[Chem. Pharm. Bull. 17(6)1115—1119(1969)]

UDC 547.833.1.04 : 541.144

Organic Photochemistry. I.[1] 3,4-Dihydroisoquinolines from Tetrahydroisoquinoline N-Tosylates

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(Received July 3, 1968)

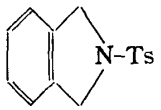
Photolysis of 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline N-tosylates (Va—d) with high pressure mercury lamps (100W and 400W) in neutral (EtOH) or basic [80% (v/v) EtOH containing Na_2CO_3] media was examined. Under these conditions, 3,4-dihydro compounds (VIIa—d) were formed in moderate yields.

p-Toluene sulfonyl group has long been used as a protective group[3] of amino or hydroxy, in such cases as the syntheses of secondary amines from primary amines or of peptides.

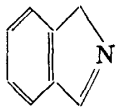
In general, *p*-toluene sulfonamides are formed easily. However, removal of the group sometimes meets considerable difficulty.

Hydrolysis of sulfonamides is usually performed with strong mineral acids or reductive conditions[4] to afford the corresponding amines.

On the other hand, the reactions of sulfonamides with bases were studied by Ingold, *et al.*[5] and for example I was converted to isoindoline (II) under mild conditions. In addition to this finding, Proctor, *et al.*[6] recently claimed that some sulfonamides (III) were transformed to their Schiff bases in the presence of sodium alkoxide in toluene at room temperature.



I



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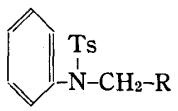

III : R=COPh,
R=PhNO$_2$(*p*)

Chart 1

From these data, it might be expected that amines and/or Schiff bases would be produced from sulfonamides with ultraviolet irradiation instead of basic catalysts. This exceptation together with the fact that few photochemical reactions of sulfonamides were investigated so far prompted us to examine photochemical behavior of 1-substituted 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline N-tosylates in neutral or basic conditions.

Expectedly, *p*-toluenesulfinyl anion (though not isolated) were eliminated from N-tosylates to give the corresponding 3,4-dihydroisoquinolines in moderate yields. The starting materials, N-tosylates (Va—d), were synthesized from the corresponding tetrahydroisoquinolines (IVa—d) by Schotten-Baumann method.

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2) Location: *12, Ichigayafunagawara-machi, Shinjuku-ku, Tokyo.*
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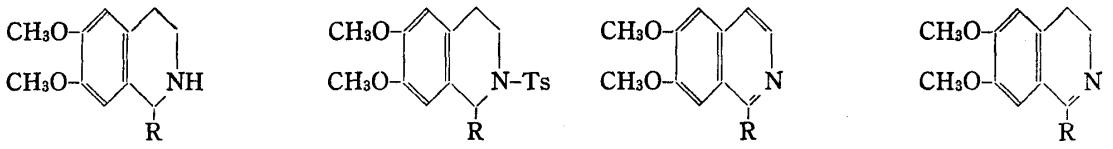

IVa : R=H
IVb : R=CH_3
IVc : R=Ph
IVd : R=CH_2Ph

Va—d VIa—d VIIa—d

Chart 2

Firstly, irradiation of Va—c in EtOH (15—20°) with high pressure mercury lamp (100 W) in an atmosphere of nitrogen was continued, until spots due to the starting materials on thin-layer chromatography (TLC) disappeared. In the present experiments, it took about 6—8 hr and the TLC showed a newly formed 2—3 spots, all having smaller *Rf* values than those of the starting materials. The residues obtained from Va—c upon removal of the solvent under reduced pressure were subjected to chromatographic purification (Florisil or silicic acid) yielding 6,7-dimethoxy-3,4-dihydroisoquinoline (VIIa)[7] (51.2%, picrate, mp 201—206°); 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIIb)[8] (56.6%, mp 99—101°), Vb (17%), and 1-methyl-6,7-dimethoxyisoquinoline (VIb)[9] (14.9%, picrate, mp 235—240°); 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIIc)[10] (46%, mp 113—116.5°), respectively.

Since chromatographic separation of the products from Vd was fruitless, the resultant products were directly reduced with $NaBH_4$ in MeOH followed by chromatography to give 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVd)[11] (37.6%, oxalate, mp 228—231°), and 1-benzyl-6,7-dimethoxyisoquinoline (VId)[12] (19.6%) as an oil.

Secondly, in the presence of Na_2CO_3 (one equivalent for each Va—c), disappearance of the starting materials on TLC was attained after 7—9 hr' irradiation of Va—c in 80% (v/v) EtOH under the same conditions as described above. Usual work-up and chromatography of the reaction mixtures yielded 6,7-dimethoxyisoquinoline (VIa),[13] VIIa, and Va; VIb, and VIIb; 1-phenyl-6,7-dimethoxyisoquinoline (VIc),[14] VIIc, and IVc,[15] respectively.

Table I

Compound (mg)		Condition	Reaction time (hr)	Yield (%) of products			Recovery (%) of V
				VI	VII	IV	
Va	100.0	A	8.5	—	51.2	—	—
	300.0	B	7.0	19.4	38.0	—	33.3
Vb	180.0	A	7.0	14.9	56.6	—	17.0
	180.0	B	9.0	11.3	47.2	—	—
Vc	212.8	A	7.5	—	46.0	—	—
	200.0	B	8.0	32.0	23.6	16.5	—
Vd	100.0	A	8.0	19.6	—	37.6	—
	220.0	B	7.0	2.7	—	40.4	—

A: EtOH B: 80% (v/v) EtOH containing Na_2CO_3

7) F. L. Pyman, *J. Chem. Soc.*, **95**, 1619 (1909).
8) E. Späth and N. Polger, *Monatsch.*, **51**, 198 (1929).
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In addition, $NaBH_4$ treatment of the products from Vd gave both VId and IVd. Results were shown in Table I.

Further, in the hope of shortening reaction time and improving yield of 3,4-dihydro compounds, a high pressure mercury lamp (400 W) was used in the same conditions as noted above and the results were shown in Table II.

Table II

Compound (mg)		Condition	Reaction time (hr)	Yield (%) of products			Recovery (%) of V
				VI	VII	IV	
Va	347.0	A	2.5	22.2	11.4	—	23.6
	270.0	B	2.0	13.8	24.3	—	16.0
Vb	500.0	A	3.0	26.5	54.5	—	26.1
	500.0	B	3.5	24.0	47.2	—	—
Vc	423.5	A	3.0	22.8	39.4	31.5	15.6
	423.5	B	3.0	33.2	34.4	30.9	—
Vd	429.7	A	3.5	23.8	—	51.9	10.1
	437.0	B	3.0	11.1	—	42.6	—

A: EtOH B: 80% (v/v) EtOH containing Na_2CO_3

Although reaction time was shortened as expected, the yield of 3,4-dihydro compound (VIIa) was reduced in neutral condition and that of isoquinolines (VIa—d) increased. Furthermore, IVc, VIc, and VIIc were obtained irrespective of reaction media in the case of Vc. The fact that IVc was obtained under every conditions except 100 W lamp's irradiation in a neutral medium suggested that its formation might be due to photo-reduction, but the exact reason was still ambiguous.

From the above experiments, the formation of 3,4-dihydro compounds (VIIa—d) appeared to be decreased in the following order; neutral (100 W), basic (100 W), basic (400 W), and neutral (400 W).

On the other hand, the fact that isoquinolines (VIa—d) were produced in every case except in the case of Vc (100 W, neutral medium) seemed to be promissing for easy conversion of N-tosylates themselves or 3,4-dihydro compounds to the corresponding isoquinolines by means of photo-oxidation.

Experimental[16]

Preparations of N-Tosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline derivatives (Va—d)——N-Tosylates were prepared by Schotten–Baumann reaction of the corresponding amines (IVa—d) with tosyl chloride and their melting points and analyses were shown in Table III.

Irradiation of N-Tosyl-1,2,3,4-tetrahydroisoquinoline (Va)——1. a) A solution of Va (100 mg) in EtOH[17] (160 ml) was irradiated for 8.5 hr. After removal of the solvent under reduced pressure and extraction of the product with $CHCl_3$, the $CHCl_3$ layer was rinsed with saturated $NaHCO_3$ solution, brine and dried

16) All melting points were uncorrected using a Yanagimoto micro melting point measuring apparatus. Products were isolated by column chromatography on silicic acid (Mallinckrodt, Chemical Works) unless otherwise noted and their identifications were performed by gas liquid chromatography (GLC) using a Shimadzu GC–1C gaschromatograph (hydrogen flame ionization detector) with 2% SE–30 on Shimalite W (80—100 mesh) as stationary phase, thin–layer chromatography (TLC) run on silicagel G (Merck) with C_6H_6–MeOH (3:1) as developing solvent and by infrared (IR) spectroscopy using a Hitachi EPI–S_2. Irradiations were carried out at 10—25° in solution [a) neutral and b) basic media], with a quartz reactor and high pressure mercury lamps [1) 100 W and 2) 400 W, Ōsawa UV-HT] without light filter, under N_2 stream purified through sodium anthraquinone-β-sulfonate solution and concd. sulfuric acid.

17) Absolute ethanol (commercial grade).

Table III

Compound	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Va	141 —143	$C_{18}H_{21}O_4NS$	62.23	6.09	4.03	62.34	6.09	4.10
Vb	150.5—152.5	$C_{19}H_{23}O_4NS$	63.14	6.41	3.88	62.80	6.41	3.89
Vc	119 —120.5	$C_{24}H_{25}O_4NS$	68.05	5.96	3.31	67.90	5.96	3.38
Vd	oil[a]							

a) The compound was directly used as a starting material after purification (single spot on TLC) by column chromatography on Al_2O_3 (Merck) (elution with benzene), since much efforts to crystallize or distill under reduced pressure failed.

(K_2CO_3). Removal of the solvent gave an oil (63.3 mg) which was chromatographed on Florisil (60—100 mesh) to afford an oil [28.1 mg (51.2%), single spot on TLC; picrate, mp 201—206° (MeOH): elution with $CHCl_3$–MeOH (100:1)—(100:16)], which was identical with 6,7-dimethoxy-3,4-dihydroisoquinoline (VIIa) (lit.[7] picrate, mp 206 —208°) by their IR spectral comparison and by mixed fusion of each picrate, and another oil (21 mg) [elution with $CHCl_3$–MeOH (100:16)—(1:1)] which was not characterized as Va.

b) A solution of Va (300 mg) and Na_2CO_3 (90 mg) in 80% (v/v) EtOH (85 ml) was irradiated for 7 hr. After removal of the solvent under reduced pressure and addition of brine to the residue, the product was taken up in $CHCl_3$. On extraction of the $CHCl_3$ layer with 10% HCl solution, the acidic solution was basified with Na_2CO_3 (powder) and the product was extracted with $CHCl_3$. The $CHCl_3$ layer was rinsed with brine and dried (K_2CO_3). Evaporation of the solvent gave an oil (98.9 mg), which was chromatographed on Florisil to afford an oil [21.1 mg (19.4%), single spot on TLC; picrate, mp 219—220° (MeOH): elution with $CHCl_3$–MeOH (100:0.1)] which was characterized as 6,7-dimethoxyisoquinoline (VIa) (lit.[13] picrate, mp 218—220°) by their IR spectral comparison and by mixed fusion of each picrate, and VIIa [41.8 mg (38.0%): elution with $CHCl_3$–MeOH (100:2)], respectively. A neutral oil [99.9 mg (33.3%)] was characterized as Va.

2. a) An ethanolic solution (270 ml) of Va (347 mg) was irradiated for 2.5 hr. The same treatment as noted in 1-b) gave a basic oil (146.6 mg) and Va [82 mg (23.6%)] respectively. Chromatography of the former gave VIa [37 mg (22.2%): elution with $CHCl_3$–MeOH (100:1)] and VIIa [16.6 mg (11.4%): elution with $CHCl_3$–MeOH (100:2)], respectively.

b) A solution of Va (270 mg) and Na_2CO_3 (85 mg) in 80% (v/v) EtOH (280 ml) was irradiated for 2 hr. The similar work-up as noted above yielded a basic oil (123.2 mg) and Va [43.2 mg (16%)]. The former was purified by chromatography on Florisil to give VIa [17.0 mg (13.8%): elution with $CHCl_3$ and $CHCl_3$–MeOH (100:0.5)] and VIIa [30.3 mg (24.3%): elution with $CHCl_3$–MeOH (100:1)—(100:2)], respectively.

Irradiation of N-Tosyl-1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vb)——1. a) Photolysis of an ethanolic solution (80 ml) of Vb (180 mg) was carried out for 7 hr to afford a basic oil (80.5 mg) and Vb [30.6 mg (17.0%)].

The former was chromatographed to give an oil [12.5 mg (14.9%), single spot on TLC; picrate, mp 235—240°: elution with $CHCl_3$ and $CHCl_3$–MeOH (100:1)] which was identical with 1-methyl-6,7-dimethoxyisoquinoline (VIb) (lit[9] mp 107—108°; picrate, mp 247—249°) by comparison of their IR spectra and retention times of GLC and by mixed fusion of each picrate, and crystals [48 mg (56.6%), mp 99—101° (*n*-hexane), single spot on TLC: elution with $CHCl_3$ and $CHCl_3$–MeOH (100:1)], which were identical with 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIIb) (lit.[8] mp 106—107°) by their IR spectral comparison and by mixed fusion.

b) Irradiation of a solution of Vb (180 mg) and Na_2CO_3 (53 mg) in 80% (v/v) EtOH (70 ml) for 9 hr yielded a basic oil (76.6 mg) and a neutral one (21.0 mg; not identical with Vb) respectively. Chromatography of the former gave VIb [11.4 mg (11.3%): elution with $CHCl_3$] and VIIb[48.3 mg (47.2%): elution with $CHCl_3$–MeOH (100:1)—(100:4)], respectively.

2. a) Photolysis of an ethanolic solution (270 ml) of Vb (500 mg) was carried out for 3 hr to yield a basic oil (232.6 mg), which was purified by chromatography to afford VIb [55 mg (26.5%): elution with $CHCl_3$ and $CHCl_3$–MeOH (100:1)] and VIIb [104.5 mg (54.5%): elution with $CHCl_3$–MeOH (100:1)—(100:4)] and Vb [130.3 mg (26.1%)].

b) Irradiation of a solution of Vb (500 mg) and Na_2CO_3 (147 mg) in 80% (v/v)EtOH (280 ml) for 3.5 hr gave a basic oil (292.1 mg) and a neutral one (33.3 mg; not identical with Vb) respectively. The former was chromatographed to give VIb [67.5 mg (24%): elution with $CHCl_3$ and $CHCl_3$–MeOH (100:1)] and an oil [200.9 mg: elution with $CHCl_3$–MeOH (100:1)—(3:1)], which was re-chromatographed to afford VIIb [148.2 mg (47.2%): elution with $CHCl_3$–MeOH (100:3)—(100:8)].

Irradiation of N-Tosyl-1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vc)——1. a) Photolysis of an ethanolic solution (80 ml) of Vc (212.8 mg) for 7.5 hr afforded an oil (156 mg). Chromatography of the oil gave crystals [61.7 mg (46%), mp 113—116.5° (AcOEt): elution with $CHCl_3$] which were identical with 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (VIIc) (lit.[10] mp 120—121°) by comparison of their IR spectra and retention time of GLC and by mixed fusion.

b) Photolysis of a solution of Vc (200 mg) and Na_2CO_3 (50 mg) in 80% (v/v) EtOH (140 ml) for 8 hr gave an oil (146.6 mg) which was subjected to chromatographic purification. Elution with $CHCl_3$ gave an oil [40 mg (32%), single spot on TLC; picrate, mp 183—185° (MeOH). *Anal.* Calcd. for $C_{23}H_{18}O_9N_4$: C, 55.87, H, 3.67, N, 11.23. Found: C, 56.03, H, 3.94, N, 11.39], which was identified with 1-phenyl-6,7-dimethoxyisoquinoline (VIc) (lit.[14] picrate, mp 250°) by their IR spectral comparison and by mixed fusion of each picrate, and VIIc [29.8 mg (23.6%)] successively. Elution with $CHCl_3$ and $CHCl_3$–MeOH (100:3) gave an oil [20.7 mg (16.5%), single spot on TLC; picrate, mp 221—223.5° (MeOH). *Anal.* Calcd. for $C_{23}H_{21}O_9N_4$: C, 55.42, H, 4.45, N, 11.24. Found: C, 55.12, H, 4.68, N, 11.24], which was identical with 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVc) (lit.[15] mp 124—125°) by their IR spectral comparison and by mixed fusion of each picrate.

2. a) Photolysis of an ethanolic solution (270 ml) of Vc (423.5 mg) for 3 hr furnished an oil (370 mg) which was chromatographed to afford Vc [65.8 mg (15.6%)] and VIc [51.0 mg (22.8%)] from eluate with $CHCl_3$ successively, VIIc [89.0 mg (39.4%)] from eluate with $CHCl_3$–MeOH (100:0.5)—(100:1.5), and IVc [71.5 mg (31.5%)] from eluate with $CHCl_3$–MeOH (100:3), respectively.

b) Photolysis of a solution of Vc (423.5 mg) and Na_2CO_3 (106 mg) in 80% (v/v) EtOH (270 ml) was carried out for 3 hr. Usual treatment followed by chromatography gave VIc [89.3 mg (33.2%): elution with $CHCl_3$], VIIc [91.9 mg (34.4%): elution with $CHCl_3$ and $CHCl_3$–MeOH (100:1)] and IVc [83.2 mg (30.9%): elution with $CHCl_3$–MeOH (100:2)—(100:5)], respectively.

Irradiation of N-Tosyl-1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (Vd)——1. a) An ethanolic solution (60 ml) of Vd (100 mg) was irradiated for 8 hr. The residue (99.6 mg) obtained after a usual work-up was dissolved in MeOH and a methanolic solution was treated with $NaBH_4$ (100 mg) under stirring at room temperature for 1 hr and the mixture was heated for additional 2 hr. After removal of the solvent water was added to the residue and the product was taken up in $CHCl_3$. Evaporation of the solvent gave an oil (78.1 mg) which was chromatographed to afford an oil [12.5 mg (19.6%): elution with $CHCl_3$–MeOH (100:0.1)—(100:0.2)] which was identical with 1-benzyl-6,7-dimethoxyisoquinoline (VId) (lit.[12] mp 69—70°) by comparison of their IR spectra and retention time of GLC and an oil (24.2 mg (37.6%); oxalate, mp 228—231° (decomp.) (MeOH): elution with $CHCl_3$–MeOH (100:0.5)—(100:3)] which was characterized as 1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IVd) [lit.[11] oxalate, mp 231—232° (decomp.)] by comparison of their IR spectra and retention time of GLC and by mixed fusion of each oxalate.

b) A solution of Vd (220 mg) and Na_2CO_3 (53 mg) in 80% (v/v)EtOH (90 ml) was irradiated for 7 hr. The same treatment of the reaction mixture as noted above gave an oil (133.9 mg) which was chromatographed to yield VId [3.8 mg (2.7%): elution with $CHCl_3$] and IVd [56.9 mg (40.4%): elution with $CHCl_3$–MeOH (100:1)—(100:3)], respectively.

2. a) Photolysis of an ethanolic solution (260 ml) of Vd (429.7 mg) for 3.5 hr gave an oil (297 mg), whose chromatography afforded Vd [43.2 mg (10.1%): elution with $CHCl_3$], VId [58.7 mg (23.8%): elution with $CHCl_3$ and $CHCl_3$–MeOH (100:1)] and IVd (130.1 mg (51.9%): elution with $CHCl_3$–MeOH (100:1)—(100:5)], respectively.

b) Photolysis of a solution of Vd (437 mg) and Na_2CO_3 (106 mg) in 80% (v/v)EtOH (260 ml) for 3 hr gave an oil (304 mg), which was chromatographed to furnish VId [30.9 mg (11.1%): elution with $CHCl_3$] and IVd [120.5 mg (42.6%): elution with $CHCl_3$–MeOH (100:1)—(100:3)], respectively.

Acknowledgement The authors wish to thank Dr. I. Iwai of Sankyo Co., Ltd. and Prof. M. Hamana of Kyushu University for their interest in this work. They are indebted to Dr. T. Moroe of Takasago Perfumery Co., Ltd. for his kind supply of the starting material. Thanks are also due to Dr. Y. kishida and Dr. H. Mishima of Central Research Laboratories of Sankyo Co., Ltd. for valuable discussions and elemental analyses.