Synthesis and Circular Dichroism of (5S)-1-Azabicyclo[3.2.0]heptan-7-one

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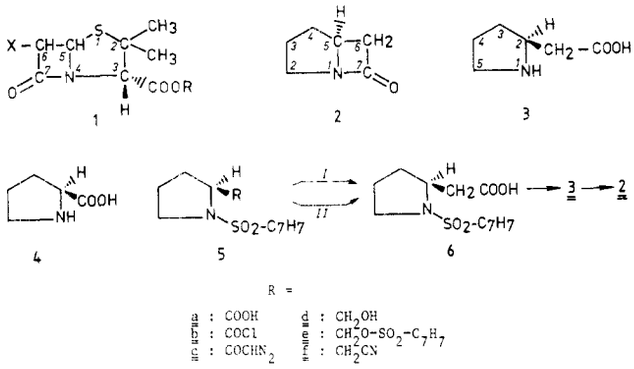
(5S)-1-Azabicyclo[3.2.0]heptan-7-one or epi-1-carbapenam was prepared by cyclization of (2S)-2-pyrrolidylacetic acid. The optical purity of this homoproline, which was obtained for the first time in an active form, was established by carrying out its synthesis by two independent reaction sequences. The circular dichroism curve of epi-1-carbapenam showed a negative Cotton effect at 231 nm with a shoulder at about 212 nm. This result was compared to our findings for the CD of penicillanates.

In relation to our previous studies[1] on the circular dichroism (CD) of penicillanates (**1**), it seemed of interest to determine the CD of 1-azabicyclo[3.2.0]heptan-7-one (**2**), a carbon analogue of penicillins. Compound **2** will be further designated as epi-1-carbapenam.[2]

The racemic form of **2** has been prepared by Moll[3] by cyclization of the acid chloride of 2-pyrrolidylacetic acid (**3**). We have prepared this compound from optically active 2-pyrrolidylacetic acid, which was synthetized from L-proline (**4**), by two independent reaction sequences.

Compound **3**, which can also be called homoproline, was prepared in the first scheme by an Arndt–Eistert synthesis.[4,5] *N*-Tosyl-L-proline (**5a**), prepared by reaction of L-proline (**4**) with *p*-toluenesulfonyl chloride, was converted into the chloride **5b**, which, upon treatment with ethereal diazomethane, afforded crystalline (2S)-1-tosyl-2-pyrrolidyl diazomethyl ketone (**5c**) in 82% yield. The photochemically induced Wolff rearrangement of **5c** gave a mixture from which (2S)-1-tosyl-2-pyrrolidylacetic acid (**6**) could be isolated as



an oil in a variable yield (19–58%). Better results of the Wolff rearrangement were obtained by treatment of **5c** with silver benzoate[6] or silver nitrate in dioxane–water solution in the presence of an excess of triethylamine. In this manner the yield of crude (2S)-1-tosyl-2-pyrrolidylacetic acid amounted to about 60%, and it could be isolated in a pure crystalline form with mp 144–145 °C and $[\alpha]_D$ −97.5°. Since the Wolff rearrangement of diazo ketones has been shown[7] to proceed with retention of configuration, an *S* configuration was assigned to the asymmetric C-2 center.

In order to confirm the stereochemical assignment of **6**, the compound was also prepared by a reaction sequence involving the intermediates **5a**, **5d**, **5e**, and **5f**. This alternative route was longer and therefore no effort was made to improve the yields of the different reaction steps. The reduction of **5a** to the carbinol **5d** was effected by lithium aluminum hydride with a yield of 70%. Carbinol **5d** was then converted into the nitrile **5f** via the tosylate **5e**. The nucleophilic displacement of the *O*-tosyl group by the cyanide ion was carried out in Me_2SO at room temperature for a period of 48 h. In this way a yield of 50% of optically active nitrile **5f**, having a rotation of −122.5° ($CHCl_3$), was obtained. It should be noted that the use of a higher temperature (80 °C) for the substitution reaction resulted in the formation of a completely racemized product, probably via an elimination–addition mechanism. Finally, hydrolysis of the nitrile with concentrated hydrochloric acid gave (2S)-1-tosyl-2-pyrrolidylacetic acid (**6**), which had the same melting point and rotation as the compound prepared via the Arndt–Eistert synthesis.

The *N*-tosyl group of **6** was removed with hydrogen bromide in glacial acetic acid in the presence of phenol.[8] After purification of the resulting hydrobromide by ion exchange chromatography, the cyclic β-imino acid **3** was isolated as a crystalline hydrochloride salt from ethanol with a yield of 70%. It had mp 202–203 °C and a rotation of +35° (HCl, 2 N), whereas the free amino acid melted at 185 °C and had $[\alpha]_D$ +4° (H_2O). The fact that **3** could be transformed back into a tosyl derivative **6** having the same rotation as the starting compound proved that the stereochemical integrity of the molecule was preserved during the cleavage of the sulfonamido group. It is interesting to note that this β-amino acid followed the Clough–Lutz–Jirgensons rule,[9] which states that if the rotation of an amino acid is shifted in a positive direction upon the addition of acid to its aqueous solution, the amino acid has the L configuration. A few years ago, Tomita et al.[10] reported the isolation from cured tobacco leaves of a new natural amino acid, which they identified as 2-pyrrolidylacetic acid. A mp of 166–168 °C for the free amino acid and of 168–171 °C for the hydrochloride salt was given, but no mention was made of the specific rotation of this substance. The difference in melting point observed by Tomita et al. and the value reported here may be due to racemization of their compound during the curing process of the harvested tobacco leaves.[11]

The cyclization of **3** was carried out by treating a dilute solution of its acid chloride hydrochloride in dioxane with triethylamine. This method led to the formation of the desired compound **2** in a fairly good yield (>40%) as shown by GLC. However, after evaporation of the solvent and purification of the resulting oil by silica gel column chromatography, only 12% of pure β-lactam could be isolated, and in a few instances the yield was even less than 1%. Similar difficulties in preparing or isolating β-lactams having a five-membered homocyclic ring fused to the 1–4 position of the β-lactam ring have been encountered by other investigators,[12,13] especially when unsubstituted members of this class were employed.[14] The optically active epi-1-carbapenam **2** obtained here as an oil had a rotation of −113° (MeOH), and its IR spectrum in CCl_4 showed the characteristic β-lactam CO absorption at 1770 cm^{-1}. Other physical data were in agreement with the values already reported by Moll for the racemic compound.[3] In this respect, it should be noted that all measurements have been made as rapidly as possible after the product was isolated, since the fused ring β-lactam is rapidly transformed into a polymeric substance [ν_{CO} (CH_2Cl_2) 1620 cm^{-1}].[3] This transformation should be avoided because the newly formed peptide chromophore might interfere with the β-lactam chromophore.

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The CD spectrum of (5S)-1-azabicyclo[3.2.0]heptan-7-one is represented in Figure 1. The curve shows a negative Cotton effect at 231 nm ($\Delta\epsilon = -3.8$) and a shoulder at about 212 nm which may be due to the presence of a weak positive Cotton effect ($\Delta\epsilon = \sim+1$) near this wavelength. At first sight, it seems reasonable to correlate the longer wavelength peak with the n → π* transition of the β-lactam amide, the only chromophoric system being present in this bare 1-carbapenam. However, from the quadrant rule given by Schellman[16] for the amide chromophore, a positive Cotton effect is anticipated for **2** by the presence of a positive quadrant substituent (i.e., the pyrrolidyl ring). Similarly, application of the Ogura rule[17] for β-lactams, which states that the sign of the n → π* Cotton effect depends solely on classification of the compound into two types (A (−Ve) and B (+Ve)), also leads to the prediction of a positive Cotton effect for compound **2**. In this light, although it is difficult to draw an exact parallel between a bicyclic lactam like **2** and simple monocyclic β-lactams for which the validity of these rules has been tested, it seems more probable to associate the normal amide n → π* transition with the positive but hidden lower wavelength band at about 212 nm. This assignment is further supported by the fact that the band at 231 nm occurs at an unusually high wavelength for a strained peptide n → π* band. In fact the nonplanarity of the β-lactam nitrogen impressed upon the system by the cis ring fusion would be expected to cause a blue shift of the n → π* transition as compared to the average amide.[18]

The Cotton effect at 231 nm strongly resembles the band observed at about 230 nm in the CD spectrum[1] of different penicillanates (**1**). Indeed, for all compounds studied having the 5S-stereochemistry (regardless of the configuration of the other asymmetric centers), a negative Cotton effect was observed, whereas the sign was positive for the penicillanates with a 5R configuration. For several reasons, this high wavelength band has been associated[18] with the vicinal effect of the thiazolidine S atom on the β-lactam group. On the basis of a theoretical study, Boyd et al.[19] have shown that the band represents a superposition of several transitions, the main ones being designated as S–N π → amide π* and S n → amide π*. Such a mixing of molecular orbitals is obviously not pertinent to the 1-carbapenam molecule. However, in analogy with the analysis of the penam chromophore, it is believed that the Cotton effect of **2** near 231 nm may be attributed to a transition involving the lone pair on the amide N atom. Such a transition may be designated as amide N n → amide π* according to a notation suggested by Boyd.[20] The asymmetry of the fused system and the inherently dissymmetric nature of this transition then accounts for the relatively strong CD signal and explains why the sign of this Cotton effect is determined only by the ring geometry of the bicyclic skeleton and not by interaction with asymmetrically placed vicinal moieties as is observed experimentally for penicillanates with different configurations.[1] A similar relationship between the skeletal geometry and the sign of the n → π* Cotton effect has been observed before for bridged ring lactones and lactams.[21]

Experimental Section

Melting points were uncorrected. TLC was performed on silica gel F-254 plates (Merck) using the following systems: I, C_6H_6–Me_2CO, 95:5; II, $CHCl_3$–Me_2CO–HCOOH, 60:40:1; III, C_6H_6–Me_2CO, 80:20; IV, n-BuOH–H_2O–HOAc, 4:1:1. The rotations were determined on a Thorn-NPL automatic polarimeter Type 243, and circular dichroism was measured at 20 °C with a Cary 61 spectropolarimeter. The measurement was made in a quartz cell of 0.1-cm path length and for a concentration of 0.15 mg mL^{-1}. Spectroscopic grade methanol was used without further purification. The CD spectrum was expressed in terms of molar ellipticity $[\theta]$ in deg cm^2 $(dmol)^{-1}$, defined by $[\theta] = \theta M/10lc$, where θ is the measured ellipticity in degrees, l is the path length in centimeters, c is the concentration in grams per milliliter, and M is the molecular weight.

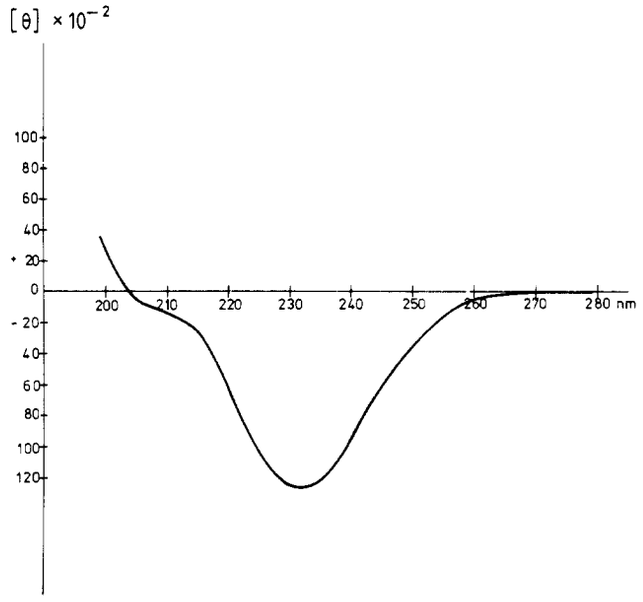

Figure 1. CD spectrum of epi-1-carbapenam **2**, in MeOH at 20 °C.

***N*-Tosyl-L-proline (5a).** To a solution of 11.5 g (100 mmol) of L-proline in 100 mL of 2 N NaOH (200 mmol) was added 19 g (100 mmol) of *p*-toluenesulfonyl chloride, and the suspension was heated at 70 °C until a clear solution resulted. After cooling, the reaction mixture was acidified with concentrated HCl and extracted three times with ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4), and evaporated to leave an oil which crystallized out after further azeotropic drying with benzene. Recrystallization from 100 mL of benzene resulted in 28.3 g (92%) of pure *N*-tosyl-L-proline (**5a**) as a hemibenzenate[22] (from NMR): mp 91–92 °C; $[\alpha]^{25}_D$ −147° (*c* 2.3, H_2O + 2 equiv NaOH). For *N*-tosyl-L-proline an $[\alpha]^{25}_D$ −163° (*c* 2.3, H_2O + 2 equiv NaOH) is reported.[22]

***N*-Tosyl-L-prolyl Chloride (5b).** *N*-Tosyl-L-proline hemibenzenate (**5a**) (27.7 g, 90 mmol) and PCl_5 (37.5 g, 180 mmol) were suspended in anhydrous ether (300 mL) and the mixture was stirred at 40 °C for 15 min.[23] After cooling, the excess PCl_5 was removed by filtration and the solvent was evaporated. The resulting oil was taken up in light petroleum ether and stored in the refrigerator overnight. The crystalline acid chloride was filtered off, washed with petroleum ether, and dried over solid caustic soda and paraffin wax. The yield was 24.4 g (85 mmol, 94.5%), and the mp was 55.5–57 °C (lit.[22,23] mp 56–57.5 °C). The optical purity of **5b** was checked by its conversion into the methyl ester by reacting 0.5 g of the acid chloride with absolute methanol and 0.5 mL of pyridine at 0 °C for 1 h and overnight at room temperature. After evaporation and washing the residue with 0.1 N HCl, the methyl ester was obtained as a crystalline compound from ether: $[\alpha]^{25}_D$ −97.5° (*c* 1, $CHCl_3$). The methyl ester of *N*-tosyl-L-proline, obtained by esterification of the free acid with diazomethane and crystallization from ether, had $[\alpha]^{25}_D$ −98° (*c* 1, $CHCl_3$) and mp 75–76 °C.

(2S)-1-Tosyl-2-pyrrolidyl Diazomethyl Ketone (5c). A solution of **5b** (28.7 g, 100 mmol) in 700 mL of anhydrous ether was added dropwise over the course of 2 h to a cooled and stirred solution of diazomethane (250 mmol, titrated) in 900 mL of ether. The mixture was stirred further for 2 h and after concentration the yellow crystalline diazo ketone **5c** was collected and washed with cold ether: yield 27.8 g (95%); mp 86–88 °C; TLC (system I) R_f 0.27; IR (KBr) 2110 cm^{-1} (diazo).

(2S)-1-Tosyl-2-pyrrolidylacetic Acid (6). A. Silver-Catalyzed Rearrangement. In a two-neck flask fitted with a dropping funnel and a reflux condenser connected to a gas measuring device were placed 23.5 g (80 mmol) of diazo ketone **5c** in 250 mL of dioxane (purified by distillation over $LiAlH_4$ under nitrogen), 30 mL of water, and 30 mL of triethylamine. Soon after the addition of a few milliliters of a solution of silver nitrate (3 g in 25 mL of water), the reaction mixture turned black and evolution of nitrogen commenced. The remainder of the silver nitrate solution was then added dropwise over a period of half an hour. After stirring for a further 30 min, 90% of the theoretical amount of nitrogen had been collected. After the addition of a little charcoal, the mixture was heated to reflux for a few minutes and then filtered. The filtrate was evaporated and the resulting oil was taken up in 2 N HCl (100 mL) and extracted four times with

benzene. The combined organic phases were washed with water and extracted with 1 M $NaHCO_3$ (4 × 50 mL). After being washed with ethyl acetate, the water layer was treated with charcoal, acidified with concentrated HCl to pH 1.8, and again extracted with benzene (4 × 50 mL). Finally, the benzene layer was washed with water, dried (Na_2SO_4), concentrated, and allowed to stand overnight, yielding 6.4 g (22.5 mmol, 28%) of pure crystalline (2*S*)-1-tosyl-2-pyrrolidylacetic acid **6**. As shown by TLC, the filtrate still contained a large amount of **6**; this filtrate was evaporated to leave 6.5 g (29%) of a slightly impure oil which was used without further purification in the detosylation step. Recrystallization of the solid material from benzene afforded an analytical sample of **6**: mp 144–145 °C; TLC (system II) R_f 0.65 (**5a**: R_f 0.50); $[\alpha]^{25}_D$ −97.5° (*c* 2.3, H_2O + 2 equiv NaOH); *m/e* 283 (M^+ very weak), 224 ($M^+ - CH_2COOH$); NMR ($CDCl_3/Me_2SO$-d_6) δ 1.70 (m, 3-CH_2 and 4-CH_2), 2.41 (s, CH_3), 2.10–3.50 (m, 5-CH_2 and α-CH_2), 3.96 (m, 2-CH), 7.52 (m, C_6H_4), and 9.40 (s, COOH).

B. Photochemically Induced Rearrangement. A stirred solution of **5c** (5 g) in dioxane (45 mL) and water (5 mL), contained in a quartz vessel, was irradiated with an ultraviolet light source for 4 h. After evaporation of the solvent, the oily residue was taken up in 1 N NaOH (40 mL), washed with ether, and treated with charcoal. The aqueous solution was acidified and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water, dried (Na_2SO_4), and evaporated to leave the acid **6** as a slightly impure oil. Further purification by repeated extractions was unsuccessful. The yield for different runs fluctuated between 0.900 g (19%) and 2.750 g (58%).

(2*S*)-1-Tosyl-2-pyrrolidylmethyl Alcohol (5d). A solution of 24.6 g (80 mmol) of **5a** hemibenzenate in 200 mL of anhydrous ether and 20 mL of dioxane was slowly added to a stirred suspension of 3.6 g (95 mmol) of $LiAlH_4$ in 100 mL of ether. After the mixture was stirred overnight at room temperature, 45 g of Seignette salt in 150 mL of water was dropped in, the ether layer was separated, and the aqueous phase was extracted with ether. The combined organic layers were washed with water, dried, and concentrated to yield 14.2 g (70%) of crystalline **5d** in three fractions. Recrystallization from Et_2O afforded an analytical sample: mp 88–89 °C; $[\alpha]^{25}_D$ −92° (*c* 1, $CHCl_3$); TLC (system III) R_F 0.47; *m/e* 255 (M^+ very weak), 224 ($M^+ - CH_2OH$).

(2*S*)-1-Tosyl-2-pyrrolidylmethyl *p*-Toluenesulfonate (5e). (2*S*)-1-Tosyl-2-pyrrolidylmethyl alcohol (**5d**) (11.48 g, 45 mmol) and 16.5 g (87 mmol) of *p*-toluenesulfonyl chloride in 135 mL of dry pyridine were stirred at room temperature for 18 h. The reddish solution was poured into ice–water and the organic material was extracted with benzene (3 × 75 mL). The benzene layers were washed with 2 N HCl and then with water, dried, and evaporated to give after crystallization from ether 15.5 g (85%) of the tosylate **5e**: mp 103–104 °C; $[\alpha]^{25}_D$ −118° (*c* 1, $CHCl_3$); TLC (system III) R_f 0.78; *m/e* 409 (M^+ very weak), 224 ($M^+ - CH_2OTos$).

(2*S*)-1-Tosyl-2-pyrrolidylacetonitrile (5f). The tosylate **5e** (6.135 g, 15 mmol) was dissolved in 45 mL of dimethyl sulfoxide (dried over molecular sieve), and after addition of 1.080 g (22 mmol) of sodium cyanide the mixture was stirred at room temperature for 48 h. The reaction mixture was then poured into water containing ammonium chloride and extracted with methylene chloride. The extract was washed with water, dried, and evaporated to give 4.5 g of crude **5f** as an oil. The nitrile was purified by silica gel column chromatography (40 g) with benzene–acetone (99:1) as eluent, yielding 2.0 g (50%) of pure nitrile **5f** after crystallization from Et_2O: mp 75–76 °C; $[\alpha]^{25}_D$ −122.5° (*c* 1, $CHCl_3$); TLC (system III) R_f 0.71; *m/e* 264 (M^+ weak), 224 ($M^+ - CH_2CN$).

Hydrolysis of 5f to (2*S*)-1-Tosyl-2-pyrrolidylacetic Acid (6). A solution of the nitrile **5f** (2.1 g, 8 mmol) in 2 mL of acetic acid and 10 mL of concentrated HCl was heated at 95 °C for 3 h. The reaction mixture was then cooled and extracted with ether. The ether extract was washed once with water and extracted with 1 N NaOH (2 × 20 mL) to remove the acidic material. The aqueous phase containing the sodium salt of **6** was acidified with concentrated HCl to pH 2 and extracted with benzene (3 × 25 mL). Finally, the benzene layer was washed with water, dried, and concentrated to yield 1.2 g (53%) of pure crystalline **6** having, within experimental error, the same mp (146–147 °C) and rotation ($[\alpha]^{25}_D$ −98° (*c* 2.3, H_2O + 2 equiv NaOH)) as the acid obtained by the Arndt–Eistert reaction sequence.

(2*S*)-Pyrrolidylacetic Acid (3). (2*S*)-1-Tosyl-2-pyrrolidylacetic acid (**6**) (12.73 g, 45 mmol) and phenol (9 g) were dissolved in 90 mL of a 40% solution of hydrogen bromide in acetic acid, and the sealed reaction vessel was allowed to stand at room temperature for 40 h, a procedure previously used for the hydrolysis of 1-tosyl-4-chloro-L-proline.[24] The crude hydrobromide of **3** was then precipitated by pouring the mixture into 900 mL of anhydrous ether with stirring. The ether was decanted and the residue was dissolved in 30 mL of water, washed with ether, and then adsorbed on a Dowex 50 cation-exchange column in the H^+ form. After the column was washed thoroughly with distilled water, the β-amino acid was eluted with 0.4 M NH_3. The eluate was evaporated to dryness to remove the excess of ammonia, and after being dissolved in water, the residue was treated with a little charcoal and acidified with 2 N HCl to pH 1.5. Crystallization from alcohol–ether gave in three fractions 5.5 g (74%) of **3**·HCl. Recrystallization from absolute alcohol afforded an analytical sample: mp 202–203 °C; TLC (system IV) R_f 0.13 (L-proline, R_f 0.10), visible as a yellow spot after treatment with ninhydrin; $[\alpha]^{25}_D$ +35° (*c* 1, HCl 2 N); *m/e* 129 (M^+ weak), 70 ($M^+ - CH_2COOH$); NMR (D_2O/DSSA) δ 2.00 (m, 3-CH_2 and 4-CH_2), 2.92 (m, α-CH_2), 3.38 (m, 5-CH_2), 3.88 (m, 2-CH); IR (KBr) 2750, 2680, 2550, 2480, 1590, 825 (NH_2^+), 1720 cm^{-1} (CO).

Anal. Calcd for $C_6H_{11}O_2N$·HCl: C, 43.52; H, 7.31; N, 8.46. Found: C, 43.28; H, 7.21; N, 8.33.

In another run, the residue obtained by evaporation of the eluate of the column was treated with a mixture of absolute ethanol and acetone, yielding the free amino acid **3** in crystalline form: mp 185 °C dec; $[\alpha]^{25}_D$ +4° (*c* 1, H_2O).

(5*S*)-1-Azabicyclo[3.2.0]heptan-7-one (2). Freshly distilled thionyl chloride (30 mL) was added dropwise over a period of 30 min to a stirred suspension of **3**·HCl (4.95 g, 30 mmol, dried over P_2O_5 under vacuo for 5 h) in 60 mL of anhydrous chloroform, and after addition of 6 μL of pyridine, the suspension was stirred overnight at 40 °C. The reaction mixture was then heated to reflux for 15 min, cooled to room temperature, and evaporated under reduced pressure. The residue was taken up in dry benzene and the solvent once more evaporated to remove any residual thionyl chloride. Anhydrous ether was added and the crystalline (2*S*)-2-pyrrolidylacetyl chloride hydrochloride was filtered off, washed with Et_2O, and dried over K_2CO_3 and $CaCl_2$ under vacuo for 1 h: yield 5.13 g (94%), mp 123–125 °C dec. The acid chloride was finely powdered and suspended in 250 mL of carefully purified dioxane (distilled from $LiAlH_4$ under nitrogen) and added dropwise during a period of 3 h to a stirred solution of 25 mL of freshly distilled triethylamine in 750 mL of dioxane. After the reaction mixture was stirred overnight at room temperature under nitrogen, 6.2 g (75%) of triethylamine hydrochloride was filtered off, and the filtrate was evaporated under vacuo at a bath temperature of 17 °C. At this stage, contact with moisture was avoided as much as possible. The residue was taken up in benzene and filtered again to remove any residual triethylamine hydrochloride, as the product was likely to be very susceptible to acid hydrolysis.[13] The benzene solution was evaporated to dryness. The residue was dissolved in chloroform and purified by silica gel column chromatography (10 g) using chloroform–acetone (99:1) as eluent. The fractions containing the desired compound were pooled and evaporated to yield 0.380 g (12%) of (5*S*)-1-azabicyclo[3.2.0]heptan-7-one (**2**) as an oil: $[\alpha]^{25}_D$ −113° (*c* 0.5, MeOH); TLC (system III) R_f 0.55; *m/e* 111 (M^+), other intense peaks were found at 69, 68, 67, and 55 in accordance with ref 3; IR (CCl_4) 1770 cm^{-1} (CO, β-lactam); UV (MeOH) λ_{max} 222 nm (ε 1100); GLC (5 ft column with 3% QF-1 as stationary phase, *T* 95 °C) R_t 7 min. Upon standing the product was readily converted into a polymeric substance [IR (CH_2Cl_2) ν 1620 cm^{-1} (CO, disubstituted amide)[3]], which could be easily removed however, by filtration after dissolution of the oil in CCl_4.

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Registry No.—**2**, 67506-08-5; **3**, 56633-75-1; **3**·HBr, 67488-63-5; **3**·HCl, 53912-85-9; **5a**, 51077-01-1; **5a** hemibenzenate, 67488-64-6; **5a** methyl ester, 67488-65-7; **5b**, 54731-09-8; **5c**, 67488-66-8; **5d**, 55456-48-9; **5e**, 52682-03-8; **5f**, 67488-67-9; **6**, 67488-68-0; **6** Na salt, 67488-69-1; L-proline, 147-85-3; *p*-toluenesulfonyl chloride, 98-59-9; (2*S*)-2-pyrrolidylacetyl chloride hydrochloride, 67488-70-4.

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Rearrangements of Allyl-Substituted Naphthalenones with Oxygen at the Migration Origin[1]

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Replacement of alkyl substituents at quaternary carbons of β-naphthalenones by methoxy or acetoxy groups significantly changes the reactions of these molecules. Thermal migration of an allyl group proceeds by a 3,4 shift, rather than the expected 3,3 shift, when a methoxy group is at the migration origin. Acid-catalyzed migration of the allyl group proceeds by the expected 3,4 path, although at a rate which is accelerated by the presence of the methoxy substituent. Migration of a crotyl group in the methoxy-substituted naphthalenone also proceeds solely by 3,4 shifts in acetic acid or acetic anhydride, with no evidence for the 1,5 or 1,4 shifts observed in the absence of a methoxy substituent. The presence of an acetoxy substituent at C-1 invariably leads to reduction, rather than rearrangement of a β-naphthalenone. Rationales are offered to explain the effects of methoxy groups at C-1 on the reactions of β-naphthalenones.

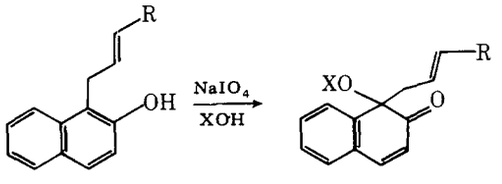
Miller and Saidi have shown that migrations of allyl groups in acid-catalyzed rearrangements of α- and β-naphthalenones can proceed by 1,2, 1,3, 1,4, 1,5, 3,3, or 3,4 shifts. The choice of routes in each reaction depends on the nature of the migrating group and of the solvent.[2,3]

Up to this time, there have been no investigations of the effects of substituents at the migration origins on the nature and rates of migrations of allyl groups in naphthalenones. Alkoxy and hydroxy groups, in particular, would be expected to have marked effects on the course of rearrangement since they can significantly stabilize the carbonium ions formed by allyl migration.

The syntheses of naphthalenones bearing allyl groups and oxygen atoms on the quaternary carbons have not been reported, and few examples are known of cyclohexadienones with this type of substitution.[4]

In this paper we report the syntheses and rearrangements of α- and β-naphthalenones bearing methoxy and allyl groups at the quaternary carbons.

Syntheses. Attempts to oxidize **1** and **2** to **3a** and **4a** were unsuccessful (see Experimental Section) as were attempts to hydrolyze the acetates, **3c** and **4c,** despite reported success in analogous cases.[5] However, sodium periodate oxidation of **1** and **2** in 1:1 water–methanol solutions gave **3b** and **4b** in 13 and 10% yields, respectively.

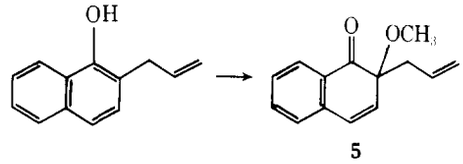


1, R = H
2, R = CH_3

3a, R = H; X = H
b, R = H; X = CH_3
c, R = H; X = C(=O)CH_3

4a, R = CH_3; X = H
b, R = CH_3; X = CH_3
c, R = CH_3; X = C(=O)CH_3

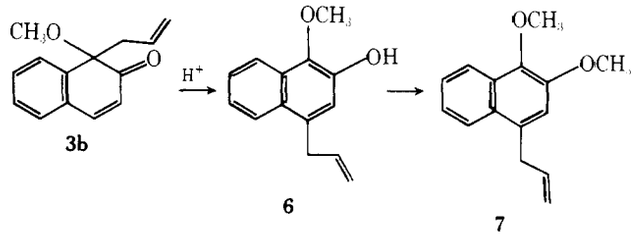
Oxidation of 2-allyl-1-naphthol gave naphthalenone **5** in



5

0.53% yield. The low yield is not surprising since a free para position in the naphthol is available for oxidation.

Rearrangements. Rearrangement of **3b** in a 1% solution of sulfuric acid in acetic acid at room temperature gave a single product, which was a phenol isomeric with **3b.** The same phenol was obtained by thermal rearrangement of **3b** in refluxing *N,N*-dimethylaniline for 24–48 h. The infrared and NMR spectra of the product were consistent with those expected of the formal 1,4 or 3,4 migration product **6.** The assignment of structure **6** to this phenol was confirmed by its



3b **6** **7**

methylation to **7,** which was identical with the diether formed by methylation of **7a,** obtained by thermal or acid-catalyzed

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