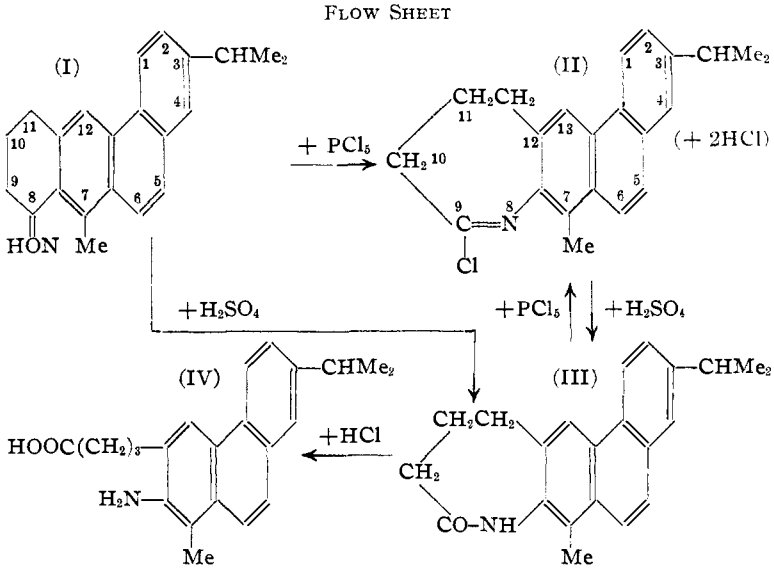

(8) Stephen and Bleloch, *J. Chem. Soc.*, 886 (1931).
(9) Beckmann and Liesche, *Ber.*, **56**, 1 (1923).
(10) Ekstrand, *Ann.*, **185**, 75 (1877).
(11) Komppa and Wahlforss, THIS JOURNAL, **52**, 5009 (1930).
(12) Wallach, (a) *Ann.*, **277**, 156 (1893); (b) **278**, 304 (1894); (c) **312**, 187, 197, 203 (1900); (d) **346**, 253 (1906).

National Academy of Sciences, for financial assistance in the purchase of the necessary retene; and to the Hooker Electrochemical Company of Niagara Falls, New York, for a generous supply of anhydrous aluminum chloride. We are indebted also to Mr. Saul Gottlieb of these laboratories, by whom the requisite analyses were conducted.

Experimental

3-Isopropyl-7-methyl-8-keto-8,9,10,11-tetrahydrobenz[a]anthracene.—β-Retoylpropionic acid, prepared from retene and succinic anhydride,[1] and melting not lower than 194–196°, was reduced by the Clemmensen method, and preferably in an all glass apparatus, to the γ-3-retylbutanoic acid yield, 10 g., from 25 g. of the retolylpropionic acid; m. p. 179–180° (cor.) (lit.[1] 179–179.5°, cor.).

The cyclization of the retylbutanoic acid was effected with fuming anhydrous stannic chloride, but our yields were not so good as those reported by Adelson and Bogert.[1] It was found necessary to heat the reaction flask to 110–115° and keep it there for two hours, in order to get 1.5 g. of the ketone from 5 g. of the initial acid. Unchanged initial acid was best recovered from the crude ketone by extraction with 500 cc. of a 2.5% solution of potassium hydroxide. The m. p. of the pure product was 139–140° (cor.) (lit.[1] 139.5–140°, cor.). Distillation of the stannic chloride just prior to use, proved of no advantage.

The filtered potassium hydroxide extract was acidified with dilute hydrochloric acid, filtered hot and air-dried. Crystallized twice from glacial acetic acid, 1 g. of unaltered initial retylbutanoic acid was recovered, sufficiently pure for direct cyclization.

Oxime (I).—The oximation was performed as described by Adelson and Bogert,[1] except that the time of refluxing was reduced 50%, and ordinary methyl alcohol was substituted for absolute methanol. By filtering the hot reaction mixture and diluting the filtrate with water, the major part of the oxime was precipitated. This crude oxime was collected and dried. The solid filtered out of the original hot reaction mixture was dried and extracted thrice with small portions of hot benzene. To these combined extracts, there was added a benzene solution of the oxime precipitated by dilution of the filtrate from the initial reaction mixture. As the solution cooled, the oxime separated in shining white plates, m. p. 200–202° (cor.), which m. p. was raised to 202.5–203.5° (cor.), by recrystallization from benzene (lit.,[1] m. p. 203–204°, cor.); yield, 93%.

Unchanged original ketone remained in the benzene solution. It was found also that pyridine could be substituted for barium carbonate in this reaction, as recommended by Bachmann and Boatner.[3]

In order to assure ourselves as to the *homogeneity* of our oxime, it was examined first under a strong magnifying glass, but only one form of crystals was visible. A sample, m. p. 202.5–203.5° cor., was then subjected to *fractional crystallization* from three different solvents, and three crops of crystals were collected from each. In every case the oxime was dissolved by heating, the solution was cooled slowly, the crystals filtered out, the mother-liquor concentrated, and the process repeated. The corrected melting points obtained in this procedure were as follows.

	Benzene	Toluene	95% Ethanol
Crop 1	202.5–203.5	202.5–203.5	203.5–204.5
2	202.5–203.5	202.5–203.5	202.5–203.5
3	202.5–203.5	202.5–203.5	202.5–203.5

There was, therefore, no evidence of the presence of any isomer or other contaminant.

Hydrolysis of the Oxime.—A mixture of 0.5 g. of the oxime with 8 cc. of concentrated hydrochloric acid was heated in a sealed tube for five hours at 100°. The mixture was then allowed to cool, the solid removed, dried, and crystallized four times from *n*-propyl alcohol. About 0.1 g. of product was secured, m. p. 139–140° (cor.), which m. p. remained unchanged when this compound was mixed with an authentic specimen of the initial ketone.

Hydrochloride.—A solution of 0.2 g. of the oxime in 10 cc. of anhydrous ether was subjected to a stream of dry hydrogen chloride for about a minute. A pale yellow granular precipitate separated almost immediately. It was removed, washed with three small portions of cold dry ether, and then appeared as a pale yellow solid, m. p. 185–188° (cor.), with decomposition; yield, 0.2 g.

Anal. Calcd. for $C_{22}H_{24}ClN$: C, 74.7; H, 6.5. Found: C, 75.0; H, 6.8.

Further treatment with hydrogen chloride did not affect this compound, but hydrolysis with dilute alkali liberated the initial oxime.

Picrate.—The picrate was prepared in absolute ethanol and was purified by three recrystallizations from the same solvent. It formed brilliant orange plumes, m. p. 206.5–207.5° (cor.); yield, about 0.15 g. of picrate from 0.1 g. of the oxime.

Anal. Calcd. for $C_{28}H_{26}N_4O_8$: C, 61.5; H, 4.8. Found: C, 61.7; H, 4.9.

The oxime was easily separated from the picric acid by passing a benzene solution of the former through a column of alumina.

9-Chloro-11,12-dihydro-3-isopropyl-7-methyl-10-phenanthr[2,3-*b*]azepine Dihydrochloro Addition Product (II, 2HCl).—To a solution of 2 g. of the oxime (I) in 40 cc. of hot anhydrous thiophene-free benzene, in a 3-necked flask equipped with reflux condenser and calcium chloride tube, 3 g. of pure (not necessarily freshly sublimed) phosphorus pentachloride was added in small portions, by means of a small flask connected by flexible rubber tubing with one of the necks of the reaction flask. After two hours of refluxing, the solvent was removed, the residue treated with cracked ice, and washed free of hydrochloric acid and phosphorus pentachloride by dilute alkali and water, by which time the crude product usually had solidified. Dried in the air and recrystallized thrice from glacial acetic acid, it formed shining white platelets, m. p. 215–216°, cor., with decomposition; yield, 1 g. It gave a positive Beilstein test for halogen, and decomposed slowly when left in the air.

Anal. Calcd. for $C_{22}H_{24}Cl_3N$: C, 64.5; H, 5.9; Cl, 26.1; N, 3.4. Found: C, 64.8; H, 5.6; Cl, 25.3; N, 3.2.

The lactam (III), described beyond, when subjected

to the same treatment with phosphorus pentachloride as recorded above for the oxime, gave exactly the same product (II), of identical m. p. and in similar yield. A mixture of the two trichlorides melted also at 215–216°, cor., with decomposition.

11,12-Dihydro-3-isopropyl-7-methyl-10-phenanthr[2,3-*b*]azepin-9(8)-one (III). *Dihydrochloro Addition Product.*—A mixture of 0.5 g. of the trichloride (II, 2HCl) with 30 cc. of 50% sulfuric acid was refluxed for two hours at 165–175°. Refluxing with 80% acetic acid for three hours, accomplished the same result. The mixture, when cooled and filtered, yielded a slimy brown solid and a pale yellow filtrate. This filtrate when diluted with water gave no additional precipitate, but did give a positive test for halogen ions. The solid material was air-dried, recrystallized thrice from glacial acetic acid and once from 95% ethanol. There resulted white crystals, m. p. 259–260° (cor.), with decomposition; yield, 0.2 g.

Anal. Calcd. for $C_{22}H_{25}OCl_3N$: C, 67.7; H, 6.4; Cl, 18.2; N, 3.6. Found: C, 67.3; H, 6.2; Cl, 18.0; N, 3.9.

Partial hydrolysis of the trichloride (II + 2HCl) to (III + 2HCl) occurred also when it was left in water for forty-eight hours, or was dissolved in acetic acid and precipitated hot with aqueous hydrochloric acid.

The dichloride (III + 2HCl) was unaffected by treatment with aqueous alkali and, when treated with alcoholic potassium hydroxide solution, with concentrated hydrochloric acid in a sealed tube, or with sodium and absolute alcohol, gave only tars, from which no pure compounds could be isolated. Nor could any quinone be prepared, as a clue to the location of the chlorine atoms.

Free Base (III).—In a 500-cc. flask, 3 g. of the oxime (I) was introduced carefully, so as not to adhere to the side walls. There was then added 150 cc. of well-cooled 50% sulfuric acid, avoiding any shaking of the flask, or some of the oxime would stick to the flask above the level of the acid. The mixture was heated for fifteen minutes at 165–175°, by which time a dark oily layer had formed. The cooled mixture was poured into ice water and, on stirring, the oil congealed to a yellow solid, which was removed, washed with water, dried, and finally washed with two portions of hot chloroform. The white solid (2.9 g.) so obtained was crystallized once from 95% ethanol and once from acetic acid, and then melted at 204–206° (cor.). Further crystallization resulted in a lower and more spreading m. p. Huntress and Moore[6] had a similar experience in their attempts to purify fluorenone oxime. In general, washing with hot chloroform after a crystallization caused a rise of 1° in m. p., and from these chloroform extracts some lactam (III) was isolated. This **intermediate product** (m. p. 204–206°, cor.), gave a qualitative test for sulfur, but no reproducible analytical figures. An attempt to purify it by picrate formation, gave a 30% yield of the lactam (III) picrate instead, due to its instability. The intermediate product was also partially hydrolyzed by standing in water for forty-eight hours.

A suspension of 2 g. of this sulfur-containing intermediate in 150 cc. of 80% acetic acid was refluxed for two hours. The resulting solution was cooled and poured into ice water. The white solid which separated, after coagulation by a few minutes of boiling, was collected, air-dried, and crystallized twice from Skelly Solvent D, using Norit. The product (III) formed white plates, m. p. 210–211° (cor.); yield, 1.2 g. Mixed with original oxime (I), the m. p. was 183–185° (cor.).

Anal. Calcd. for $C_{22}H_{23}NO$: C, 83.2; H, 7.3; N, 4.4. Found: C, 83.4; H, 7.5; N, 4.7.

Picrate.—Prepared in absolute ethanol solution and crystallized thrice from the same solvent, this picrate was obtained as a yellow powder, m. p. 235–236° (cor.); yield from 0.1 g. of the lactam (III), about 0.15 g.

Anal. Calcd. for $C_{28}H_{26}N_4O_8$: C, 61.5; H, 4.8. Found: C, 61.6; H, 4.8.

γ-(2-Aminoretyl-3)-butanoic Acid (IV).—A suspension of 0.5 g. of the lactam (III) in 10 cc. of concentrated hydrochloric acid was heated in a sealed tube for six hours at 100°. During the heating the suspended material turned first bright pink and then dull yellow. The solid filtered out from the cooled tube contents was washed with three 30 cc. portions of boiling Skelly Solve D. On concentration and cooling of these washings, about 0.2 g. of unchanged initial lactam (III) was recovered. The solid undissolved by the Skelly Solve treatment was warmed with a 10% ammonium hydroxide solution. An amorphous halogen-free product resulted, which proved difficult to purify. It was therefore dissolved in glacial acetic acid containing a few drops of hydrochloric acid and the solution cooled. The hydrochloride of the amino acid (IV) precipitated in glistening white flakes which, after a recrystallization from acetic acid, melted at 212–213° (cor.); yield, 0.2 g. This salt was moderately soluble in hot water, and freely soluble in dilute alkali.

Anal. Calcd. for $C_{22}H_{26}NO_2Cl$: C, 71.1; H, 7.0; N, 3.8. Found: C, 71.1; H, 7.1; N, 4.0.

To a solution of about 20 mg. of this hydrochloride in 95% ethanol, several drops of hydrochloric acid were added, followed by some crystals of sodium nitrite. After a few minutes, an excess of urea was added, the solution made alkaline, and some crystals of "H acid" dropped in. The solution assumed immediately a beautiful deep purple color.

Summary

1. 3-Isopropyl-7-methyl-8-keto-8,9,10,11-tetrahydrobenz[a]anthracene ketoxime suffers a normal Beckmann rearrangement under the influence of 50% sulfuric acid, with formation of a 10-phenanthr[2,3-*b*]azepine, the first representative of a new tetracyclic system.

2. With phosphorus pentachloride, the same ketoxime underwent a Beckmann rearrangement accompanied by the addition of two molecules of hydrogen chloride to the azepine produced.

3. The structure of the azepine noted in (1) was proved by its hydrolysis to an aminoretylbutanoic acid. The nitrogen of the azepine cycle is therefore in immediate union with the phenanthrene nucleus.

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