BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 1955—1958 (1969)

Reactions of Cycloalkanone Oxime *p*-Toluenesulfonates

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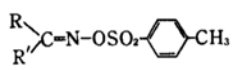
(Received September 24, 1968)

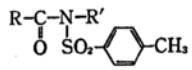
The reactions of cyclohexanone and cyclopentanone oxime *p*-toluenesulfonates were studied. It was found that cyclohexanone oxime *p*-toluenesulfonate (IIIa) afforded a tetrahydroazepine derivative (Va), while cyclopentanone oxime *p*-toluenesulfonate (X) afforded δ-valerolactam *p*-toluenesulfonate (XIII), when both compounds were heated in benzene.

The rearrangement of ketoxime *p*-toluenesulfonates (I) into *N*-*p*-toluenesulfonamides (II) has been known as one type of Beckmann rearrangement and has been extensively studied. The rearrangements of cyclohexanone and cyclopentanone oxime *p*-toluenesulfonates have been reported by Heldt[1] and by Grob *et al.*[2] Cyclohexanone oxime *p*-toluenesulfonate (IIIa) is thermally unstable and defragnates at room temperature, particularly when its purity is not high. In connection with our studies of pyrolysis, we carried out reactions with these compounds and obtained results different from those reported.

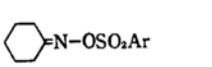
Heldt reported that when IIIa was left standing in dry chloroform at 25°C for one year, it yielded a compound (named Compound A)to which the structure IV could be assigned. He showed that Compound A melted at 124.6—125°C, and had strong bands at 1710 and 1640 cm^{-1} in its infrared spectrum.



I

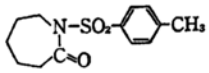


II



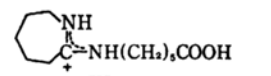
IIIa: Ar=H_3C-

b: Ar=

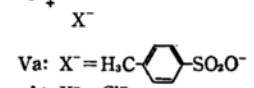


IV

We refluxed IIIa in dry benzene for 3 hr, and obtained in a 54% yield a compound (named Compound B) which showed characteristics similar to those of Compound A.*1 Compound B melted at 124°C and had strong bands at 1720 and 1640 cm^{-1} in its infrared spectrum. However, Compound B was confirmed to be 6-(3,4,5,6-tetrahydro-2*H*-azepin-7-ylamino)-hexanoic acid *p*-toluenesulfonate (Va) by the following evidence. The *p*-toluenesulfonyl moiety was assumed to be combined with the tetrahydroazepine moiety through salt-type linkage, not through sulfonamide-type linkage as is the case for the structure IV, because *p*-toluenesulfonic acid was immediately isolated as an addition compound with 2,4-dinitrophenylhydrazine (DNPH), upon the addition of a DNPH reagent[3] to Compound B. When Compound B was dissolved in 18% hydrochloric acid and the solution was concentrated *in vacuo* at room temperature, hydrochloride Vb crystallized out. Vb showed infrared bands at 1720 and 1640 cm^{-1} and had a pK_a value of 4.45. Furthermore, Vb was identical with the authentic sample prepared from ε-caprolactam and phosgene.[4] From the reaction



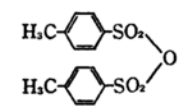
X



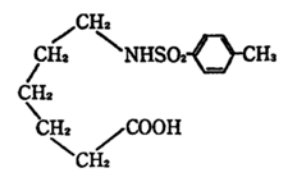
Va: X^-=H_3C-

b: X^-=Cl^-

c: X^-=



VI



VII

1) W. Z. Heldt, *J. Am. Chem. Soc.*, **80**, 5880 (1958).

2) C. A. Grob, H. P. Fischer, W. Raudenbusch and J. Zergenyi, *Helv. Chim. Acta*, **47**, 1003 (1964).

*1 The identity of Compounds A and B was not established because neither Compound A nor its complete spectrum was available. The differences in elemental analyses between the two compounds were: C, 0.01—0.73; H, −0.02—0.07; N, 0.50—0.52%.

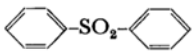
3) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, New York, N. Y. (1956), p. 219.

4) H. R. Meyer, *Kunststoffe-Plastics*, **3**, 160 (1956); *Chem. Abstr.*, **52**, 11781f (1958).

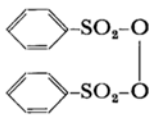
mixture of IIIa in benzene we isolated as by-products ε-caprolactam, *p*-toluenesulfonic anhydride (VI), and a compound with a mp of 123°C (named Compound C). Compound C showed only one absorption band at 1685 cm^{-1}, in the carbonyl region in the infrared spectrum; it was thus obviously different from Compounds A and B. The structure IV was assigned to Compound C because it was identical with the product obtained by the thermal dehydration of 6-(*p*-toluenesulfonamido)-hexanoic acid (VII).

The same results were obtained when chloroform or carbon tetrachloride was used in place of benzene as the solvent for the reaction of IIIa.

When cyclohexanone oxime benzenesulfonate (IIIb) was refluxed in benzene for 3 hr, a benzenesulfonate derivative, Vc, corresponding to Va was obtained. Vc was converted into the hydrochloride Vb by treating it with 18% hydrochloric acid. Diphenyl sulfone (VIII) was isolated in this case as the sole by-product. It was found that benzenesulfonyl peroxide (IX), when refluxed in benzene, afforded VIII. These facts induced us to suggest that the reaction IIIb→Vc proceeded through a



VIII

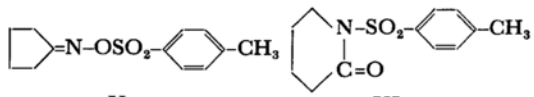


IX

radical fission in IIIb, although no further experimental evidence was obtained. The same type of reaction as those of IIIa→Va and IIIb→Vc has been reported by Oxley and Short[5] with benzophenone oxime *p*-toluenesulfonate.

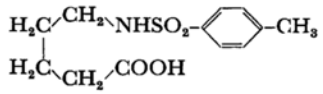
The reaction of cyclopentanone oxime *p*-toluenesulfonate (X) was studied next. Grob and his coworkers[2] reported that when X was allowed to stand for 3.5 hr at 23°C in 80% ethanol containing an equivalent amount of triethylamine, it yielded δ-valerolactam and *N*-*p*-toluenesulfonyl-δ-valerolactam (XI, mp 144—145°C). Heldt[1] reported that the heating of X in glacial acetic acid at 35°C for 2 hr yielded a compound with a mp of 151—152°C (named Compound D); he assigned the structure XII to this compound.

When X was refluxed in benzene for 3 hr, an oil was obtained which, on standing in the air, crystallized to give a compound with a mp of 147°C (named Compound E). Compounds D and E were found to be identical by synthesizing Compound D according to the method reported by Heldt. It was found, however, that the assignment of the structure XII to Compound D, made by Heldt, was unacceptable, because the authentic compound with the structure XII (mp 92°C, named Compound F) which was prepared from 5-aminopentanoic acid

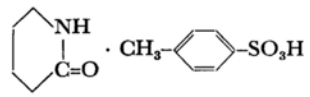


X

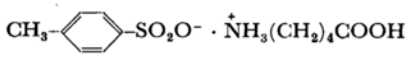
XI



XII



XIII



XIV

and *p*-toluenesulfonyl chloride was different from Compounds D and E*2. The structure XII for Compound F was confirmed by the fact that Compound F afforded XI (mp 144—145°C), upon thermal dehydration under the same conditions as those used for the dehydration of VII into IV. The infrared spectrum of XI was identical with that of IV.

It was concluded that the structure XIII should be assigned to Compounds D and E, because Compound E was prepared by just mixing δ-valerolactam and *p*-toluenesulfonic acid in acetone and afforded XIV on hydrolysis.

Reactions with other types of ketoxime *p*-toluenesulfonates are now being studied.

Experimental

Reaction of Cyclohexanone Oxime *p*-Toluenesulfonate (IIIa) in Benzene. A solution of cyclohexanone oxime *p*-toluenesulfonate (IIIa)[1] (5 g) in 50 ml of dry benzene was refluxed for 4 hr. The solution gradually turned yellow and then brown. The benzene was then evaporated *in vacuo*, and water was added. 0.3 g of a solid material was filtered out (solid: named M), and the filtrate was concentrated *in vacuo*. Acetone was added, and the solution was left to stand overnight. A solid material appeared which was recrystallized from a mixture of dioxane and 2-methoxyethanol to afford 2 g of pure Va, mp 124°C.

Found: C, 57.16; H, 7.57; N, 7.12%. Calcd for $C_{19}H_{30}O_5N_2S$: C, 57.29; H, 7.54; N, 7.04%.

IR spectrum (cm^{-1}): 1720 (s), 1640 (vs), 1217 (vs), 1160 (vs).

When a small amount of Va was added to the 2,4-dinitrophenylhydrazine reagent (DNPH),[3] an addition compound of DNPH and *p*-toluenesulfonic acid, mp

5) P. Oxley and W. F. Short, *J. Chem. Soc.*, **1948**, 1514.

*2 Heldt[1] reported that when δ-valerolactam was treated successively with 95% sulfuric acid, with aqueous sodium hydroxide, and with *p*-toluenesulfonyl chloride, crystals with a melting point of 143.5—144.5°C resulted. To these crystals he assigned a structure of XII in the monohydrated form. We followed his method, but we obtained Compound F, mp 92°C.

213°C, was obtained. This material did not show a melting point depression on admixture with an authentic sample of the addition compound.

The solid M obtained above was immediately recrystallized from ligroin to afford 0.2 g of crystals; mp 127°C (mother liquor: named N). The compound was found to be identical with the authentic sample of *p*-toluenesulfonic anhydride (VI)[6] from a study of its infrared spectrum and by a mixed-melting-point determination. The mother liquor N was then evaporated *in vacuo*, and water was added. The solution was kept overnight at room temperature, and the water was evaporated *in vacuo*. Ligroin was added to the residue and a small amount of an insoluble material (*p*-toluenesulfonic acid) was removed with charcoal. The ligroin was evaporated *in vacuo*, and a solid material was obtained. The material was recrystallized from ligroin to afford a compound with a mp of 121°C. The compound was found to be *N*-*p*-toluenesulfonyl-ε-caprolactam (IV) by a study of its infrared spectrum and by a mixed-melting-point determination with the authentic sample.

The Conversion of Va into the Hydrochloride Vb. A solution of Va (1 g) in 10 m*l* of 18% hydrochloric acid was concentrated *in vacuo* at temperature below 40°C, and then acetone was added to the residue. The solid material which appeared was recrystallized from a mixture of dioxane and 2-methoxyethanol to afford Vb, mp 150°C. This compound was found to be identical with the authentic sample of Vb by a study of its infrared spectrum and by a mixed-melting-point determination.

6-(3,4,5,6-Tetrahydro-2*H*-azepin-7-ylamino)-hexanoic Acid Hydrochloride (Vb). This compound was prepared in the following modification of a method described in the literature.[4] To a stirred solution of phosgene (4 g) in 10 m*l* of chloroform, there was added, drop by drop, ε-caprolactam (4.5 g) in 10 m*l* of chloroform at a temperature between 30°C and 40°C. After the addition was complete, the reaction mixture was stirred for an additional 3 hr at a temperature between 30°C and 40°C, and then the chloroform was evaporated *in vacuo*. When a small amount of ether was added, a solid appeared. This solid was filtered and dissolved in 50 m*l* of 18% hydrochloric acid. The solution was then refluxed for 30 min and concentrated *in vacuo*. Upon the addition of acetone to the residue, a solid was obtained which was recrystallized from a mixture of dioxane and 2-methoxyethanol to afford Vb, mp 148°C (lit[4] mp 152—153°C).

Found: C, 54.88; H, 8.85; N, 10.53%. Calcd for $C_{12}H_{22}N_2O_2 \cdot HCl$: C, 54.86; H, 8.76; N, 10.68%.

IR spectrum (cm^{-1}): 1730 (s), 1645 (vs), 1155 (vs).

NMR spectrum (in CF_3COOH): δ 7.6 (broad, 2H), δ 3.5 (multiplet, 4H), δ 2.7 (multiplet, 4H), δ 1.8 (multiplet, 12H).

pK_a: 4.45.

***N*-*p*-Toluenesulfonyl-ε-caprolactam (IV).** 6-(*p*-Toluenesulfonamido)hexanoic acid (VII)[1] (2 g) was heated in a small still under a vacuum (1 mmHg) at 125°C for 15 hr. The residue was then stirred in a 5% sodium bicarbonate solution for 2 days. The insoluble material was recrystallized from a mixture of water and acetone to afford a small amount of IV, mp 123°C.

Found: C, 58.43; H, 6.31; N, 5.32%. Calcd for $C_{13}H_{17}NO_3S$: C, 58.43; H, 6.34; N, 5.24%.

IR spectrum (cm^{-1}): 1685 (vs), 1354 (vs), 1170 (vs).

Cyclohexanone Oxime Benzenesulfonate (IIIb). To a stirred solution of cyclohexanone oxime (5.6 g) in 10 m*l* of pyridine, benzenesulfonyl chloride (8.8 g) in 15 m*l* of pyridine was added, drop by drop, at such a rate that the reaction temperature did not exceed 0°C. After the addition was complete, the reaction mixture was stirred for an additional 3 hr at 0°C. The reaction mixture was poured into a mixture of ice and sulfuric acid (containing 8 g of sulfuric acid). The yellow oil was immediately extracted with 80 m*l* of benzene. The benzene solution was washed with water two times and dried over anhydrous sodium sulfate in a refrigerator overnight. The solution was then used directly for the next process.

Reaction of Cyclohexanone Oxime Benzenesulfonate (IIIb) in Benzene. The benzene solution of cyclohexanone oxime benzenesulfonate (IIIb) obtained above was refluxed for 4 hr. The benzene was then evaporated *in vacuo*, and water was added. The solid material was filtered out (solid: named P), and the filtrate was evaporated *in vacuo*. Acetone was added to the residue, and the solution was left to stand overnight. The solid material thus obtained was recrystallized from a mixture of dioxane and 2-methoxyethanol to afford 2.4 g of Vc, mp 99°C.

Found: C, 56.27; H, 7.26; N, 7.06%. Calcd for $C_{18}H_{28}N_2O_5S$: C, 56.25; H, 7.30; N, 7.30%.

IR spectrum (cm^{-1}): 1720 (s), 1640 (vs), 1215 (vs), 1165 (vs), 1125 (vs).

Compound Vc was converted to the hydrochloride Vb in the same way as was Va converted into Vb.

The solid P was recrystallized from ligroin to afford a small amount of diphenyl sulfone (VIII), mp 121°C (lit[7] mp 125°C).

Found: C, 66.14; H, 4.60%. Calcd for $C_{12}H_{10}O_2S$: C, 66.06; H, 4.59%.

The infrared spectrum of this material was identical with the published spectrum of VIII.[8]

Reaction of Benzenesulfonyl Peroxide (IX) in Benzene. A solution of benzenesulfonyl peroxide (IX)[9] (3 g) in 30 m*l* of benzene was refluxed for 2 hr and then evaporated *in vacuo*. The residue was recrystallized from ligroin to afford 1 g of diphenyl sulfone (VIII), mp 121°C.

Reaction of Cyclopentanone Oxime *p*-Toluenesulfonate (X) in Benzene. A solution of cyclopentanone oxime *p*-toluenesulfonate (X)[1] (2 g) in 20 m*l* of dry benene was refluxed for 3 hr. The benzene was then evaporated *in vacuo*. The solid material which appeared when the solution was left in the air was recrystallized from dioxane to afford 1.9 g of δ-valerolactam *p*-toluenesulfonate (XIII), mp 147°C. The compound was found to be identical with the authentic sample by a study of its infrared spectrum and by mixed-melting-point determination.

δ-Valerolactam *p*-Toluenesulfonate (XIII). To a solution of δ-valerolactam (2.3 g) in 10 m*l* of acetone

6) H. Meyer, *Monatsh. Chem.*, **34**, 573 (1913).

7) F. Mauthner, *Ber.*, **39**, 3594 (1906).

8) DMS Card, "Documentation of Molecular Spectroscopy," Butterworths Scientific Publications, London.

9) R. F. Weinland and H. Lewkowitz, *Ber.*, **36**, 2702 (1903).

there was added a solution of *p*-toluenesulfonic acid (4 g) in 20 m*l* of acetone. The solid material which appeared was recrystallized from dioxane to afford 6 g of XIII, mp 147°C.

Found: C, 53.34; H, 6.56; N, 4.79%. Calcd for $C_{12}H_{17}NO_4S$: C, 53.14; H, 6.30; N, 5.17%.

IR spectrum (cm^{-1}): 2300 (w), 1685 (s), 1220 (vs), 1120 (vs), 1025 (vs), 1000 (s).

Reaction of Cyclopentanone Oxime *p*-Toluenesulfonate (X) in Acetic Acid. This reaction was carried out under conditions identical with those described by Heldt.[1] Crystals with a mp of 147°C were obtained; they were identical with the authentic sample of XIII. Repeated recrystallizations from glacial acetic acid did not raise the melting point.[1]

Hydrolysis of δ-valerolactam *p*-Toluenesulfonate (XIII). A solution of δ-valerolactam *p*-toluenesulfonate (XIII) (2 g) in 20 m*l* of water was refluxed for 2 hr. The water was then evaporated *in vacuo*; an oily residue, which soon solidified, was recrystallized from dioxane to afford 2 g of 5-aminopentanoic acid *p*-toluenesulfonate (XIV), mp 142°C. The compound was found to be identical with the authentic sample of XIV by a study of its infrared spectrum and by a mixed-melting-point determination.

5-Aminopentanoic Acid *p*-Toluenesulfonate(XIV). δ-Valerolactam (1 g) and *p*-toluenesulfonic acid (2 g) were dissolved in 50 m*l* of water. The solution was refluxed for 5 hr, and the water was evaporated *in vacuo*. An oily material soon solidified. Recrystallization from dioxane afforded 3 g of XIV, mp 142—142.5°C.

Found: C, 49.87; H, 6.73; N, 4.55%. Calcd for $C_{12}H_{19}NO_5S$: C, 49.83; H, 6.57; N, 4.84%.

IR spectrum (cm^{-1}): 1700 (s), 1215 (vs), 1164 (vs), 1115 (s), 1025 (s), 1000 (s), 810 (m).

5-(*p*-Toluenesulfonamido)pentanoic Acid (XII). To a solution of 5-aminopentanoic acid hydrochloride[10] (2.5 g) in a sodium hydroxide solution (1.4 g of sodium hydroxide in 7.5 m*l* of water), there was added a solution of *p*-toluenesulfonyl chloride (3.5 g) in 15 m*l* of acetone below 30°C. The solution was then stirred for 3 hr and neutralized with hydrochloric acid. The solution was freezing-dried, and the residue was extracted with ethyl acetate. After the ethyl acetate had been evaporated, the residual solid was recrystallized from water. Crystals with a mp of 92°C (1.25 g) were obtained.

Found: C, 53.44; H, 6.38; N, 5.21%. Calcd for $C_{12}H_{17}NO_4S$: C, 53.14; H, 6.30; N, 5.17%.

IR spectrum (cm^{-1}): 1686 (s), 1330 (s), 1155 (vs).

***N*-*p*-Toluenesulfonyl-δ-valerolactam (XI).** This compound was prepared by the dehydration of XII in the same way as was VII dehydrated into IV. Recrystallization from a mixture of benzene and ligroin afforded crystals of XI, mp 140°C (lit[2] mp 145°C).

IR spectrum: 1675 (vs), 1350 (vs), 1170 (vs), 825 (s), 675 (s).

10) L. E. Schniepp and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 1557 (1935).