[Chem. Pharm. Bull. 19(5) 892—895 (1971)]

UDC 547.869.04 : 547.866.07

Syntheses of Heterocyclic Compounds involving Sulfur. II.[1] Syntheses of 3-Tosyl-1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*]phenothiazine-1,2-dione, 2-Tosyl-1, 2-dihydroimidazo[4,5,1-*kl*]phenothazine-1-one, and N,N'-Bis[tosyl(1-phenothiazinyl)]oxalamide from Reaction between 1-Tosylaminophenothiazine and Oxalyl Chloride

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(Received July 25, 1970)

Reaction of 1-tosylaminophenothiazine (IV) and oxalyl chloride gave 3-tosyl-1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*]phenothiazine-1,2-dione (VI), N,N'-bis[tosyl(1-phenothiazinyl)]oxalamide (VII), and 2-tosyl-1,2-dihydroimidazo[4,5,1-*kl*]phenothiazine-1-one (VIII).

Reduction of VI with lithium aluminum hydride afforded 1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*]phenothiazine (X), and a similar reaction of VIII gave IV, accompanied with ring-opened product.

In a previous paper,[1] we reported that the reaction between 1-aminophenothiazine (I) and oxalyl chloride gave the expected cyclized product, 1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*]phenothiazine-1,2-dione (II), in a very low yield, majority of the product being a bis-type compound, N,N'-bis(1-phenothiazinyl)oxalamide (III), and that the reaction of 1-tosylaminophenothiazine (IV) with ethylene bromide gave the corresponding cyclized 3-tosyl-1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*]phenothiazine (V) in 50% yield (Chart 1).

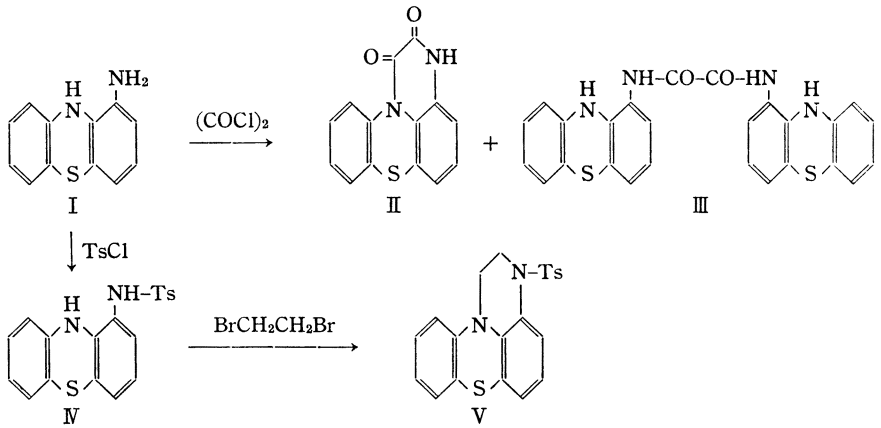

Chart 1

In anticipation of a more facile reaction, IV was reacted with oxalyl chloride but increase in the yield of the cyclized product was not achieved. However, some interesting facts were found in this reaction, which will be reported herein.

Treatment of the sodium salt of IV, obtained from IV and sodium hydride, with freshly prepared oxalyl chloride in xylene at −15° gave three products; yellow prisms (VI), mp>300°, yellow prisms (VII), mp 205—206°, and colorless plates (VIII), mp 244—245°, in weight ratio

1) Part I: H. Shirai, T. Hayazaki, and T. Aoyama, *Chem. Pharm. Bull.* (Tokyo), **18**, 1987 (1970).
2) Location: *1, Tanabedori 3-chome, Mizuho-ku, Nagoya.*

of 6.9:1:2.3. The elementary analysis of VI agreed with the formula of $C_{21}H_{14}O_4N_2S_2$, and its infrared (IR) spectrum did not show the NH stretching vibration present in IV and two carbonyl bands newly appeared at 1730 and 1692 cm^{-1}. From these facts, VI is undoubtly 3-tosyl-1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*]phenothiazine-1,2-dione, the objectivecy clized compound.

The composition of VII agreed well with the formula of $C_{40}H_{30}O_6N_4S_4$ and identified with the bis–type product formed by the reaction of two moles of IV and one mole of oxalyl chloride. Three types of structure, VIIa, VIIb, and VIIc, were considered for VII, as shown in Chart 2. Its IR spectrum showed the NH stretching vibration at 3470 cm^{-1}, and the SO_2 stretching vibrations at 1370 and 1180 cm^{-1} to have shifted respectively by 30 and 27 cm^{-1} to a higher region than those in IV, and indicated characteristics of a tertiary sulfonamide. From all these data, VII is probably N,N'-bis[tosyl(1-phenothiazinyl)]oxalamide (VIIa).

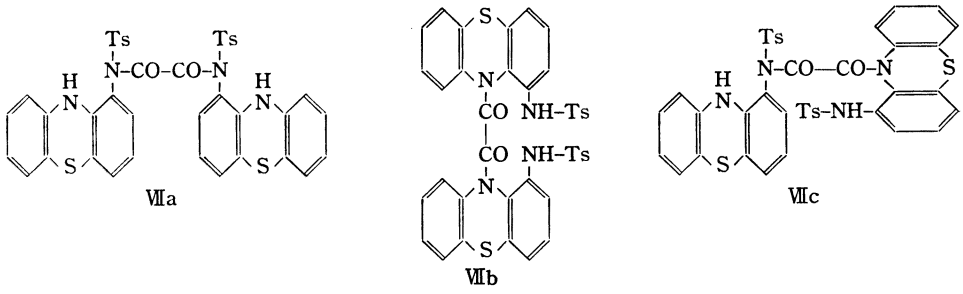

Chart 2

The elementary analysis of VIII, mp 244—245°, agreed with the formula of $C_{20}H_{14}O_3N_2S_2$ which was less by CO from the composition of VI. In its IR spectrum, the NH stretching vibration was not found as in VI but one carbonyl band appeared at 1748 cm^{-1}, which was assumed to indicate the presence of a five–membered ureido group. From these facts, VIII was presumed to be 2-tosyl-1,2-dihydroimidazo[4,5,1-*kl*]phenothiazine-1-one and identified with its authentic sample obtained by tosylation of 1,2-dihydroimidazo[4,5,1-*kl*]phenothiazine-1-one[1] (IX) and tosyl chloride in the presence of sodium hydride. This result indicates that a partial decarboxylation occurred in the reaction between IV and oxalyl chloride to give VIII. It was considered that sodium hydroxide produced from the decomposition of excess sodium hydride by water induced decarboxylation of the dioxo compound (VI), and the reaction of VI with alkali was examined.

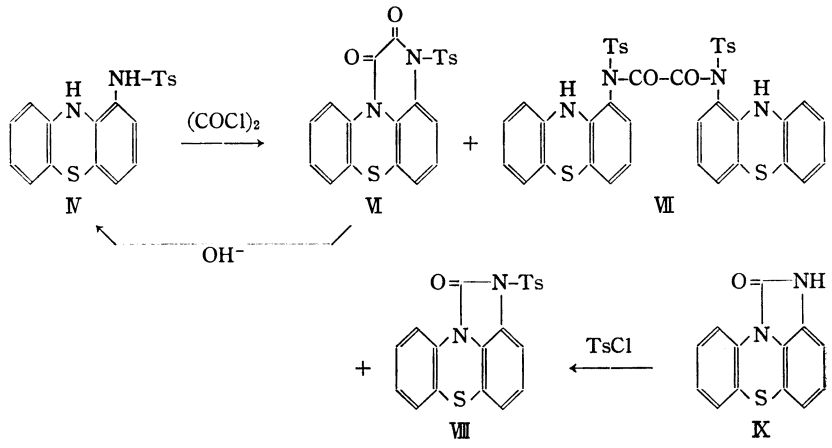

Chart 3

The reaction of VI with 1% ethanolic sodium hydroxide did not produce VIII and VI was recovered, but in the same reaction with 5% ethanolic sodium hydroxide at room temperature, the reaction progressed smoothly and treatment of the reaction mixture did not give the imidazole compound (VIII) but afforded IV in a high yield. Therefore, it was assumed that the by-product (VIII) was not formed during after-treatment of the reaction mixture but was formed by the reaction between IV and oxalyl chloride. The reason for this phenomenon is still obscure at present (Chart 3).

Finally, examination was made on the synthesis of 1,2-dihydro-3*H*-pyrazino[3,2,1-*kl*] phenothiazine (X) and 1,2-dihydroimidazo[4,5,1-*kl*]phenothiazine (XI) by the reductive detosylation of VI and VIII with lithium aluminum hydride. In the reduction of VI, X was obtained in a low yield, but in the similar reaction of VIII, XI was not obtained and the open-ring product (IV) was obtained in a very high yield. Considering the example of the reaction of the dioxo compound (VI) with alkali, this ring opening reaction must be due to the alkali produced from the decomposition of excess lithium aluminum hydride with water. Therefore, the reaction of VIII with 5% ethanolic sodium hydroxide was tried, but IV was not obtained and the detosylated compound (IX) was obtained in a quantitative yield (Chart 4).

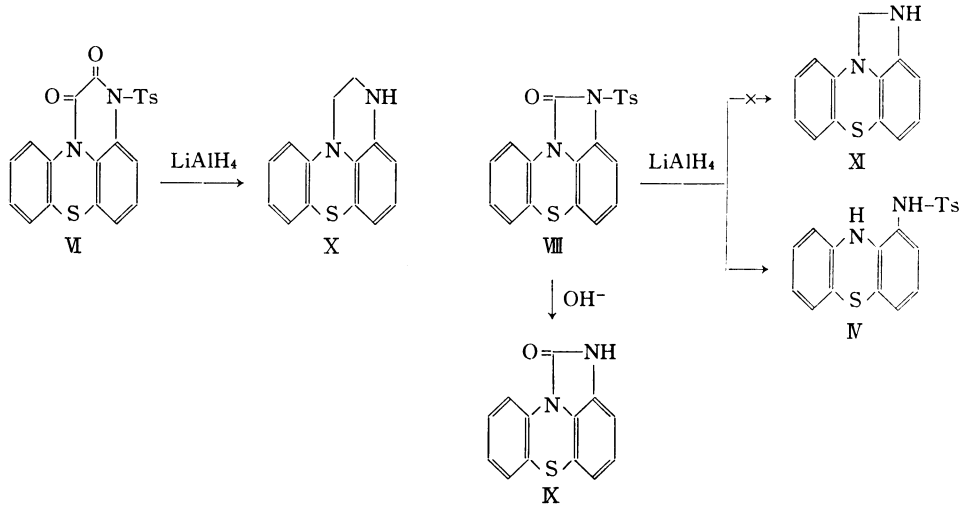

Chart 4

From these data, it was clarified that the reduction of VI with lithium aluminum hydride was accompanied with detosylation to give X while treatment of VI with ethanolic sodium hydroxide induced ring fission to give IV. In contrast, the reduction of VIII with lithium aluminum hydride resulted in ring fission to give IV, while treatment of VIII with ethanolic sodium hydroxide gave IX, accompanied with detosylation.

Detosylation of VI and VIII with 90% sulfuric acid or 25% hydrochloric acid was examined, but the objective compound II or IX was not obtained, resulting in black resinous product.

Experimental

Reaction of 1-Tosylaminophenothiazine (IV) with Oxalyl Chloride——A mixture of 2 g of IV, 0.57 g of NaH (50% dispersion in mineral oil), and 80 ml of dry xylene was refluxed for 9 hr in N_2 atmosphere. The mixture was chilled to −15°, a solution of 0.76 g of oxalyl chloride in 20 ml of dry xylene was added to this solution during 10 min, and the mixture was stirred at the same temperature for 30 min, at 0° for 1 hr, and then at room temperature for 1 hr. The excess of NaH was decomposed with 1.4 ml of sat. aqueous NH_4Cl solution and the resultant precipitate was filtered off. To this filtrate was added 40 ml of water and the

precipitated crystals were collected, washed with water, and dried. Recrystallization from benzene gave 664 mg (29%) of 3-tosyl-1,2-dihydro-3*H*-pyrazino [3,2,1-*kl*] phenothiazine-1,2-dione (VI) as yellow prisms, mp>300°. *Anal.* Calcd. for $C_{21}H_{14}O_4N_2S_2$: C, 59.70; H, 3.34; O, 15.15; N, 6.63. Found: C, 59.78; H, 3.42; O, 15.31; N, 6.71. IR ν_{max}^{KBr} cm^{-1}: 1730, 1692 (C=O), 1375, 1173 (SO_2).

Above filtrate, separated from the crude crystals of VI, was extracted with $CHCl_3$, which was washed with water and dried. The solvent was evaporated to dryness and the residue was purified by chromatography over SiO_2 gel in $CHCl_3$. The first eluate gave 96 mg (4.5%) of N,N'-bis [tosyl (1-phenothiazinyl)] oxalamide (VII) as yellow prisms (from benzene), mp 205—206°. *Anal.* Calcd. for $C_{40}H_{30}O_6N_4S_4$: C, 60.73; H, 3.82; O, 12.14; N, 7.09; mol. wt. 790.93. Found: C, 60.88; H, 3.90; O, 12.26; N, 7.06; mol. wt. 800 (Rast). IR ν_{max}^{KBr} cm^{-1}: 3470 (NH), 1695 (C=O), 1370, 1180 (SO_2).

The second eluate gave 219 mg (10%) of 2-tosyl-1,2-dihydroimidazo [4,5,1-*kl*] phenothiazine-1-one (VIII) as colorless plates (from benzene), mp 244—245°. *Anal.* Calcd. for $C_{20}H_{14}O_3N_2S_2$: C, 60.89; H, 3.53; O, 12.17; N, 7.10. Found: C, 60.91; H, 3.62; O, 11.93; N, 7.15. IR ν_{max}^{KBr} cm^{-1}: 1748 (C=O), 1370, 1165 (SO_2).

2-Tosyl-1,2-dihydroimidazo [4,5,1-*kl*] phenothiazine-1-one (VIII)——A mixture of 120 mg of 1,2-dihydroimidazo [4,5,1-*kl*] phenothiazine-1-one[1] (IX), 50 mg of NaH (50% dispersion in mineral oil), and 40 ml of dry toluene was refluxed for 10 hr in N_2 atmosphere. When cooled, 230 mg of TsCl was added to this solution, the mixture was stirred at room temperature for 1 hr and then refluxed for 3 hr. The hot reaction mixture was filtered, the filtrate was evaporated to dryness and the residue was recrystallized from benzene to give 155 mg(76%) of VIII as colorless plates, mp 244—245°, which was identified with an authentic sample obtained from the reaction between IV and oxalyl chloride by IR spectrum and mixed melting point.

Reaction of 3-Tosyl-1,2-dihydro-3*H*-pyrazino [3,2,1-*kl*] phenothiazine-1,2-dione (VI) with 5% NaOH–EtOH——A mixture of 100 mg of VI and 10 ml of 5% NaOH–EtOH was stirred for 5 min at room temperature. The reaction mixture was poured into 100 ml of water, acidified with 10% HCl, and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to dryness. The residue was recrystallized from benzene to give 62 mg (71%) of 1-tosylaminophenothiazine (IV) as colorless prisms, mp 162—163°, which was identified with an authentic sample.[1]

Reaction of 3-Tosyl-1,2-dihydro-3*H*-pyrazino [3,2,1-*kl*] phenothiazine-1,2-dione (VI) with $LiAlH_4$——A mixture of 0.5 g of VI, 0.8 g of $LiAlH_4$, and 30 ml of dry ether was refluxed for 15 hr. The excess of $LiAlH_4$ was decomposed with water and the resultant precipitate was filtered off. The filtrate was washed with water, dried, and evaporated to dryness. The residue was purified by chromatography over SiO_2 gel in benzene to give 32 mg (11%) of 1,2-dihydro-3*H*-pyrazino [3,2,1-*kl*] phenothiazine (X) as a yellow oil, which was identified with an authentic sample.[1]

Reaction of 2-Tosyl-1,2-dihydroimidazo [4,5,1-*kl*] phenothiazine-1-one (VIII) with $LiAlH_4$——A mixture of 0.25 g of VIII, 0.3 g of $LiAlH_4$, and 100 ml of dry ether was refluxed for 15 hr. The excess of $LiAlH_4$ was decomposed with water and the resultant precipitate was filtered off. The filtrate was washed with water, dried, and evaporated to dryness. The residue was recrystallized from benzene to give 160 mg (65%) of 1-tosylaminophenothiazine (IV) as colorless prisms, mp 162—163°, which was identified with an authentic sample.[1]

Reaction of 2-Tosyl-1,2-dihydroimidazo [4,5,1-*kl*] phenothiazine-1-one (VIII) with 5% NaOH–EtOH——A mixture of 100 mg of VIII and 10 ml of 5% NaOH–EtOH was stood overnight at room temperature. The reaction mixture was poured into 100 ml of water and extracted with $CHCl_3$. The extract was washed with water, dried, and evaporated to dryness. The residue was recrystallized from EtOH to give 55 mg (97%) of 1,2-dihydroimidazo [4,5,1-*kl*] phenothiazine-1-one (IX) as colorless needles, mp 291—292°, which was identified with an authentic sample.[1]

Acknowledgement The authors are indebted to the members of the Analysis Center of this University for elemental analyses.