Summary

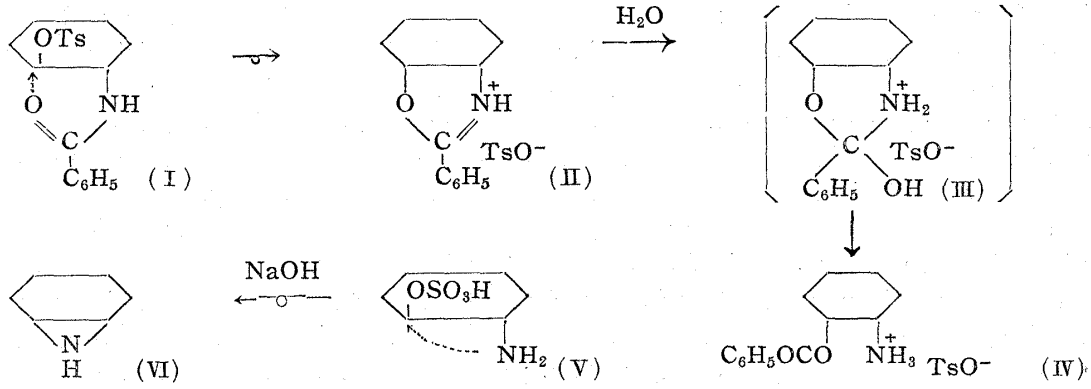
The dehydrogenation of the insecticidal distillate of birch tar oil with selenium was carried out in order to elucidate its chemical structure. The product obtained was a light yellow oil of b.p_7 117°, n^{21} 1.5219, whose analytical data corresponded to the formula of $C_{13}H_{14}$ or $C_{15}H_{16}$. However, this substance was not identical with synthetic 1,2,7-trimethylnaphthalene from the present experimental results which suggest that the possible structures which meet the requirements would be tetralene or indene derivatives.

(Received June 9, 1955)

69. Tanezo Taguchi and Masaharu Kojima : Studies in Stereochemistry. VI.[1] Solvolysis Reactions of *dl-cis*-2-Benzoylaminocyclohexyl Tosylate.

(*Pharmaceutical Institute, Medical Faculty, University of Kyushu**)

It has been reported by McCasland,[2] Winstein,[3] and Taguchi[4] separately that solvolysis of *dl-trans*-2-benzoylaminocyclohexyl tosylate (I) in the presence of water or ethanol gave rise to *dl-cis*-2-benzoyloxycyclohexylamine tosylate (IV) in a good yield via *dl-cis*-2-phenyl-4,5-cyclohexanoöxazolinium tosylate (II). The formation of the *dl-cis*-oxazolinium salt (II) as an intermediate was proved by its isolation and due to the anchimeric property of the neighboring acyl group, suggesting a probable reaction mechanism for the solvolysis. It is properly supposed that the two geometrical isomers of 2-aminocyclohexanols, owing to the difference of the steric configuration, vary from each other in their chemical properties. In the *trans* isomer, the two functional groups, hydroxyl and amino, can interconvert between *aa* ⇄ *ee* conformations. Therefore, the amino group can easily approach the carbon atom with the hydroxyl group from behind. For example, treatment of *dl-trans*-2-aminocyclohexylsulfuric acid (V) with aqueous sodium hydroxide causes the formation of *meso-cis*-cyclohexenimine[5] (VI) by the anchimeric property of the neighboring amino group. In *dl-trans*-2-benzoylaminocyclohexyl tosylate (I) the N-acyl group has a larger driving force due to its anchimeric property than a naked amino group, and therefore, treatment of (I) only with boiling dry

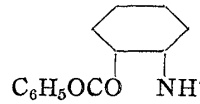


* Katakasu, Fukuoka (田口胤三, 小島正治).

1) Part V : J. Pharm. Soc. Japan, **75**, 666(1955).
2) G. E. McCasland, R. K. Clark, H. E. Carter : J. Am. Chem. Soc., **71**, 637(1949).
3) S. Winstein, R. Boschan : *Ibid.*, **72**, 4669(1950).
4) T. Taguchi, M. Nakayama : *Ibid.*, **73**, 5679(1951).
5) O. E, Paris, P. E. Fanta : *Ibid.*, **74**, 3007(1952).

benzene[3] gives rise to the *dl-cis*-oxazolinium salt (II).

In *dl-cis*-2-aminocyclohexanol, conformation of amino and hydroxyl groups is *e-a* or *a-e*, hence the amino group, even if N-acylated, is probably hard to approach the carbon atom with the hydroxyl group from the back, in the prohibitively strained cyclohexane ring. Experimentally, it has been shown by Winstein[6] that the participation of neighboring group was affected less in *cis* form than in *trans* form. In spite of Winstein's description[6] that the solvolysis of *dl-cis*-2-benzoylaminocyclohexyl tosylate (VII) is far from simple and that the matter will be dealt with in a subsequent article, no publication concerning the solvolysis has been found. Therefore, the solvolysis of (VII) was attempted in the present series of expriments. *dl-cis*-2-Benzoylaminocyclohexyl tosylate (VII) had been independently prepared by McCasland[2] and Winstein,[3] but its melting point was listed as 163~165° by the former and 162~163° by the latter. On repeating the two procedures and recrystallizing from ethanol, (VII) showed a melting point of 174~175° in both cases. Besides, McCasland's procedure resulted in the formation of *dl-cis*-2-tosylaminocyclohexyl benzoate[7] (XIII), m.p. 178~179°, as a by-product. *dl-cis*-2-Benzoylaminocyclohexyl tosylate solvolyzed under the following four conditions: (a) In absolute ethanol, (b) in 60% aqueous ethanol, (c) in water, and (d) in dry acetic acid. Under the conditions a, b, and c, the solvolysis reaction hardly took place at the boiling point of the solvents, and therefor, it was worked up by heating at 130~140° in a sealed tube. Under the condition d, the reaction occurred easily at the boiling point of the solvent. In the reaction products, following substances were found.

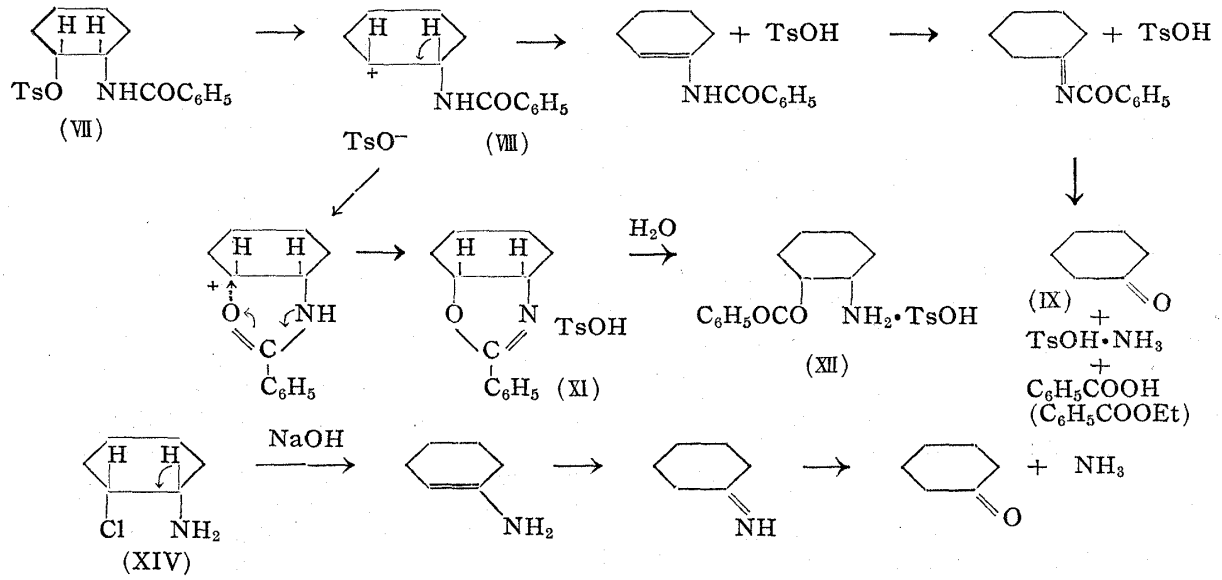


(XIII)

Reaction conditions	Substances found in the reaction products
a	Cyclohexanone(IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate(XII), *dl*-2-ethoxycyclohexylamine benzoate(XVIII), ethyl benzoate, and TsOH·NH_3
b	Cyclohexanone(IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate(XII), *dl-trans*-2-benzoyloxycyclohexylamine tosylate(XVII), ethyl benzoate, benzoic acid, and TsOH·NH_3
c	Cyclohexanone(IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate(XII), *dl-trans*-2-benzoyloxycyclohexylamine tosylate(XVII), benzoic acid, and TsOH·NH_3
d	Cyclohexanone(IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate(XII), benzoic acid, and TsOH·NH_3

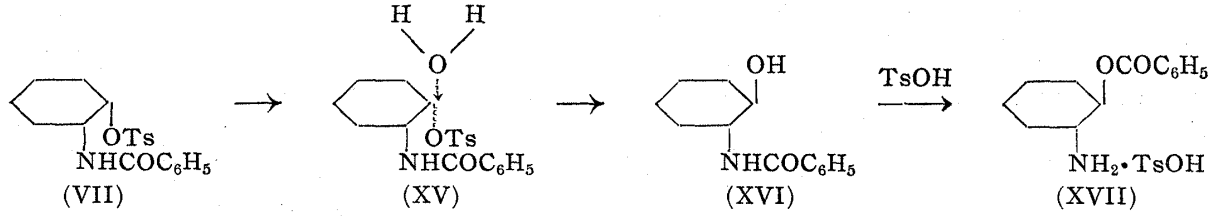
In general, the results could not be explained satisfactorily by the participation of the neighboring group as seen in the case of *dl-trans*-2-benzoylaminocyclohexyl tosylate (I). The formations of cyclohexanone (IX) and *dl-cis*-2-benzoyloxycyclohexylamine tosylate (XII) were common to solvolysis under all of the sets of conditions, resulting in the assumption of following reaction mechanism. The reactions are probably first order reactions which are usually started by the liberation of TsO^- and the formation of a carbonium cation (VIII). When the formation of 1-benzoylaminocyclohexene is followed through *trans*-elimination of *p*-toluenesulfonic acid, it is subsequently tautomerized to the ketone (IX). The result is analogous with Paris' finding[5] that cyclohexanone was obtained by the basic solvolysis of *dl-cis*-2-chlorocyclohexylamine (XIV). Otherwise when the carbonium cation (VIII) is attacked by oxygen of the benzoyl group, *dl-cis*-benzoyloxycyclohexylamine is formed as the end-product via *dl-cis*-oxazoline(XI), cleavage of which is known to occur easily in the presence of TsOH. It is due to being less strained, that the ring formation of oxazoline is orientated rather to *cis* than to *trans* configuration.

6) S. Winstein, E. Grunwald: J. Am. Chem. Soc., **68**, 119(1946).
7) G. Fodor, J. Kiss: *Ibid.*, **72**, 3495(1950).



The yield of cyclohexanone in each case was inferior to the yield calculated on the basis of quantities of *p*-toluenesulfonic acid and ammonia obtained. The disparity in yield may arise from side reactions. Actually in the present solvolysis there were always obtained small amounts of oily products whose constitutions were not identified.

dl-trans-2-Benzoyloxycyclohexylamine tosylate (XVII) was found only in the solvolysis products in the presence of water, viz. in 60% ethanol (condition b) or water (condition c) and never in absolute ethanol (condition a) or dry acetic acid (condition d). If the formation of (XVII) is interpreted as a second order substitution involving liberation of TsO^- with the participation of the neighboring benzoyl group, there are no reasons why (XV) is found on treatment in the presence of water, but never on treatment with absolute ethanol or dry acetic acid. Therefore, it is assumed that, having no connection with acyl participation, the formation of (XVII) occurred through Sn_2 displacement at the carbon with a tosyloxy group by water with inversion, followed by acyl migration N→O as depicted by formulae (VII)→(XV)→(XVI)→(XVII).



Only on treatment of (VII) with absolute ethanol (condition a), there was obtained one geometric form of *dl*-2-ethoxycyclohexylamine tosylate (XVIII), whose configuration was presumably *trans* because the reaction is supposed to proceed through the same mechanism as the formation of (XVII) illustrated above.

The authors are indebted to the Ministry of Education for the Grant in Aid for Scientific Research and to Messrs. T. Hattori and J. Maeda for the microanalyses.

Experimental[8]

***dl-cis*-2-Benzoylaminocyclohexyl Tosylate (VII)**—a) By McCasland's procedure[2]: To a suspension of 30 g. of *dl-cis*-2-benzoylaminocyclohexanol in 60 cc. of pyridine was added 30 g. of *p*-toluenesulfonyl chloride under chilling in an ice-water bath and the mixture was al-

8) All melting points are uncorrected.

lowed to stand for 3 days at 25~28°. Under cooling with ice and salt, the reaction mixture was neutralized with 350 cc. of 10% aq. HCl, 250 cc. of water added, and the precipitate was filtered off; m.p. 151~159°; yield, 41 g. Recrystallization from 800 cc. EtOH gave colorless needles, m.p. 171~173°, raised to 174~175° after another recrystallization. *Anal.* Calcd. for $C_{20}H_{23}O_4NS$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.21; H, 5.78; N, 3.87.

EtOH mother liquor was evaporated to 150 cc. and the precipitate, after cooling, was collected; m.p. 159~163°; Yield, 0.95 g. After recrystallization from EtOH, it showed m.p. 184~185° and no depression of m.p. on admixture with an authentic sample of *dl-cis*-2-benzoylaminocyclohexanol.

The benzene solution was evaporated to dryness and left 6 g. of a residue, m.p. 161~164°. Recrystallization from EtOH gave colorless prisms, but in spite of successive recrystallizations m.p. did not rise beyond 168~170°. It melted at 165~167° on admixture with an authentic sample of (VII), m.p. 174~175°. Admixture with an authentic sample of *dl-cis*-2-tosylaminocyclohexyl benzoate (XIII), m.p. 178~179°, showed intermediate values. The elemental analyses of this crude product correspond approximately to $C_{20}H_{23}O_4NS$ (VII or XIII). *Anal.* Calcd. for $C_{20}H_{23}O_4NS$: C, 64.32; H, 6.21; N, 3.75. Found: C, 63.75; H, 6.05; N, 3.54. It was presumed that the material consists of (XIII) contaminated with a small amount of (VII). Therefore, in order to eliminate (VII), 20 cc. of 70% EtOH was added to 4 g. of the material and the suspension was heated in a sealed tube at 130~140° for 3 hrs. After cooling, the precipitate was filtered and weighed 1.2 g. Recrystallization from EtOH gave colorless needles, m.p. 178~179°, also in admixture with (XIII). *Anal.* Calcd. for $C_{20}H_{23}O_4NS$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.04; H, 6.04; N, 3.70.

The decomposition products of (VII), cyclohexanone, and ammonium tosylate were isolated from EtOH mother liquor.

b) By Winstein's procedure[3]: A mixture of 7 g. of *dl-cis*-2-benzoylaminocyclohexanol, 7 g. of *p*-toluenesulfonyl chloride, and 70 cc. dry pyridine was warmed until a clear solution was obtained. The solution was set aside for 3 days. Then it was poured on ice, neutralized with conc. HCl, and the precipitate was filtered off; m.p. 155~168°. Yield, 9 g. After extraction with 50 cc. of boiling benzene, 6 g. of undissolved substance remained[9]; m.p. 164~174°; m.p. 174~175° after recrystallization from 150 cc. EtOH. Yield, 4.6 g. After cooling, 1.69 g. of colorless needles appeared in the benzene solution and were filtered; m.p. 162~165°; m.p. 174~175° after two recrystallizations from EtOH. Yield, 1.27 g. The benzen solution was evaporated to dryness and the residue was recrystallized twice to colorless needles, m.p. 174~175°. Yield, 0.21 g. The three substances obtained above were the same and proved as (VII) by mixed m.p. determinations. Total yield, 6.08 g.

***dl-cis*-2-Tosylaminocyclohexyl Benzoate (XIII)**—The process of Fodor and Kiss[7] was used. Recrystallization from EtOH yielded colorless needles or prisms, m.p. 178~179°.

Solvolysis of *dl-cis*-2-Benzoylaminocyclohexyl Tosylate (VII)—a) In abs. EtOH: Isolations of cyclohexanone (IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate (XII), *dl*-2-ethoxycyclohexylamine benzoate (XVIII), ethyl benzoate, and ammonium tosylate: A mixture of 2 g. of (VII) and 10 cc. of abs. EtOH was heated in a sealed tube at 130~140° for 3 hrs. and a light yellowish solution resulted. After cooling, the precipitate was filtered and recrystallized from EtOH. Resulting colorless needles did not melt till 250° and weighed 0.42 g. When to a small amount of the material were added water and then aq. NaOH, NH_3 gas evolved. *Anal.* Calcd. for $C_7H_{11}O_3NS$ (Ammonium tosylate): C, 44.40; H, 5.86; N, 7.45. Found: C, 44.51; H, 5.65; N, 7.20.

EtOH mother liquor was distilled and to the distillate was added EtOH solution of 2,4-dinitrophenylhydrazine hydrochloride. Orange yellow plates precipitated and were collected, m.p. 155~157°. Yield, 0.07 g. Recrystallization from EtOH yielded orange yellow plates, m.p. 157~158°, which were identical with cyclohexanone 2,4-dinitrophenylhydrazone by admixture. *Anal.* Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.95; H, 4.79; N, 20.59.

To the EtOH residue was added 10 cc. of water and submitted to distillation. An oily product distilled out with water. Extraction with ether and evaporation left a colorless oily product, b.p_{25} 98~109°. Yield, 0.37 g.

The oily product has the odor of ethyl benzoate and alkaline hydrolysis gave benzoic acid. Therefore, the material was concluded to be ethyl benzoate.

To the residue remaining after removal of water, 10 cc. of water and 10 cc. of ether were added and the mixture was shaken to get a clear solution. On allowing to stand for several minutes, small colorless needles appeared and were filtered. Yield, 0.11 g.; m.p. 152~154°; m.p. 155~156° (small colorless needles) after recrystallization from EtOH. *Anal.* Calcd. for $C_{15}H_{21}O_2N$

9) In the literature,[3] (VII) is described as easily soluble in benzene but it was found not to be so soluble.

(*dl*-2-Ethoxycyclohexylamine benzoate) : C, 72.82; H, 8.56; N, 5.66. Found : C, 72.61; H, 8.35; N, 5.96.

The ether layer was separated from the aqueous layer, washed 3 times with 3 cc. each of water and evaporated to dryness, yielding 0.06 g. of the ethoxy compound (XVIII) and a small amount of a light yellowish brown gummy product. The aqueous layer was combined with washing water and the aqueous solution was evaporated to dryness. To the residue was added a small amount of EtOH and filtered to leave ammonium tosylate. Yield, 0.15 g. The filtrate left a gummy product on evaporation. To the gummy product dissolved in water a saturated solution of sodium picrate was added and the yellow precipitate was filtered; m.p. 214~217°. Yield, 0.26 g. Recrystallization from EtOH gave yellow needles which changed to deep yellow plates of same m.p. on allowing to stand in EtOH; m.p. 223°(decomp.), also in admixture with *dl-cis*-2-benzoyloxycyclohexylamine picrate. *Anal.* Calcd. for $C_{19}H_{20}O_9N_4$: N, 12.50. Found : N, 12.15.

b) In 60% aquous ethanol : Isolations of cyclohexanone (IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate (XII), *dl-trans*-2-benzoyloxycyclohexylamine tosylate (XVII), ethyl benzoate, benzoic acid, and ammonium tosylate : A mixture of 2 g. of (VII) and 10 cc. of 60% aq. EtOH was heated in a sealed tube at 130~140° for 3 hrs. and a light yellowish solution was obtained. To the solution was added 5 cc. EtOH and distilled. From the distillate, cyclohexanone (IX) was separated as its 2,4-dinitrophenylhydrazone, m.p. 155~157°. Yield, 0.09 g. To the residue was added 10 cc. of water and distilled. From the distillate with water, 0.40 g. of ethyl benzoate was obtained. Then to the remaining solid were added 6 cc. of water and 5 cc. of ether to obtain a clear solution. After a while, a precipitate appeared and was filtered off. Yield, 0.10 g., m.p. 223~227°, m.p. 234~235°(colorless small needles) after recrystallization from EtOH. On treatment with aq. NaOH an oily product separated and then crystallized, which was identical with *dl-trans*-2-benzoylaminocyclohexanol suggesting that the parent substance of m.p. 234~235° is *dl-trans*-2-benzoyloxycyclohexylamine tosylate (XVII). *Anal.* Calcd. for $C_{20}H_{25}O_5NS$ (*dl-trans*-2-Benzoyloxycyclohexylamine tosylate) : C, 61.34; H, 6.43; N, 3.58. Found : C, 61.00; H, 6.16; N, 3.70. Picrate : Yellow needles, m.p. 204~205°, after recrystallization from EtOH. *Anal.* Calcd. for $C_{19}H_{20}O_9N_4$: C, 50.87; H, 4.49; N, 12.50. Found : C, 51.11; H, 4.81; N, 12.31.

The mixture of ethereal and aqueous solutions was separated into two layers. The ether solution was washed with 3 lots of 3 cc. water, then with a sat. aq. solution of $NaHCO_3$ and evaporated to dryness. There remained a brownish gummy residue which had a fragrant odor. Yield, 0.13 g.

When $NaHCO_3$-solution was acidified with HCl, benzoic acid precipitated. Yield, 0.11 g. after filtration and drying. The aq. solution was combined with the washing water and evaporated to dryness under a reduced pressure. Treatment of the residue with 0.5 cc. of abs. EtOH left ammonium tosylate undissolved. Yield, 0.58 g. EtOH solution was evaporated to dryness, water and then a sat. aq. solution of sodium picrate were added. The precipitate was filtered off. Yield, 0.14 g. Recrystallization from EtOH gave yellow needles, m.p. 203~206°(decomp.), one part of which changed to deep yellow plates in EtOH for recrystallization. The mixture of the two forms of crystals was suspended in a small amount of EtOH and warmed on a water bath until the needles disappeared. EtOH was immediately decantated, leaving the plates. After one more recrystallization the plates melted at 223°(decomp.), which were identified with *dl-cis*-2-benzoyloxycyclohexylamine picrate (XII picrate) by admixture. After concentration the ethanolic solution gave yellow needles. Still after successive recrystallizations m.p. of the needles failed to rise above 207°. Admixtures with (XII) picrate and (XVII) picrate melted at 207~208° and 198°, respectively, suggesting that the material is probably a combination of (XII) picrate with (XVII) picrate.

c) In water : Isolation of cyclohexanone (IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate (XII), *dl-trans*-2-benzoyloxycyclohexylamine tosylate (XVII), benzoic, acid and ammonium tosylate: Two grams of (VII) and 10 cc. of water were heated in a sealed tube at 130~140° for 3 hrs. and a yellowish brown oily product appeared. After cooling the oily product solidified and colorless needles precipitated. After filtration the collected material was dissolved in ether. There soon appeared colorless needles and were filtered, m.p. 231~233°. Yield, 0.07 g. Recrystallization from EtOH yielded colorless needles of m.p. 234~235°, which were identical with (XVII) by admixture. After washing with 3 cc. of water 3 times, the ether liquor was shaken with a sat. aq. solution of $NaHCO_3$ and the $NaHCO_3$ solution was acidified with HCl, yielding 0.36 g. of benzoic acid. The ether solution was evaporated to dryness, giving a small amount of light brownish gummy residue which had fragrant odor. The ether and washings were added to the aq. solution from the solvolysis and distilled. From the distillate cyclohexanone separated as semicarbazone. Yield, 0.10 g, m.p. 163~164°, m.p. 164~165° after recrystallization from EtOH. *Anal.* Calcd. for $C_7H_{13}ON_3$: C, 54.14; H, 8.44; N, 27.02. Found: C, 54.08; H, 8.04; N, 27.03. The residue consisted of crystals and a gummy product. Extraction with abs. EtOH

left 0.66 g. of ammonium tosylate. The ethanolic extract was further treated as procedure b) after the isolation of ammonium tosylate. There was obtained 0.06 g. of crude picrate, m.p. 204~205°(decomp.), which was separated to (XII) picrate, m.p. 222°(decomp.), and a small amount of the mixture, m.p. 207°(decomp.), consisting presumably of (XII) and (XVII) picrates.

d) In dry AcOH: Isolations of cyclohexanone (IX), *dl-cis*-2-benzoyloxycyclohexylamine tosylate (XII), benzoic acid, and ammonium tosylate: Two grams of (VII) and 10 cc. of dry AcOH were refluxed for 3 hrs. and a reddish brown solution was obtained. The solution was evaporated to dryness and from the distillate 0.12 g. of cyclohexanone was isolated as 2,4-dinitrophenylhydrazone. The residue was extracted with 10 cc. of water and the oily remainder, after decantation, was dissolved in ether. After washing with 3 cc. of water, the ether solution was shaken with a sat. aq. solution of $NaHCO_3$. $NaHCO_3$ solution was acidified with conc. HCl and benozoic acid precipitated. Yield, 0.04 g. after filtration and drying. The ether liquor, after evaporation, gave a brownish gummy product which had a fragrant odor. The aq. extract was combined with the washing water and evaporated to dryness. The residue was treated with a small amount of EtOH and the undissolved substance, after filtration and recrystallization, was proved as ammonium tosylate.

Further treatment of the ethanolic extract was made as procedure b) after the isolation of ammonium tosylate. There were obtained (XII) picrate, m.p. 222~223°(decomp.), and crude picrate, m.p. 170~175°, which failed to be identified because of poor quantity.

Summary

dl-cis-2-Benzoylaminocyclohexyl tosylate was submitted to solvolysis in four of the sets of conditions: (a) In absolute ethanol, (b) in 60% ethanol, (c) in water, and (d) in dry acetic acid. The reactions gave rise to cyclohexanone and *dl-cis*-2-benzoyloxycyclohexylamine tosylate commonly in a, b, c, and d, *dl-trans*-2-benzoyloxycylohexylamine tosylate in b and c, and *dl*-2-ethoxycyclohexylamine tosylate only in a. The reaction mechanisms were discussed. By adaptation of Winstein's and McCasland's procedures the *dl-cis*-N-benzoyl-O-tosylate was synthesized and showed m.p. 174~175°, higher than those reported by these authors. Besides, by McCasland's procedure, *dl-cis*-2-tosylaminocyclohexyl benzoate was formed.

(Received June 8, 1955)

---

70. Torizo Takahashi, Kan-ichi Ueda, and Toshiro Ichimoto: Sulfur-containing Pyridine Derivatives. XLIV.* Synthesis of β,γ-Disubstituted Pyridine Derivatives and Mercaptopyrido[3,4 : 4′,5′]thiazoles.

(*Pharmaceutical Institute, Medical Faculty, Uuiversity of Kyoto***)

The synthesis of β,γ-disubstituted pyridine derivatives containing a sulfur atom was undertaken with a view to investigating their anticancer activities. This paper describes pyridine derivatives prepared from 3-nitro-4-mercaptopyridine (I). Their results on anticancer activity will be reported elsewehere.

In one of the preceding papers of this series,[1] it was reported that 3-nitro-4-allylthiopyridine was formed by the condensation of the potassium salt of (I) with allyl bromide. Because of its insolubility in water, however, this compound was converted into its water-soluble quaternary ammonium derivatives (II~IV) by treatment with alkyl halides such as methyl or ethyl iodide, and allyl bromide.

---

* Part XLIII: This Bulletin, **3**, 92(1955).

** Yoshida-konoe-cho, Sakyo-ku, Kyoto (高橋酉蔵, 上田寛一, 櫟本敏郎).

1) T. Takahashi, K. Ueda, T. Ichimoto: This Bulletin, **2**, 197(1954).