Acta Chemica Scandinavica B 30 (1976) 377—382

Synthesis of Penicillin Analogs, (—)-Methyl 6-*epi*-6-Bromobisnorpenicillanate and (±)-Methyl 6-*epi*-6-Bromopenicillanate*

NILS GUNNAR JOHANSSON **

Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm 70, Sweden

The [(4-methoxycarbonylthiazolidino)carbonyldihalomethyl]phenylmercury compounds *2a,b* and *5a,b* have been synthesized. When heated in refluxing bromobenzene they form halogenated penicillin analogs. (−)-Methyl 6-*epi*-6-bromobisnorpenicillinate (*3a*) and methyl 6-*epi*-6-bromopenicillinates (*6a,b*) have been prepared and isolated.

As the result of a search for new synthetic methods for β-lactam syntheses that would allow the preparation of penicillin analogs modified in the thiazolidine part, two methods have been developed by Åkermark *et al.*, namely photocyclization of α-oxoamides [1] and thermal decomposition and ring closure of organic mercury compounds.[2-4]

This communication reports the syntheses of (−)-methyl 6-*epi*-6-bromobisnorpenicillanate (*3a*) and (±) methyl 6-*epi*-6-bromopenicillanate (*6a*) by the decomposition of the mercury compounds *2a* and *5a*, respectively. The synthesis of (+)-methyl 6-*epi*-6-bromopenicillanate (*6b*) has been reported as a preliminary communication.[5]

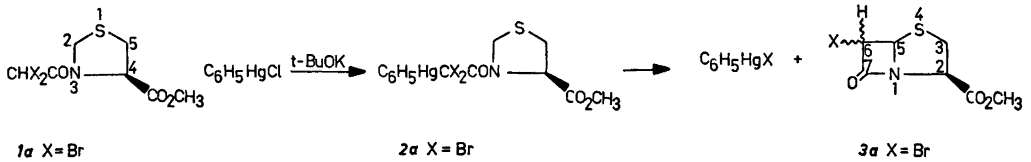
Preparation and isolation of the mercury compounds 2 a, b *and* 5 a, b. A 35−40 % yield of *2a* was obtained when *1a* and phenylmercury chloride were consecutively added to *t*-BuOK in THF at −75 °C.[3] The yield of the dichloro analog *2b* was only about 10 % by this procedure, whereas each of the compounds *5a* and *5b* was isolated in 80 % yield.

The racemic phenylmercury compound *5a* crystallized nicely when treated with diethyl ether. This was not the case with the optically active compounds *2a, b* and *5b*. Attempts to crystallize these from common organic solvents or to extract them selectively from the crude reaction mixtures resulted in decomposition. However, they were successfully purified on a silica gel column at −10 to −20 °C.

Thermal decomposition of the mercury compounds 2a, b and 5a, b. The mercury compounds *2a, b* and *5a, b* decomposed almost completely on refluxing in bromobenzene for 2−3 h. The crude reaction products all exhibited IR absorptions at 1780−1785 cm^{-1}, characteristic of the β-lactam carbonyl of the halogenated penicillin analogs *3a, b* and *6a, b*.[6] From IR data the yields were estimated to be 10−35 %. However, due to decomposition during

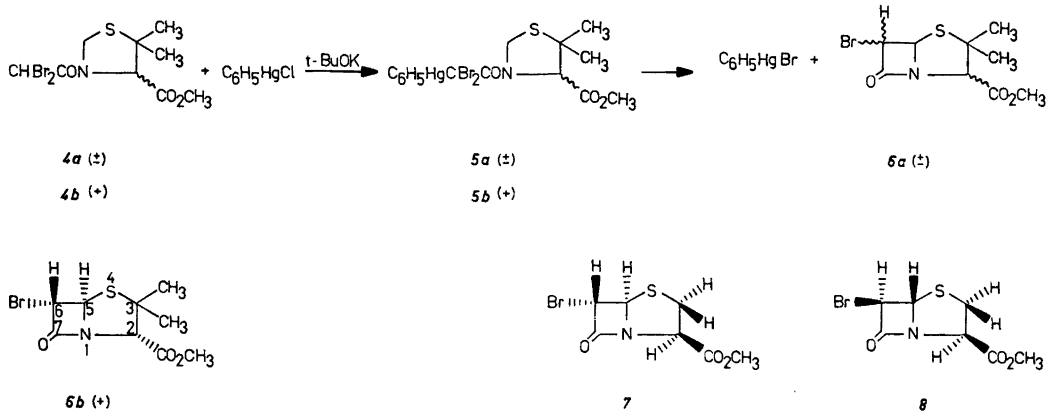
* Strained Heterocyclic Compounds. 6. Part 5. Åkermark, B., Byström, S., Florin, E., Johansson, N.-G. and Lagerlund, I. *Acta Chem. Scand. B 28* (1974) 375.

** Present address: Research and Development Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden.



1a X=Br *2a* X=Br *3a* X=Br

1b X=Cl *2b* X=Cl *3b* X=Cl



4a (±)
4b (+)
5a (±)
5b (+)
6a (±)
6b (+)
7
8

the isolation process, the yields of the pure compounds *3a* and *6a, b* were lower (4 – 9 %). Compound *3a* completely decomposed during the isolation process.

Phenylmercury halides (35 – 90 %) were isolated from the decomposition products of each of the compounds *2a, b* and *5a, b*. The dihaloacetamides *1a, b* and *4a, b* (IR 1660 cm^{-1}), were also produced during the decomposition of the corresponding mercury compounds. In addition, unknown substances with IR absorptions at 1660 – 1680 cm^{-1} were formed in minor amounts.

Configurations of the bromo-β-lactams 3a *and* 6a, b. (+)-Methyl 6-*epi*-6-bromopenicillanate *6b*, formed from *5b* is identical with an authentic sample prepared from 6-aminopenicillanic acid [6] (m.p., mixed m.p., $[\alpha]_D$, IR, ^1H NMR and mass spectra). The ^1H NMR and mass spectra of the racemic compound *6a* are also identical with those of the authentic sample. The 6-CH NMR coupling constant is 1.4 Hz, characteristic of a 5-CH and 6-CH *trans*-relationship.[3,7–9] The mass spectrometric fragmentations of *6a, b* are analogous to those of methyl 6-*epi*-6-chloropenicillinate [10] and other penicillin derivatives.[10–12]

The mass spectrum of compound *3a* is analogous to that of *6a, b*. A difference between the spectra is a strong peak at $m/e = 158$ ($C_6H_8NO_2S$) for *3a*, the equivalent of which is lacking for *6a, b*.

The ^1H NMR coupling constants for 5-CH and 6-CH of the bromo-β-lactam *3a* are 1.4 Hz, indicating a *trans*-arrangement.[3,7–9] Compound *3a* may be assigned either of the configurations *7* or *8*. It is not possible to make a definite choice between these two configurations on the bases of available data. However, *8* is the favoured configuration, since a *trans*-relationship was established between 2-CH and 5-CH in the formation of *6a* and *6b* and it is reasonable to assume that the formation of *3a* is analogous.

Discussion of the thermal decomposition of the mercury compounds 2a, b *and* 5a, b. The formation of β-lactams and phenylmercury halides by the thermal decomposition of the compounds *2a, b* and *5a, b*, probably occurs *via* carbenoid intermediates.[3] However, the solvent has a great effect upon the course of the decomposition reaction and the hetero-atoms of the thiazolidine ring also influence the reaction.

The mercury compound *2a* was decomposed in different solvents. Decompositions in chloro-, bromo- and iodobenzene produced β-lactams (IR 1785 cm^{-1}) whereas no β-lactam was observed when *2a* was decomposed in dimethoxyethane, *o*-xylene, methyl benzoate, or 1-bromoheptane.

Besides the solvent, the sulfur atom and possibly also the ester group exert an influence on the decomposition of the dichloro compound *2b*. When heated in refluxing bromobenzene, *2b* decomposed almost completely within 2 h, which is the same time as that required for the decomposition of the dibromo analog *2a*. By contrast, the decomposition of (piperidinocarbonyldichloromethyl)phenylmercury is about ten times slower than the decomposition of the corresponding dibromo compound [2,3] and the bromochloro compound.[4]

The sulfur atom is a good ligand for mercury [13] and forms ylides with carbenes.[14–16] Possibly, the ester group also could influence the decomposition reaction by binding to a carbenoid intermediate. Unstable oxygen ylides have been suggested as intermediates in the reaction between carboalkoxycarbenes and ketones or ethers,[17–20] and for the reaction between dichlorocarbene and carboxylic acids.[21]

For comparison the decomposition reactions of halomethylphenylmercury compounds may be mentioned. Seyferth and coworkers [22,23] studied the decomposition of (bromodichloromethyl)phenylmercury in the presence of olefins. They postulated that free or very weakly complexed dichlorocarbene was first formed and then added to the olefins. One of the arguments put forward by them in support of this postulate was the indifference of the reaction to polar or non-polar solvents. However, reactions between trihalomethylphenylmercury compounds and compounds containing atoms with lone-pair electrons gave complex mixtures of reaction products, and are not believed to involve free dihalocarbenes.[24]

EXPERIMENTAL

Melting points are uncorrected. The IR spectra of liquids were determined neat and those of solids in KBr. ^{1}H NMR spectra were recorded in $CDCl_3$/TMS with a Varian A-60 instrument. Mass spectra were recorded with a LKB 9000 instrument (70 eV). Unless otherwise stated column chromatography was performed with silica gel (Merck 0.05–0.2 mm), using increasing amounts of distilled ether in distilled light petroleum as eluent. THF was purified as described previously.[3]

(−)-3-(Dibromoacetyl)thiazolidine-4-carboxylic acid methyl ester (1a). Dibromoacetylchloride [2] (57.6 g) in dry ether (100 ml) was slowly added to a vigorously stirred ice-cold solution of (−)-thiazolidine-4-carboxylic acid methyl ester [25] (35.7 g) and triethylamine (24.5 g) in dry ether (750 ml). After the addition was complete, the precipitate formed was removed by filtration and washed with chloroform. The chloroform solution and the ether filtrate solution were each washed with water, combined and dried (Na_2SO_4). Evaporation of the solvent and recrystallization of the residue from toluene gave (−)-3-(dibromoacetyl)thiazolidine-4-carboxylic acid methyl ester (*1a*) (46 g, 55 %) m.p. 127–129 °C. $[\alpha]_D^{25}$ −102 (*c*, 1.12, $CHCl_3$). (Found: C 24.4; H 2.26; Br 45.88. Calc. for $C_7H_9NO_3SBr_2$: C 24.23; H 2.61; Br 46.05.) ^{1}H NMR: δ 3.2–3.4 (m, 5-CH), 3.8 (s, CH_3), 4.82 (broad d, *J* 7 Hz, 2-CH), 5.0–5.2 (m, 4-CH), 6.2 (s, $CHBr_2$, the chemical shift is dependent on the concentration). IR: 1750, 1660 C=O.

(−)-3-(Dichloroacetyl)thiazolidine-4-carboxylic acid methyl ester (1b). Prepared in the same way as *1a* (yield 78 %), m.p. 94–96 °C. $[\alpha]_D^{25}$ −132 (*c*, 1.1, $CHCl_3$). (Found: C 32.71; H 3.63; Cl 27.36. Calc. for $C_7H_9NO_3SCl_2$: C 32.57; H 3.51; Cl 27.47.) ^{1}H NMR: δ 3.2–3.4 (m, 5-CH), 3.78 (s, CH_3), 4.82 (broad d, *J* 5 Hz, 2-CH), 4.95–5.15 (m, 4-CH), 6.3 (s, $CHCl_2$, the chemical shift is dependent on the concentration). IR: 1750, 1670 C=O.

(±)-3-(Dibromoacetyl)5,5-dimethylthiazolidine-4-carboxylic acid methyl ester (4a). (±)-5,5-Dimethylthiazolidine-4-carboxylic acid [26] was suspended in dry ether and vigorously stirred and treated with diazomethane. The crude ester product had a m.p. of 25–30 °C and was spectroscopically pure (IR, ^{1}H NMR). It was used without further purification.

Dibromoacetylchloride (19.2 g) in dry ether (100 ml) was slowly added to a vigorously stirred ice-cold solution of (±)-5,5-dimethylthiazolidine-4-carboxylic acid methyl ester (14.2 g) and triethylamine (8.2 g) in dry ether (400 ml). After the addition was complete the precipitate was filtered off and washed with ether. The filtrate and the ether washed solutions were combined, washed with water and dried (Na_2SO_4). Evaporation of the solvent and purification by chromatography on a silica gel column yielded (±)-3-(dibromoacetyl)-5,5-dimethylthiazolidine-4-carboxylic acid methyl ester (*4a*). (22 g, 72 %) m.p. 78–80 °C. (Found: C 29.02; H 3.48; Br 42.47. Calc. for $C_9H_{13}NO_3SBr_2$: C 28.82; H 3.49; Br 42.61.) ^{1}H NMR: δ 1.46, 1.60 (two s, *gem* CH_3), 3.76 (s, CO_2CH_3), 4.55 (s, 4-CH), 4.95 (s, 2-CH), 6.2 (s, $CHBr_2$, the chemical shift is dependent on the concentration). IR: 1745, 1660 C=O.

(+)-3-(Dibromoacetyl)5,5-dimethylthiazolidine-4-carboxylic acid methyl ester (4b). This was prepared from dibromoacetylchloride (3.8 g) and (+)-5,5-dimethylthiazolidine-4-carboxylic acid methyl ester [26,27] (3.4 g) in the same way as *4a* (6.9 g, 94 %) m.p. 72–73 °C. $[\alpha]_D^{25}$ +55 (*c*, 1.0, $CHCl_3$). (Found: C 29.01; H 3.57; Br 42.41. Calc. for $C_9H_{13}NO_3SBr_2$: C 28.82; H 3.49; Br 42.61.) ^{1}H NMR: Identical to that of *8a*. IR: 1750, 1660 C=O.

(−)-[(4-Methoxycarbonylthiazolidino)carbonyldibromomethyl]phenylmercury (2a). The glass equipment was dried and the reaction was performed in an atmosphere of purified nitrogen.

t-BuOK [3] (23 ml of a 0.95 M THF solution) in THF (225 ml) was stirred with a magnetic stirrer and cooled to −75 °C. (−)-3-(Dibromoacetyl)thiazolidine-4-carboxylic acid methyl ester *1a* (7.6 g) in THF (75 ml) was added over 10 min, immediately followed by the addition of phenylmercury chloride (6.8 g) in THF (100 ml) also over 10 min. The solution was stirred at −75 °C for an additional 30 min,

after which the temperature was raised to +10 °C. The solvent was removed as described previously [3] and the crude product was chromatographed on a silica gel column, maintained at −20 °C by circulating cold ethanol in a jacket. (−)-[(4-Methoxycarbonylthiazolidino)-carbonyldibromomethyl]phenylmercury (*2a*) was obtained (5.2 g, 38 %) m.p. 45−50 °C. $[\alpha]_D^{25}$ −80° (*c*, 1.0, benzene). (Found: C 25.13; H 2.47; Br 25.72; Hg 32.05. Calc. for $C_{13}H_{13}NO_3SBr_2Hg$: C 25.03; H 2.10; Br 25.62; Hg 32.16.) ^{1}H NMR: δ 3.1−3.3 (m, 5-CH), 3.70 (s, CH_3), 4.78 (broad d, *J* 10 Hz, 2-CH), 5.1−5.4 (m, 4-CH), 7.29 (s, arom.). IR: 1750, 1610 C=O.

(−)-3-(Dibromoacetyl)thiazolidine-4-carboxylic acid methyl ester (*1a*) (1.6 g, 21 %) was recovered.

(−)-[(4-Methoxycarbonylthiazolidino)carbonyldichloromethyl]phenylmercury (*2b*). This compound was synthesized and isolated by a method similar to that used for *2a*. Yield 9 %, m.p. 40−50 °. $[\alpha]_D^{25}$ −50° (*c*, 0.8, benzene). (Found: C 28.35; H 2.50; Cl 12.92; Hg 36.88. Calc. for $C_{13}H_{13}NO_3SCl_2Hg$: C 29.19; H 2.45; Cl 13.36; Hg 37.51.) IR: 1750, 1620 C=O.

(−)-3-(Dichloroacetyl)thiazolidine-4-carboxylic acid methyl ester (*1b*) was recovered.

(±)-[(Methoxycarbonyl-5,5-dimethylthiazolidino)carbonyldibromomethyl]-phenylmercury (*5a*). This compound was synthesized by a method similar to that used for *2a*. When the crude product was treated with dry ether at room temperature *5a* crystallized (81 %), m.p. 125 °C. (Found: C 27.42; H 2.72; Br 24.58; Hg 31.12. Calc. for $C_{15}H_{17}NO_3SBr_2Hg$: C 27.64; H 2.63; Br 24.52; Hg 30.78.) ^{1}H NMR: δ 1.46, 1.62 (two s, *gem* CH_3), 3.76 (s, CO_2CH_3), 4.53 (broad s, 4-CH), 5.3 (broad d, *J* 13 Hz, 2-CH), 7.28 (s, arom.). IR: 1750, 1600 C=O.

(+)-[(4-Methoxycarbonyl-5,5-dimethylthiazolidino)carbonyldibromomethyl]-phenylmercury (*5b*). This compound was synthesized and isolated by a method similar to that used for *2a* (yield 78 %), m.p. 118−119 °C. $[\alpha]_D^{25}$ +75° (*c*, 0.8 benzene). (Found: C 27.65; H 2.73; Br 24.39; Hg 31.02. Calc. for $C_{15}H_{17}NO_3SBr_2Hg$: C 27.64; H 2.63; Br 24.52; Hg 30.78.) ^{1}H NMR: identical to that of *5a*. IR: 1740, 1600 C=O.

Thermal decomposition of (−)-[(methoxycarbonylthiazolidino)-carbonyldibromomethyl]-phenylmercury (*2a*). The compound *2a* (4.5 g) was heated in refluxing, freshly distilled bromobenzene (700 ml) for 2 h. The solvent was removed on a rotary evaporator using a high-vacuum pump, chloroform was added to the residue and the insoluble phenylmercury bromide (1.4 g, 55 %) was removed by filtration. (Found: Br 22.34. Calc. for C_6H_5BrHg: Br 22.34.) An IR spectrum of the remaining material indicated that it contained about 10 % of the starting material (1610 cm^{-1}) and 15-25 % of a halo-β-lactam (1785 cm^{-1}).[6] Hydrogen sulfide was bubbled through the chloroform solution for 2 min to destroy the unreacted starting material, which would otherwise contaminate the β-lactam containing fractions obtained in a later stage of purification. The chloroform was evaporated and the residue was chromatographed on a silica gel column cooled to −10 °C. The β-lactam fraction (0.56 g) had IR carbonyl absorptions at 1785, 1750 and 1660. The relative intensities of these indicated the presence of approximately 60 % of the halo-β-lactam (about 20 % yield from the starting material). When this fraction was sublimated in a gradient-heated tube (45 °C, 10^{-3} mmHg) for a 35−40 h period only 75 mg of *7a* was obtained. The remainder of the material showed IR absorptions only at 1750 and 1660 cm^{-1}.

The chromatographic separation could also be successfully performed on a short column of thin-layer-grade silica gel [28] at room temperature. Separations on cooled column of aluminia (Schuckardt, neutral) or Florisil gave less satisfactory results.

(−)-Methyl 6-epi-6-bromobisnorpenicillanate (*3a*). (75 mg, 4 %). This was recrystallized from redistilled light petroleum. Colorless crystals, m.p. 57−60 °C. $[\alpha]_D^{25} = -160°$ (*c*, 1.1, $CHCl_3$). A fresh clear $CHCl_3$-solution turned yellowish after half an hour at room temperature. The ^{1}H NMR spectrum indicated an initially small peak at δ 2.15, which was observed to increase with time. (Found: C 31.63; H 3.12; Br 29.84. Calc. for $C_7H_8NO_3SBr$: C 31.59; H 3.03; Br 30.03.) ^{1}H NMR: δ 3.47 (d, *J* 1.4 Hz, 3-CHa), 3.55 (s, 3-CHb), 3.78 (s, CH_3), 4.72 (d, *J* 1.4 Hz, 6-CH), 5.0−5.2 (m, 2-CH), 5.20 (d, *J* 1.4 Hz, 5-CH). IR: 1780, 1730 C=O. MS, *m/e* (%): 265, 267 (M^+, 16); 158 ($C_5H_8NO_2S$, 100), 151, 153 (C_3H_4SBr, 50); 146 ($C_5H_8NO_2S$, 100); 86 ($C_4H_6O_2$ and C_3H_4NS, 100).

(−)-3-(Dibromoacetyl)thiazolidine-4-carboxylic acid methyl ester (*1a*) (0.50 g, 20 %) was also isolated.

Thermal decomposition 2a *in different solvents.* 15-20 mg of *2a* was dissolved in 15−25 ml of solvent and heated. IR spectra (neat) were recorded of the decomposition products. Chlorobenzene: 132 °C, 10 h. IR: 1785 (m), 1745 (s), 1680−1660 (s), 1610 (m). Iodobenzene: 150 °C 4 h. IR: 1785 (w), 1745 (s), 1680−1660 (s), 1610 (m). Dimethoxyethane: 85 °C 8 h. IR: 1745 (s), 1680−1660 (m), 1610 (m). *o*-Xylene: 144 °C 5 h. IR: 1745 (s), 1680−1660 (s), 1610 (w). Methyl benzoate: 150 °C 2 h. IR: 1745 (s), 1680−1660 (m), 1610 (m). 1-Bromoheptane: 150 °C, 1 h. IR: 1745 (s), 1680−1660 (s), 1610 (w).

Thermal decomposition of (−)-[(4-methoxycarbonylthiazolidino)carbonyldichloromethyl]-phenylmercury (*2b*). The compound *2b* (3.00 g) was subjected to a decomposition process similar to that for *2a* (2 h). The bromobenzene solution rapidly turned black. Only a small amount of phenylmercury chloride was formed (0.60 g, 35 %). An IR spectrum of the crude product showed carbonyl absorptions at 1785,

1735, 1635, and 1625. Their relative intensities were 1.0, 1.8, 1.9, and 0.3, respectively. Attempts to isolate *3b* on a cooled column gave a small quantity of material (0.34 g) which had a weak IR absorption at 1785 and decomposed on sublimation.

Thermal decomposition of (±)-[(4-methoxycarbonyl-5,5-dimethylthiazolidino)carbonyldibromomethyl]phenylmercury (5a) The compound *5a* (4.0 g) was decomposed by a process similar to that used for *2a* but the reaction time was prolonged to 3.5 h. The phenylmercury bromide formed (1.9 g, 88 %) was removed by filtration. (Found: Br 22.96. Calc. for C_6H_5Br: Br 22.34.) Chromatography of the remaining material on a cooled silica gel column gave a 0.4 g fraction that had IR absorptions at 1790, 1750 and 1660 with the relative intensities of 1.0, 1.0 and 0.4, respectively. Sublimation of this fraction yielded (±)-methyl 6-*epi*-6-bromopenicillanate (*6a*) (0.15 g, 9 %) m.p. 89–91 °C. (Found: C 36.95; H 4.24; Br 27.12. Calc. for $C_9H_{12}NO_3SBr$: C 36.75; H 4.11; Br 27.17.) ^1H NMR: δ 1.46, 1.62 (two s, *gem* CH_3), 3.76 (s, CO_2CH_3), 4.56 (s, 2-CH), 4.79–4.95 (d, J 1.4 Hz, 6-CH, the chemical shift is dependent on concentration), 5.42 (d, J 1.2 Hz, 5-CH). IR: 1785, 1735 C=O. MS, *m/e* (%): 295, 293 (M^+, 23); 181, 179 (C_6H_8SBr, 28); 174 ($C_7H_{12}NO_2S$, 100); 114 ($C_6H_{10}O_2$ and C_5H_8NS, 29).

Thermal decomposition of (+)-[(4-methoxycarbonyl-5,5-dimethylthiazolidino)carbonyldibromomethyl]phenylmercury (5b). The compound *5b* (2.15 g) was decomposed by a process similar to that used for *5a*. The phenylmercury bromide formed (0.80 g, 70 %) was removed by filtration. Chromatography of the remaining material on a cooled silica gel column, sublimation and recrystallization from light petroleum gave (+)-methyl 6-*epi*-6-bromopenicillanate (*6b*) (0.8 g, 9 %), m.p. 45–47 °C. $[\alpha]_D^{25}$ +185° (*c*, 0.4, acetone). ^1H NMR: δ 1.46, 1.62 (two s, *gem* CH_3), 3.76 (s, CO_2CH_3), 4.56 (s, 2-CH), 4.79-4.93 (d, J, 1.4 Hz, 6-CH, the chemical shift is dependent on concentration), 5.42 (d, J 1.2 Hz, 5-CH). IR: 1785, 1750 C=O. MS, *m/e* (%): 295, 293 (M^+, 23); 181, 179 (C_6H_8SBr, 28); 174 ($C_7H_{12}NO_2S$, 100); 114 ($C_6H_{10}O_2$ and C_5H_8NS, 33).

Synthesis of (+)-methyl 6-epi-6-bromopenicillanate from 6-APA (cf. Ref. 29). 6-Aminopenicillanic acid (2.15 g) was dissolved in a mixture of distilled water (25 ml), methanol (70 ml) and concentrated hydrobromic acid (48 %, 5 ml) and cooled to 0–5 °C. Sodium nitrite (1.5 g) was added in one portion. After 45 min. at 0–5 °C, chloroform (150 ml) and water (100 ml) were added. The phases were vigorously stirred, separated and the chloroform phase was washed with cool water (50 ml) and dried ($MgSO_4$). The crude product was treated with diazomethane in dry ether to give crude (+)-methyl 6-*epi*-6-bromopenicillanate (2.1 g, 70 %). This was further purified by recrystallization from light petroleum, m.p. 46–47 °C $[\alpha]_D^{25}$ +185° (*c*, 1.0, acetone). ^1H NMR, IR and MS were identical to those of *6b* obtained from *5b*.

Acknowledgements. I thank Drs. B. Åkermark and B. Sjöberg for their interest in this work and for valuable discussions. This work has been supported by The Swedish Board for Technical Development and by Astra Läkemedel AB. Miss Gurli Hammarberg recorded the spectra. Dr. Brian Pring made linguistic improvements.

REFERENCES

1. Åkermark, B., Johansson, N.-G. and Sjöberg, B. *Tetrahedron Lett.* (1969) 371.
2. Johansson, N.-G. and Åkermark, B. *Acta Chem. Scand. 25* (1971) 1927.
3. Johansson, N.-G. *Acta Chem. Scand. 27* (1973) 1417.
4. Åkermark, B., Byström, S., Florin, E., Johansson, N.-G. and Lagerlund, I. *Acta Chem. Scand. B 28* (1974) 375.
5. Johansson, N.-G. and Åkermark, B. *Tetrahedron Lett.* (1971) 4785.
6. Evrard, E., Claesen, M. and Vanderhaege, H. *Nature 201* (1964) 1124.
7. Kagan, H. B., Basselier, J.-J. and Luche, J.-L. *Tetrahedron Lett.* (1964) 941.
8. Barrow, K. D. and Spotswood, T. M. *Tetrahedron Lett.* (1965) 3325.
9. McMillan, I. and Stoodley, R. J. *Tetrahedron Lett.* (1966) 1205.
10. Richter, W. and Biemann, K. *Monatsh. Chem. 95* (1964) 766.
11. Bochkarev, N. V., Ovchinnikova, N. S., Vul'fson, N. S., Kleiner, E. M. and Khokhlov, A. S. *Dokl. Akad. Nauk*, S.S.S.R. *172* (1967) 1079.
12. Moll, F. and Hannig, M. *Arch. Pharm. (Weinheim) 303* (1970) 321.
13. Coates, G. E., Green, M. L. H. and Wade, K. *Organometallic Compounds*, Methuen, London 1967, Vol. I, pp. 153 *et seq.*
14. Ando, W., Yagihara, T., Tozune, S. and Migita, T. *J. Am. Chem. Soc. 91* (1969) 2786.
15. Ando, W., Nakayama, K., Ichibori, K. and Migita, T. *J. Am. Chem. Soc. 91* (1969) 5164.
16. Ando, W., Yagihara, T., Kondo, S., Nakayama, K., Yamato, H., Nakaido, S. and Migita, T. *J. Org. Chem. 36* (1971) 1732.
17. Kirmse, W. *Carbene Chemistry*, Academic, New York 1964, p. 106.
18. Nozaki, H., Takaya, H. and Noyori, R. *Tetrahedron Lett.* (1965) 2563.
19. Nozaki, H., Takaya, H. and Noyori, R. *Tetrahedron 22* (1966) 3393.
20. Seyferth, D. and Smith, W. E. *J. Organometal. Chem. 26* (1971) C55.

21. Seyferth, D. and Mui, J. Y.-P. *J. Am. Chem. Soc. 88* (1966) 4672.
22. Seyferth, D. and Burlitch, J. M. *J. Am. Chem. Soc. 86* (1964) 2730.
23. Seyferth, D., Mui, J. Y.-P. and Burlitch, J. M. *J. Am. Chem. Soc. 89* (1967) 4953.
24. Seyferth, D. *Accounts Chem. Res. 5* (1972) 65.
25. Ratner, S. and Clarke, H. T. *J. Am. Chem. Soc. 59* (1937) 200.
26. Clarke, H. T., Johnson, J. R. and Robinson, R., Eds., *The Chemistry of Penicillin*, Princeton University Press, Princeton 1949, p. 958.
27. Clarke, H. T., Johnson, J. R. and Robinson, R., Eds., *The Chemistry of Penicillin*, Princeton University Press, Princeton 1949, p. 67.
28. Hunt, B. J. and Rigby, W. *Chem. Ind. London* (1967) 1868.
29. McMillan, I. and Stoodley, R. J. *J. Chem. Soc. C* (1968) 2533.

Received October 4, 1975.