SYNTHESIS AND SOME TRANSFORMATIONS OF TOSYL DERIVATIVES OF 4-IMIDAZOLIN-2-ONE AND 4-IMIDAZOLINE-2-THIONE

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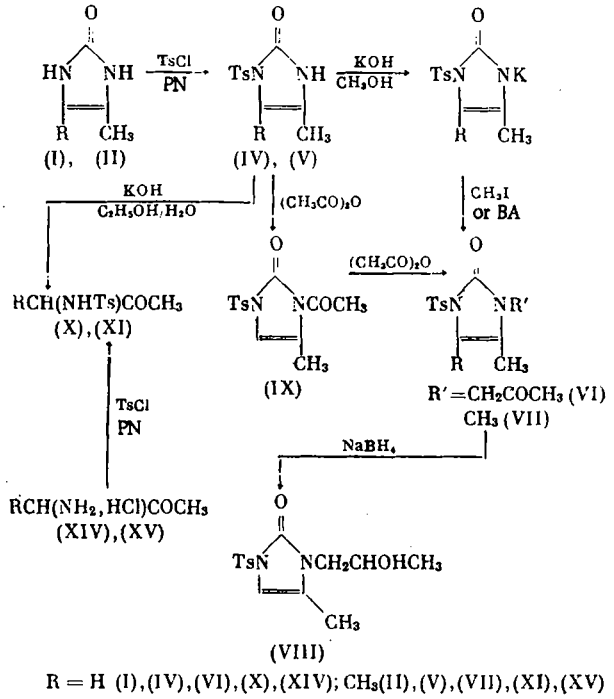
The hydroxymethylation, aminomethylation, and some other transformations of 4-imidazolin-2-one derivatives were investigated in [1-5] in connection with a study of paths for the synthesis of vitamin H and its bioprecursors. As a continuation of this research we examined in the present paper the alkylation and hydrolytic cleavage of the tosylation products of 4(5)-methylimidazolin-2-one (I), 4,5-dimethylimidazolin-2-one (II), and 4,5-dimethylimidazoline-2-thione (III).



R = H (I),(IV),(VI),(X),(XIV); CH_3(II),(V),(VII),(XI),(XV)

When treated with TsCl in pyridine (PN), (I) and (II) are converted to the N-tosyl derivatives (IV) and (V), the structure of which was confirmed by the IR and NMR spectra (see "Experimental Method"), and also by the transformations described below.

The K salts of derivatives (IV) and (V) are alkylated with bromoacetone (BA) and CH_3I at the nitrogen atom to respectively give 1-tosyl-3-acetonyl-4-methylimidazolin-2-one (VI) and 1-tosyl-3,4,5-trimethylimidazolin-2-one (VII), which have strong bands of the CO groups in the 1715-30 cm^{-1} region. The reduction of (VI) with $NaBH_4$ converts it to 1-tosyl-3-(2'-hydroxypropyl)-4-methylimidazolin-2-one (VIII), while when heated with $(CH_3CO)_2O$ it cleaves the acetonyl moiety and is converted to 1-tosyl-3-acetyl-4-methylimidazolin-2-one (IX), which is identical with the acetylation product of (IV). The long standing of (IV) and (V) with aqueous–alcohol caustic solution causes ring opening with the respective formation of

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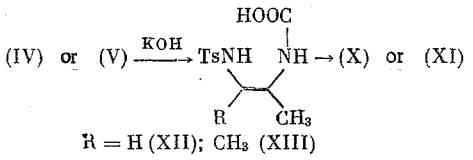
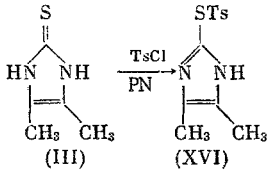
N-tosylaminoacetone (X) and N-tosyl-3-amino-2-butanone (XI), probably via the intermediate step of enamines (XII) and (XIII) by the scheme:



R = H (XII); CH_3 (XIII)

The structure of (X) and (XI) was proved by counter synthesis from TsCl and the appropriate α-aminoketone hydrochlorides (XIV) and (XV). Compound (III) is tosylated at the sulfur atom and gives 2-tosymercapto-4, 5-dimethylimidazole (XVI), the S-structure of which follows from the IR spectral data (absence of the band of the C = S group at 1520 cm^{-1}) and the inability of (XVI) to give $TsNH_2$ when oxidized with $KMnO_4$ as described in [6] (absence of the N—S bond in (XVI)).



(III) (XVI)

Attempts to obtain (XI) by treating N-tosyl-α-alanine (XVII) with $(CH_3CO)_2O$ and PN under the conditions of the Dakin—West reaction proved unsuccessful due to the cleavage of (XVII) at the N—S bond and the formation of the S-p-tolyl ester of p-toluenethiosulfonic acid (XVIII). The latter was also isolated by the thermolysis of (VI) or by the hydrolytic cleavage of (XVI).

$$\underset{\text{(XVII)}}{CH_3CH(NHTs)COOH} \xrightarrow[PN]{(CH_3CO)_2O} \underset{\text{(XVIII)}}{p\text{-}CH_3C_6H_4SSO_2C_6H_4CH_3\text{-}p}$$

In harmony with the data given in [7] on the properties of arylsulfinic acids, the conversion of (VI), (XVI) or (XVII) to (XVIII) can be depicted as a two-step process, which proceeds via the intermediate step of forming p-toluenesulfinic acid (XIX) and its subsequent disproportionation by the scheme:

$$\text{(VI), (XVI) or (XVII)} \rightarrow \underset{\text{(XIX)}}{p\text{-}CH_3C_6H_4SO_2H} \rightarrow \underset{\text{(XVIII)}}{TsSC_6H_4CH_3\text{-}p} + TsOH$$

EXPERIMENTAL METHOD

The IR spectra were taken on a UR-10 instrument. The UV spectra were taken in alcohol solution on a UF-4A instrument. The NMR spectra were measured on an RS-60 spectrometer in $CDCl_3$ solution (60 MHz), using HMDS as the internal standard..

1-Tosyl-4-methylimidazolin-2-one (IV). A mixture of 1 g of 4(5)-methylimidazolin-2-one (I) [8] and 2.2 g of TsCl in 10 ml of PN was stirred at 20°C for 5 h, after which it was diluted with 150 ml of water, let stand at 20° for 12 h, and the obtained precipitate was filtered and washed in succession with water and ether. We obtained 1.6 g (62%) of (IV), mp 160-162° (from alcohol), R_f 0.40 (here and subsequently TLC: Silufol UV_{254}, 3 : 2 ethyl acetate—benzene, development in the UV spectrum). Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 3300-2800 (NH and CH), 1716 (C = O), 1660 (C = C), 1600, 1500 [aromatic ring (AR)], 1340 (SO_2), 1180. Ultraviolet spectrum: λ_{max} 226 nm. NMR spectrum (δ, ppm): 1.87 s ($C_6H_4CH_3$-p), 2.30 s (CH_3C = C), 6.26 s (HC =), 7.10-7.90 m (C_6H_4), 9.73 s (NH). Found: C 52.42; H 4.87; N 10.93; S 13.25%. $C_{11}H_{12}N_2O_3S$. Calculated: C 52.38; H 4.79; N 11.11; S 13.08%.

1-Tosyl-4,5-dimethylimidazolin-2-one (V). The same as described above, from 4(5)-dimethylimidazolin-2-one (II) [8] we obtained (V) in 66% yield, mp 181-182° (from alcohol), R_f 0.34. Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 3500-2800 (NH and CH), 1715 (C = O), 1685 (C = C), 1600, 1500 (AR), 1320 (SO_2), 1180 (SO_2). Ultraviolet spectrum: λ_{max} 227 nm. NMR spectrum (δ, ppm): 1.82 s ($C_6H_4CH_3$-p), 2.13 s (CH_3C = C), 2.33 s (CH_3C = C), 7.10-7.90 m (C_6H_4), 9.28 s (NH). Found: C 53.95; H 5.26; S 12.41%. $C_{12}H_{14}N_2O_3S$. Calculated: C 54.14, H 5.30; S 12.02%.

1-Tosyl-3-acetonyl-4-methylimidazolin-2-one (VI). To a solution of 0.7 g of KOH in 10 ml of CH_3OH was added 3.6 g of (IV), the mixture was stirred for 15 min, then 1.1 ml of BA was added, the mixture was stirred for 1 h, let stand at 20° for 12 h, diluted with 30 ml of water, and kept at 20° for 12 h. The obtained precipitate was filtered, washed first with a solution of 0.7 g of KOH in 25 ml of water, then

with water, and dried in the air. We obtained 2.1 g (50%) of (VI), mp 95-97° (from alcohol), R_f 0.42 (1:1 acetone—benzene). Infrared spectrum (KBr, ν, cm^{-1}): 2930 (CH), 1730 (C = O), 1651 (C = C), 1600, 1500 (AR), 1380, 1180 (SO_2). Found: C 54.60; H 5.10; N 9.32; S 10.11%. $C_{14}H_{16}N_2O_4S$. Calculated: C 54.54; H 5.19; N 9.09; S 10.39%.

1-Tosyl-3,4,5-trimethylimidazolin-2-one (VII). To a solution of 0.11 g of KOH in 10 ml of alcohol were added in succession 0.5 g of (V) and 0.4 ml of CH_3I, the mixture was stirred at 20° for 3 h, let stand at 20° for 12 h, diluted with 75 ml of water, and the obtained precipitate was filtered and washed with water. We obtained 0.34 g (65%) of (VII), mp 172-173° (from alcohol), R_f 0.69 (Al_2O_3, II activity). Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 1715 (C = O), 1675 (C = C), 1600, 1500 (AR), 1380 (SO_2), 1180 (SO_2). NMR spectrum (δ, ppm): 1.83 s ($C_6H_4CH_3$-p), 2.16 s (CH_3C = C), 2.32 s (CH_3C = C), 2.90 s (CH_3N), 7.10-7.90 m (C_6H_4). Found: C 55.47; H 5.65; N 9.65; S 11.41%. $C_{13}H_{16}N_2O_3S$. Calculated: C 55.70; H 5.71; N 10.00; S 11.43%.

1-Tosyl-3-(2'-hydroxypropyl)-4-methylimidazolin-2-one (VIII). A mixture of 0.25 g of (VI) and 0.02 g of $NaBH_4$ in 10 ml of alcohol was stirred at 20° for 4 h, 0.2 ml of CH_3COOH was added, the mixture was evaporated in vacuo, the residue was treated with 50% alcohol, and the obtained precipitate was filtered. We obtained 0.19 g (75%) of (VIII), mp 91-94° (from a benzene—cyclohexane mixture), R_f 0.42 (1:1 acetone—benzene). Infrared spectrum (KBr, ν, cm^{-1}): 3440-3430 (OH), 2950-2930 (CH), 1705 (C =O, 1642 (C =C), 1600, 1500 (AR), 1377 (SO_2), 1179 (SO_2). Found: C 53.98; H 5.73; N 9.37; S 10.34%. $C_{14}H_{18}N_2O_4S$. Calculated: C 54.14; H 5.80; N 9.03; S 10.32%.

1-Tosyl-3-acetyl-4-methylimidazolin-2-one (IX). A solution of 1 g of (VI) in 30 ml of $(CH_3CO)_2O$ was refluxed for 7 h, after which it was evaporated in vacuo, the residue was treated with alcohol, and the obtained precipitate was filtered. We obtained 0.3 g (31%) of (IX), mp 88-90° (from alcohol), R_f 0.67 (1:1 acetone—benzene). Infrared spectrum (KBr, ν, cm^{-1}): 3430 (OH), 2940 (CH), 1760, 1720 (C = O), 1660 (C = C), 1600, 1500 (AR), 1380-1370 (SO_2), 1180 (SO_2). Ultraviolet spectrum: λ_{max} 230 nm. Found: C 51.56; H 4.73; N 8.88; S 10.20%. $C_{13}H_{14}N_2O_4S \cdot {}^1/_2 H_2O$. Calculated: C 51.47; H 4.94; N 9.24; S 10.56%. Compound (IX) was also obtained by the action of $(CH_3CO)_2O$ on (IV) (refluxing for 3 h) in 85% yield.

N-Tosylaminoacetone (X). To a solution of 0.5 g of KOH in 20 ml of aqueous alcohol (1:1) was added 1 g of (IV), the mixture was kept at 20° for 24 h, after which it was evaporated in vacuo, the residue was treated with 1:1 HCl solution, and the oil was extracted with benzene, which crystallized when n-heptane was added. We obtained 0.6 g (67%) of (X), mp 86-87° (from n-heptane), R_f 0.56. Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 1735 (C = O), 1600, 1500 (AR), 1350 (SO_2), 1170 (SO_2). Ultraviolet spectrum: λ_{max} 231 nm. NMR spectrum (δ, ppm): 2.03 s ($C_6H_4CH_3$-p), 2.32 s (CH_3CO), 3.75 d (CH_2), 5.56 m (NH), 7.10-7.90 m (C_6H_4). Found: C 52.74; H 5.68; N 6.24; S 14.23%. $C_{10}H_{13}NO_3S$. Calculated: C 52.83; H 5.76; N 6.17; S 14.10%.

A mixture of 1.25 g of aminoacetone hydrochloride (XIV) [8] and 4.38 g of TsCl in 10 ml of PN was kept at 20° for 12 h, after which it was evaporated in vacuo, and the residue was treated with water and then extracted with benzene. After removal of the solvent we obtained 0.11 g (4%) of (X), mp 85-88°.

N-Tosyl-3-amino-2-butanone (XI). In the same manner as described above, we obtained (XI) from (V) [8] in 57% yield, mp 73-74° (from n-heptane), R_f 0.63. Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 1725 (C = O), 1600, 1500 (AR), 1345 (SO_2), 1170 (SO_2). Ultraviolet spectrum: λ_{max} 228 nm. NMR spectrum (δ, ppm): 1.21 d (CH_3CH), 2.02 s ($C_6H_4CH_3$-p), 2.32 s (CH_3CO), 3.85 m (CH), 5.77 d (NH), 7.10-7.90 m (C_6H_4). Found: C 54.81; H 5.99; N 5.99; S 12.91%. $C_{11}H_{15}NO_3S$. Calculated: C 54.74; H 6.25; N 5.80; S 13.28%.

The same as described above, the action of TsCl on 3-amino-2-butanone hydrochloride (XV) gave (XI) in 7% yield.

2-Tosylmercapto-4,5-dimethylimidazole (XVI). A mixture of 6.7 g of aminoacetone hydrochloride and 5.8 g of KCNS in 60 ml of glacial CH_3COOH was heated at 100° for 2 h, after which it was let stand at 20° for 24 h, and the precipitate was filtered and washed with water. We obtained 2.7 g of 4,5-dimethylimidazoline-2-thione (III). Evaporation of the aqueous mother liquor in vacuo gave an additional 1.2 g of (III), the total yield of which was 3.9 g (57%), mp 268-270° [9]. A mixture of 2.5 g of (III) and 4.3 g of TsCl in 20 ml of PN was stirred at 20° for 5 h, after which it was evaporated in vacuo, the residue was treated with water and ether, and the precipitate was filtered. We obtained 3.5 g (63%) of (XVI), mp 162-163° (from alcohol), R_f 0.44 (3:2 benzene—ethyl acetate). Infrared spectrum ($CHCl_3$, ν, cm^{-1}): 3200-2800

(NH and CH), 1600, 1500 (AR), 1335 (SO_2), 1140 (SO_2). Ultraviolet spectrum: λ_{max} 239 and 305 nm. Found: C 51.42; H 5.00; N 9.91; S 22.33%. $C_{12}H_{14}N_2O_2S_2$. Calculated: C 51.05; H 4.97; N 9.97; S 22.60%.

S-p-Tolyl ester of p-toluenethiosulfonic Acid (XVIII). A mixture of 1.6 g of N-tosyl-DL-α-alanine (XVII) [10], 4 ml of $(CH_3CO)_2O$, and 4 ml of PN was heated at 90-100° for 1 h, after which it was evaporated in vacuo. and the residue was treated with water and then extracted with benzene. The benzene extract was washed in succession with aqueous $NaHCO_3$ solution and water. After removal of the solvent the reaction product was recrystallized from n-heptane. We obtained 0.4 g of (XVIII), mp 66-68°, R_f 0.75 (5:1 benzene—ethyl acetate), IR spectrum ($CHCl_3$, ν, cm^{-1}): 1600, 1500 (AR), 1330 (SO_2), 1142 (SO_2). The obtained (XVIII) failed to depress the mixed melting point with an authentic specimen (mp 65-67°) [7].

A mixture of 0.28 g of (XVI) and 10 ml of 1:1 HCl solution was refluxed for 5 h, after which it was evaporated in vacuo, and the residue was treated with water and then extracted with ethyl acetate. After removal of the solvent we obtained 0.09 g of (XVIII), mp 67-68°. Thioester (XVIII) was also isolated by heating (VI) (~200°, 20 min).

CONCLUSIONS

1. 4-Imidazolin-2-one derivatives when treated with p-toluenesulfonyl chloride in pyridine are tosylated at the nitrogen atom, while 4,5-dimethylimidazoline-2-thione is tosylated at the sulfur atom.

2. The hydrolytic cleavage of the N-tosyl 4-imidazolin-2-one derivatives in alkaline medium gives N-Ts-α-aminoketones.

3. The K salts of the N-tosylimidazolin-2-ones react with alkyl halides in alcohol medium to give the N'-alkyl derivatives.

4. The heating of N-tosyl-α-alanine with acetic anhydride and pyridine, the acid hydrolysis of 2-tosylmercapto-4,5-dimethylimidazole, or the thermolysis of 1-tosyl-3-acetonyl-4-methylimidazolin-2-one all lead to the formation of the S-p-tolyl ester of p-toluenethiosulfonic acid.

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