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# Quinazolines and 1,4-Benzodiazepines XXXVI (1). The Formation of 1,3-Dihydro and 1,5-Dihydro-1,4-benzodiazepines from Tosyl (2)- and Mesyl (2)- Substituted 1,3,4,5-Tetrahydro-5-phenyl-1,4-benzodiazepine Derivatives

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The treatment of 4-sulfonyl derivatives of 5-phenyl-1,3,4,5-tetrahydro-1,4-benzodiazepin-2-ones (I) with base was shown to result in the formation of 1,3-dihydro or 1,5-dihydro-1,4-benzodiazepin-2-ones (III and II respectively) depending upon the conditions used. The base treatment of 1-sulfonyl substituted 2,3-dihydro-1,4-benzodiazepines (V) was shown to give the vinylimines VI.

As a continuation of our studies on the synthesis and transformations of 1,4-benzodiazepines we have investigated the elimination of sulfonyl residues from the appropriately substituted 5-phenyl-1,4-benzodiazepine derivatives.

The reaction of 4-tosyl (2) and 4-mesyl (2) derivatives of 1,3,4,5-tetrahydro-5-phenyl-1,4-benzodiazepin-2-ones (Ia,b) with base, resulted in the formation of dihydro derivatives.

The elimination proceeds smoothly in a variety of solvents and can be effected by the use of a number of different bases. When the elimination is carried out in an anhydrous, nonpolar solvent, the acidic 3 proton is abstracted and compound II with the double bond in the 3,4-position is formed. Compound II was subsequently rearranged in aqueous base to give isomer III in which the double bond is in the 4,5-position. The structure of II was confirmed not only by its isomerization to III, but also by catalytic reduction to the known tetrahydro derivative IV. The n.m.r. spectrum of II (DMSO) showed the NH proton at $\delta$ 11.02, the benzylic proton as a doublet centered at $\delta$ 5.56 (J = 2 cps) and the methine proton as a doublet centered at $\delta$ 7.65 (J = 2 cps). The infrared and ultraviolet spectra were also compatible with structure II.

If, in this elimination, polar solvents or aqueous solvents are used, the more stable isomer III is isolated directly from the reaction mixture.

The attempted elimination of tosyl or mesyl groups from the corresponding 1-substituted 1,4-benzodiazepines Va and Vb gave the vinylimines VIa and VIb respectively. Hydrolysis of the imines gave the ketones VIIa,b. The structural assignment for VI was confirmed by lithium aluminum hydride reduction of VIb to the benzhydrylamine derivative VIIIb. An authentic sample of VIIIb was then prepared from the benzhydrol IXb as shown. The unknown methanesulfonamidoketone VIIb was also synthesized directly from the known aminobenzophenone X.

## EXPERIMENTAL

All melting points are corrected and were determined microscopically on a hot-stage apparatus. Infrared spectra were determined either in 3% chloroform solution or in potassium bromide pellets (1 mg./300 mg. potassium bromide) on a Beckmann IR 9 spectrophotometer. Mixture melting points were taken and infrared spectra were compared in order to confirm or exclude the expected structural changes. The n.m.r. spectra were determined with a Varian HA-100 instrument.

7-Chloro-1,3,4,5-tetrahydro-5-phenyl-4-(*p*-toluenesulfonyl)-2*H*-1,4-benzodiazepin-2-one (Ia).

A solution of 50 g. (0.184 mole) of 7-chloro-1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IV) (3) in 100 ml. of pyridine was heated to reflux. A warm solution of 42 g. (0.22 mole) of *p*-toluenesulfonyl chloride in 100 ml. of pyridine was added to the reaction mixture over a 20 minute period. The reaction mixture was heated under reflux for 1.5 hours and was then poured into 1 l. of water. The mixture was stirred until a brown solid precipitated. The precipitate was collected by filtration and washed with water (4 x 500 ml.), ethanol (2 x 300 ml.) and 200 ml. of ether. The precipitate was then recrystallized from a mixture of chloroform and ethanol giving 62.3 g. (79.4%) of product as white prisms m.p. 244–250°. Recrystallization from chloroform-ethanol gave the analytically pure compound as white prisms, m.p. 246–252°.

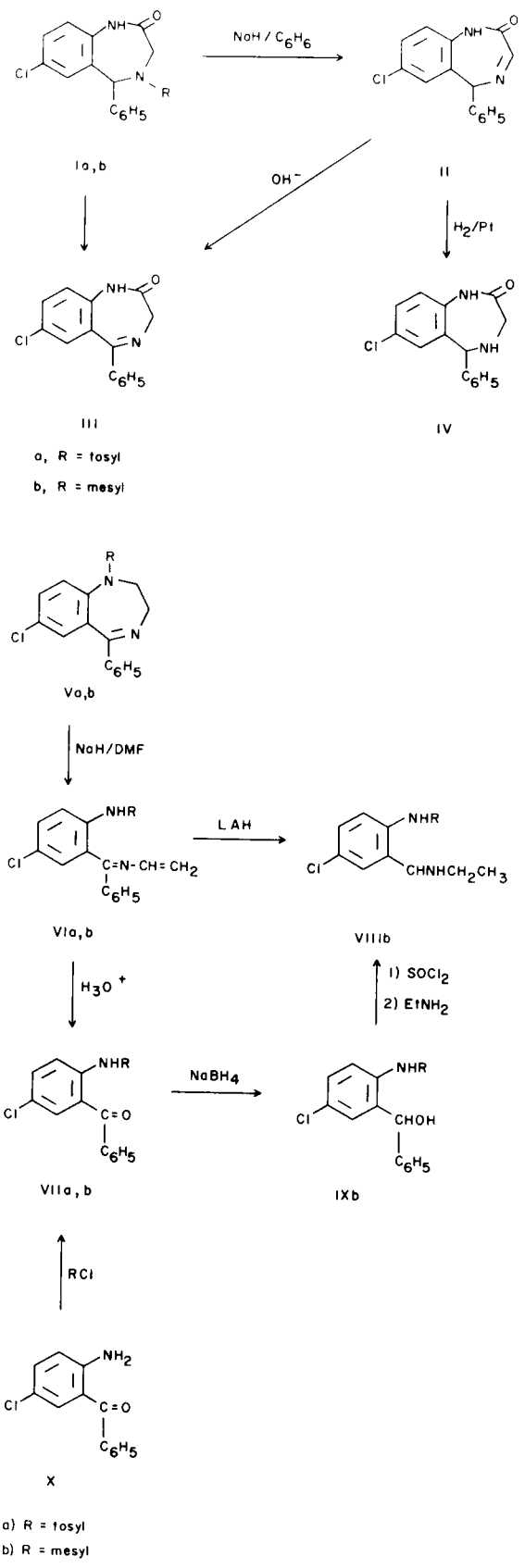
*Anal.* Calcd. for $C_{22}H_{19}ClN_2O_3S$: C, 61.89; H, 4.49. Found: C, 61.78; H, 4.42.

7-Chloro-1,3,4,5-tetrahydro-4-methanesulfonyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Ib).

A suspension of 50 g. (0.183 mole) of IV in 380 ml. of pyridine was cooled to 5° and treated with 15.6 ml. (0.201 mole) of methanesulfonyl chloride (15 minutes). The clear yellow solution was warmed to 28° and then stirred at room temperature for 2.5 hours. The reaction mixture was poured into 1.3 l. of water and stirred vigorously. The crystalline precipitate was collected by filtration and washed with water (4 x 300 ml.) followed by ether (2 x 200 ml.). Recrystallization of the product from a mixture of chloroform and ethanol gave the pure material (55.1 g., 86.0%) as white prisms, m.p. 203–206°.

*Anal.* Calcd. for $C_{16}H_{15}ClN_2O_3S$: C, 54.78; H, 4.31. Found: C, 54.77; H, 4.18.

7-Chloro-1,5-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (II).




A solution of 19.5 g. (0.0456 mole) of Ia in 150 ml. of dry benzene was treated with 4.0 g. (0.10 mole) of a 60% sodium hydride dispersion in mineral oil. The reaction mixture was heated under reflux for 20 hours and then it was poured into 300 ml. of water. The *p*H was adjusted to approximately 7 with hydrochloric acid. The layers were separated and the aqueous phase was extracted with dichloromethane (2 x 1 l.). The organic layers were combined, washed with water (3 x 500 ml.), saturated brine solution (1 x 100 ml.), dried over anhydrous sulfate, filtered and evaporated to dryness. The residual oil (12.9 g.) was crystallized from a mixture of dichloromethane-hexane to give 4.3 g. (35.0%) of II as white prisms, m.p. 202–210°.

*Anal.* Calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.61; H, 3.85; N, 10.52.

Isomerization of 7-Chloro-1,5-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (II) to 7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (III) (3).

A solution of 0.5 g. (0.002 mole) of II in 15 ml. of *N,N*-dimethylformamide was treated with a solution of sodium methoxide in methanol (0.011 mole of sodium methoxide). The mixture was allowed to stand at room temperature for 0.5 hour and then poured into 50 ml. of water. Hydrochloric acid was added until the *p*H reached approximately 7 and the mixture was extracted with dichloromethane (2 x 40 ml.). The combined dichloromethane extracts were washed with water (3 x 60 ml.), saturated brine solution (1 x 30 ml.) dried over sodium sulfate, and evaporated. The residual oil was crystallized from a mixture of dichloromethane and hexane to give III as white prisms, m.p. and m.m.p. 215-221° [lit. m.p. 216-217° (3)].

Reduction of 7-Chloro-1,5-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (II) to 7-Chloro-1,3,4,5-tetrahydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IV) (3).

A solution of 0.5 g. (0.002 mole) of II in a mixture of 40 ml. of glacial acetic acid and 40 ml. of water was treated with 150 mg. of platinum oxide and was hydrogenated for 2 hours at room temperature and at atmospheric pressure. The solution absorbed approximately 50 ml. (0.002 mole) of hydrogen. The reaction mixture was filtered over Celite, made basic (*p*H 8) with a 50% solution of sodium carbonate, and extracted with dichloromethane (2 x 100 ml.). The combined dichloromethane extracts were washed with water (3 x 200 ml.), saturated brine solution, dried over sodium sulfate, and evaporated. The residual oil was filtered over 15 g. of silica gel on a sintered glass funnel using dichloromethane as the eluant. The forerun was discarded. A second fraction was evaporated to dryness and crystallized from a mixture of ethyl acetate and hexane to give IV as white prisms, m.p. and m.m.p. 184-186° [lit. m.p. 184.5-185.5° (3)].

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (III). A. From Ia (Variation of Solvent and Base). Method 1 – Sodium Hydride/DMF.

A solution of 5 g. (0.0117 mole) of Ia in 35 ml. of *N,N*-dimethylformamide was treated with 1.0 g. (0.026 mole) (4) of a 60% sodium hydride dispersion in mineral oil. The tan solution was stirred at room temperature for 1 hour and then allowed to stand for 48 hours. The reaction mixture was poured into 200 ml. of water and extracted with 100 ml. of dichloromethane. The dichloromethane extract was washed with water (3 x 500 ml.), saturated brine solution (1 x 100 ml.), dried over anhydrous sodium sulfate and evaporated to dryness to give 3.3 g. of an oil. The oil was dissolved in dichloromethane which was concentrated and cooled. The product (0.8 g., 25.0%), obtained by filtration, was recrystallized from acetone to give III as white prisms, m.p. 212–214°.

Method 2 – Sodium Methoxide/DMF.

A solution of 3 g. (0.007 mole) of Ia in 35 ml. of *N,N*-dimethylformamide was cooled to 5° and treated with a solution of sodium methoxide in methanol (0.0154 mole of sodium methoxide). The reaction mixture was allowed to stand for 79 hours (5). The reaction mixture was poured into 200 ml. of water, hydrochloric acid was added to *p*H 7 and the solution was then extracted with 100 ml. of dichloromethane. The organic layer was separated and washed with water (3 x 300 ml.), saturated brine solution (1 x 100 ml.), dried over sodium sulfate and evaporated. The residual oil was crystallized from a mixture of dichloromethane and hexane to give the product as white prisms, m.p. 213–217°.

Method 3 – Potassium *t*-Butoxide/DMF.

A solution of 3 g. (0.007 mole) of Ia in 35 ml. of *N,N*-dimethylformamide was cooled to 5° and treated with 1.7 g. (0.0154 mole) of potassium *t*-butoxide. (The solution turned deep yellow.) The reaction mixture was stirred at 5° for 0.5 hour and then allowed to warm to room temperature and stand for 79 hours. (A visual estimation of the thin layer chromatograph indicated the presence of approximately 90% of product.) The reaction mixture was poured into 200 ml. of water, hydrochloric acid was added to *p*H 7 and the solution was then extracted with 100 ml. of dichloromethane. The dichloromethane layer was separated and washed with water (4 x 300 ml.), saturated brine solution (1 x 100 ml.), dried over sodium sulfate and evaporated. The residual oil was crystallized from a mixture of dichloromethane and hexane to give the product as white prisms, m.p. 212–216°.

Method 4 –Aqueous Sodium Hydroxide/DMF.

A solution of 2 g. (0.0047 mole) of Ia in 30 ml. of *N,N*-dimethylformamide was treated with 0.5 ml. of 0.1 *N* sodium hydroxide solution. The mixture was stirred at room temperature for 4 hours and then allowed to stand for 55 hours. The reaction mixture was poured into 100 ml. of water, hydrochloric acid was added to *p*H 7 and the solution was then extracted with dichloromethane (3 x 50 ml.). The combined dichloromethane extracts were washed with water (3 x 200 ml.), saturated brine solution (1 x 100 ml.), dried over sodium sulfate and evaporated. The residual oil was crystallized from a mixture of dichloromethane and hexane. The product was recrystallized twice from acetone to give III as white prisms, m.p. 211–214°.

Method 5 – Sodium Hydride/Tetrahydrofuran.

A solution of 5 g. (0.117 mole) of Ia in 40 ml. of tetrahydrofuran was treated with 1.0 g. (0.0258 mole) of a 60% dispersion of sodium hydride in mineral oil and the reaction mixture was stirred first at room temperature, and then at 60° for 5 hours. (A visual estimation of the thin layer chromatograph indicated a 60% conversion of III.) The reaction mixture was poured into 200 ml. of water, and extracted into 100 ml. of dichloromethane. The dichloromethane was washed with water (3 x 300 ml.), saturated brine solution (1 x 100 ml.), dried over sodium sulfate, and evaporated. The residual oil was crystallized from dichloromethane to give the product as white prisms, m.p. 210–214°.

Method 6 – Sodium Hydride/Dimethylsulfoxide.

A solution of 5 g. (0.0117 mole) of Ia in 40 ml. of dimethylsulfoxide was treated with 1.0 g. (0.0258 mole) of a 60% dispersion of sodium hydride in mineral oil. The reaction mixture was stirred at room temperature for 1 hour and was then allowed to stand for 40 hours. (The solution turned amber.)

The reaction mixture was poured into 150 ml. of water and extracted with 100 ml. of dichloromethane. The dichloromethane extract was washed with water (3 x 300 ml.), saturated brine solution (1 x 100 ml.), dried over sodium sulfate and evaporated. The residual oil (3.3 g.) was crystallized from a mixture of dichloromethane and hexane to give the product as white prisms, m.p. 210–214°.

B. From 7-Chloro-1,3,4,5-tetrahydro-4-methanesulfonyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one (Ib).

A solution of 3 g. (0.0086 mole) of Ib in 30 ml. of *N,N*-dimethylformamide was treated with 0.76 g. (0.019 mole) of a 60% sodium hydride dispersion in mineral oil. The reaction mixture was stirred at room temperature for 2 hours and then at 45° for 4 hours.

After cooling to room temperature the reaction mixture was poured into 200 ml. of water, hydrochloric acid was added to *p*H 7 and the resulting mixture was extracted with dichloromethane (2 x 75 ml.). The combined dichloromethane extracts were washed with water (3 x 300 ml.), saturated brine solution (1 x 100 ml.), dried over sodium sulfate, filtered and evaporated. The residual oil (1.7 g.) was crystallized from a mixture of dichloromethane and hexane to give unreacted starting material as white prisms, m.p. 201–205°. The mother liquors were then evaporated to dryness and crystallized from a mixture of dichloromethane and hexane to give III as white prisms, m.p. 210–214°.

7-Chloro-2,3-dihydro-5-phenyl-1-*p*-toluenesulfonyl-1*H*-1,4-benzodiazepine (Va) (6).

A solution of 50 g. (0.195 mole) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (7) in 100 ml. of pyridine was treated at reflux with a solution of 44.6 g. (0.234 mole) of *p*-toluenesulfonyl chloride in 100 ml. of pyridine. The mixture was heated under reflux for 90 minutes and then poured into 1 l. of water. The crude product, obtained by filtration was washed with water (900 ml.), cold ethanol (600 ml.) and recrystallized from a mixture of chloroform and ethanol to give 55.8 g. (70%) of Va as white prisms, m.p. 154–156°.

*Anal.* Calcd. for $C_{22}H_{19}ClN_2O_2S$: C, 64.30; H, 4.66. Found: C, 64.40; H, 4.84.

7-Chloro-2,3-dihydro-1-methanesulfonyl-5-phenyl-1*H*-1,4-benzodiazepine (Vb).

A solution of 200 g. (0.78 mole) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (7) in 800 ml. of pyridine was cooled to 10° and treated dropwise with 66.6 ml. (0.86 mole) of methanesulfonyl chloride. The mixture was stirred at room temperature for 18 hours and then poured into 4 l. of water. The crude product was separated by filtration, washed with 1.6 l. of water and 900 ml. of ether. The precipitate was dissolved in 300 ml. of chloroform which was washed with water (2 x 500 ml.), dried over sodium sulfate, concentrated to a small volume and cooled. The product was obtained by filtration and recrystallized from a mixture of chloroform and ethanol to give 160 g. (61%) of Vb as white prisms, m.p. 170–173°.

*Anal.* Calcd. for $C_{16}H_{15}ClN_2O_2S$: C, 57.39; H, 4.52; N, 8.37. Found: C, 57.31; H, 4.52; N, 8.64.

4'-Chloro-2'-(*N*-vinylbenzimidoyl)-*p*-toluenesulfonanilide (VIa).

A solution of 5 g. (0.0122 mole) of Va in 40 ml. of dry *N,N*-dimethylformamide was treated with 0.54 g. (0.0134 mole) of a 60% dispersion of sodium hydride in mineral oil and stirred for 30 hours at room temperature. The mixture was poured into 200 ml. of water and the product was extracted into dichloromethane (2 x 150 ml.). The organic extracts were combined, washed with water (3 x 100 ml.) dried over sodium sulfate and evaporated. The residual oil was dissolved in a small amount of benzene and chromatographed over 25 g. of Florisil using benzene, hexane (1:1) as the eluent. Removal of solvent gave 0.9 g. of an oil which crystallized on standing. Recrystallization from a mixture of dichloromethane and hexane gave 0.5 g. (10%) of VIa as white prisms, m.p. 140–142°.

*Anal.* Calcd. for $C_{22}H_{19}ClN_2O_2S$: C, 64.30; H, 4.66. Found: C, 64.37; H, 4.89.

4'-Chloro-2'-(*N*-vinylbenzimidoyl)methanesulfonanilide (VIb).

A solution of 80 g. (0.24 mole) of Vb in 650 ml. of dry *N,N*-dimethylformamide was treated with 21 g. (0.526 mole) of a 60% dispersion of sodium hydride in mineral oil and then heated at 60° for 1 hour. Solvent was removed under reduced pressure and the residue was triturated with 800 ml. of dichloromethane and filtered over Celite. The solution was next treated with 1 l. of water and the *p*H was adjusted to 7 with dilute hydrochloric acid. The layers were separated and the organic layer was washed with water (2 x 250 ml.), dried over sodium sulfate and evaporated. The residual oil was dissolved in benzene and filtered over 250 g. of Florisil contained in a large diameter sintered glass funnel. Removal of the solvent from the benzene filtrate gave 33 g. of almost pure VIb. By changing the eluent to ether, an additional 31 g. of VIb was obtained by removal of the solvent. The two fractions were combined and recrystallized from ether to give 41 g. (51%) of pure VIb as yellow prisms, m.p. 122-124°; nmr peaks ($CDCl_3$) at δ 3.07 (3H singlet, $CH_3S$) at δ 5.10 (1H doublet, J = 7.5 cps, $H_a$) at δ 5.65 (1H doublet, J = 15 cps, $H_b$) at δ 6.66 (1H quartet, J = 7.5, 15 cps $H_c$) $H_c$>C=C<$H_b$, $H_a$; at δ 6.95-7.75 (8H aromatic multiplet) and at δ 13.88 (1H singlet, NH): ultraviolet maxima (Carey Model 14 Spectrophotometer, isopropanol) at 236 (ε, 27,000) at 284 (ε, 10,200) and at 340 mμ (ε, 4,500).

*Anal.* Calcd. for $C_{16}H_{15}ClN_2O_2S$: C, 57.39; H, 4.52. Found: C, 57.51; H, 4.50.

5-Chloro-2-*p*-toluenesulfonamidobenzophenone (VIIa) (8).

A solution of 0.4 g. of VIa in 5 ml. of ethanol and 3 ml. of 3 *N* hydrochloric acid was heated on a steam bath for 15 minutes, 100 ml. of water was added and the residue was neutralized with dilute sodium hydroxide solution. The product was extracted into 30 ml. of dichloromethane. The organic layer was separated, washed with water (2 x 300 ml.) dried over sodium sulfate and evaporated. The residue was recrystallized from ethanol to give 0.2 g. of VIIa as white prisms, m.p. and m.m.p. with an authentic sample (8), 119–121° [lit. m.p. 120-121°].

5-Chloro-2-methylsulfonamidobenzophenone (VIIb).

A. From VIb.

A solution of 3 g. of VIb in 10 ml. of ethanol and 5 ml. of 3 *N* hydrochloric acid was heated on a steam bath for 15 minutes. Water (100 ml.) was added and the mixture was neutralized with dilute sodium hydroxide solution. The product was extracted into dichloromethane (2 x 50 ml.). The organic layers were combined, washed with water (2 x 200 ml.) dried over sodium sulfate and evaporated. The residual oil was crystallized from a mixture of hexane and dichloromethane to give 1.2 g. (43%) of VIIb as white prisms, m.p. 133–135°.

*Anal.* Calcd. for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.90. Found: C, 54.55; H, 4.24.

B. From 2-Amino-5-chlorobenzophenone (X) (8).

A solution of 10 g. (0.043 mole) of X in 40 ml. of pyridine was treated with 3.8 ml. (0.05 mole) of methanesulfonyl chloride and warmed at 60° for 1 hour. The solution was cooled, allowed to stand overnight, and then poured into 200 ml. of water. The product was separated by filtration, washed with water and ether. Recrystallization from a mixture of chloroform and ether gave 9.0 g. (67%) of VIIb as white prisms, m.p. and m.m.p. with a sample prepared as in Method A above 133–135°.

5-Chloro-2-methylsulfonamido-*N*-ethylbenzhydrylamine (VIIIb).

A. From Compound VIb.

A solution of 2 g. (0.006 mole) of VIb in 15 ml. of tetrahydrofuran was added dropwise to a solution of 0.46 g. (0.012 mole) of lithium aluminum hydride in 40 ml. of tetrahydrofuran and the resulting mixture was stirred at room temperature for 5 hours. A saturated solution of potassium bicarbonate was added until the precipitate coagulated and the reaction mixture was filtered over Celite. The filter cake was washed with 150 ml. of dichloromethane and the combined filtrates were evaporated. The residual oil was dissolved in 50 ml. of dichloromethane and water was added. The aqueous layer was neutralized with dilute hydrochloric acid and the layers were separated. The organic layer was washed with water (2 x 150 ml.) dried over sodium sulfate and evaporated to give 1.5 g. of a yellow oil. The oil was crystallized and recrystallized from a mixture of ether and hexane to give 0.6 g. (30%) of VIIIb as white prisms, m.p. 107–109°.

*Anal.* Calcd. for $C_{16}H_{19}ClN_2O_2S$: C, 56.71; H, 5.65; N, 8.27. Found: C, 56.78; H, 5.62; N, 8.31.

B. From Compound IXb.

A solution of 10 g. of IXb in 50 ml. of thionyl chloride was heated under reflux for 2 hours. Excess thionyl chloride was removed by distillation while adding 150 ml. of toluene. The toluene solution was cooled to room temperature and a solution of 1.5 g. of ethylamine in 50 ml. of toluene was added dropwise. The resulting solution was stirred at room temperature for 0.5 hours, washed with water (3 x 300 ml.), dried over sodium sulfate and evaporated. The residual oil was crystallized from a mixture of ether and hexane to give 2.3 g. (21%) of VIIIb as white prisms, m.p. and m.m.p. with a sample obtained by method A above 107-109°.

5-Chloro-2-methylsulfonamidobenzhydrol (IXb).

A solution of 65 g. (0.21 mole) of VIIb in 300 ml. of ethanol was treated with 9.9 g. (0.262 mole) of sodium borohydride and the mixture was allowed to stand at room temperature for 3 hours. Ethanol was removed under reduced pressure and the residue was treated with 800 ml. of dichloromethane and 800 ml. of water. The aqueous layer was acidified with hydrochloric acid and the layers were separated. The organic layer was washed with water (3 x 800 ml.) dried, concentrated to a small volume, treated with hexane and cooled. Filtration afforded 58.2 g. (89%) of IXb as white prisms, m.p. 143–146°.

*Anal.* Calcd. for $C_{14}H_{14}ClNO_3S$: C, 53.93; H, 4.53; N, 4.49. Found: C, 54.01; H, 4.31; N, 4.43.

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(2) Tosyl = *p*-toluenesulfonyl; mesyl = methanesulfonyl.

(3) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, 26, 4936 (1961).

(4) When one equivalent of sodium hydride was used, thin layer chromatography of the solution indicated the presence of approximately 50% of III and 50% of starting material.

(5) A visual estimation of the thin layer chromatography of the

reaction mixture showed a 50/50 mixture of starting material and product.

(6) This compound was originally synthesized by Dr. G. A. Archer of these laboratories.

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