Polycyclic Azetidines. I. The Preparation of Benzo[c]-*cis*-6-azabicyclo[3.2.0]heptane

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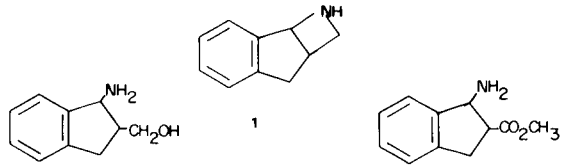
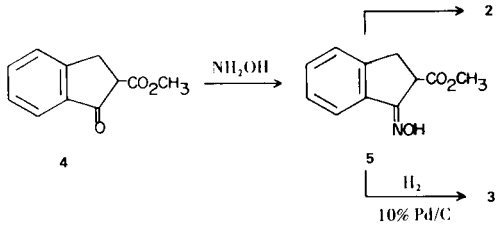
The title compound was prepared from compounds readily obtained from 2-carbomethoxy-1-indanone oxime (**5**) or from the *N*-chlorosulfonyl isocyanate adduct of indene (**9**). Apart from its ability to undergo transformation to the azetidine, compound **9** upon refluxing with excess LAH was found to undergo reductive decompostion to *cis*-2-hydroxymethyl-1-indanamine (**2**).

In connection with other work in progress in our laboratory concerning the synthesis of C_2 and C_3 functionalized azetidines of possible biological activity it became of interest for us to prepare the novel bicyclic azetidine, benzo[c]-6-azabicyclo[3.2.0]heptane (**1**). Since β-amino alcohols and β-amino esters have often been converted into azetidines in fair yeild (1), it was felt that indanes **2** and **3** would be valuable key intermediates for its synthesis.

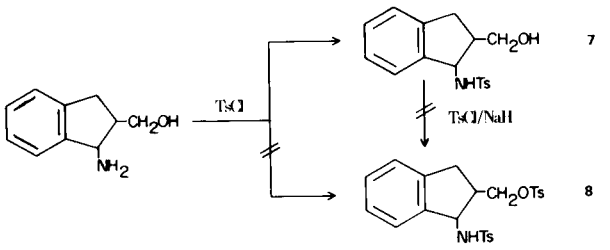


It was found that both **2** and **3** could be readily prepared from the known (2) 2-carboethoxyindanone (**4**) in two steps. Treatment of keto ester **4** with hydroxylamine afforded 2-carboethoxyindanone oxime (**5**) in 72% yield, no attempt being made to separate the geometrical isomers. Reduction of oximino ester **5** with lithium aluminum hydride gave a 30% yield of amino alcohol **2**. Alternatively, hydrogenation of **5** over 10% Pd/C in ethanolic hydrogen chloride, followed by neutralization of the amine salt with triethylamine and subsequent distillation afforded the pure amino ester **3** in 50% overall yield.



The possibility of *cis-trans* isomerism exists in both **2** and **3**. Both isomers were easily observed for **3** in the nmr; however the nmr spectrum of **2** was not definitive. In the nmr spectrum of **3** two overlapping doublets at 4.78 δ (J = 5 Hz) and 4.80 δ (J = 7 Hz) assigned to the hydrogen α to the amino group were observed. Based on analogy with the nmr assignments of other *cis-trans* 1,2-disubstituted indanes (3), the one with the larger coupling constant was assigned to the *cis* isomer. Integration of the two resonances in quesions showed **3** to be comprised of approximately equal amounts of *cis* and *trans* isomers. The adsorption of the α H in **2** was broad, possibly caused by overlapping peaks and consequently no determination of the isomer distribution could be made.

The utility of amino alcohol **2** for the synthesis of azetidine **1** was limited in that its synthesis was irreproducible at times. Furthermore all attempts to prepare the *N,O*-ditosyl derivative **6** for ring closure in base were unsuccessful; only the mono-*N*-tosyl derivative **7** was formed as shown by nmr, mass spectra and elemental analysis.



The conversion of β-amino ester **3** to **1** was carried out as shown in Scheme 1. Treatment of **3** with two equivalents of either methylmagnesium iodide or ethylmagnesium iodide according to the general method of Testa (4) afforded *cis* azetidinone **8** in 12% yield. The infrared

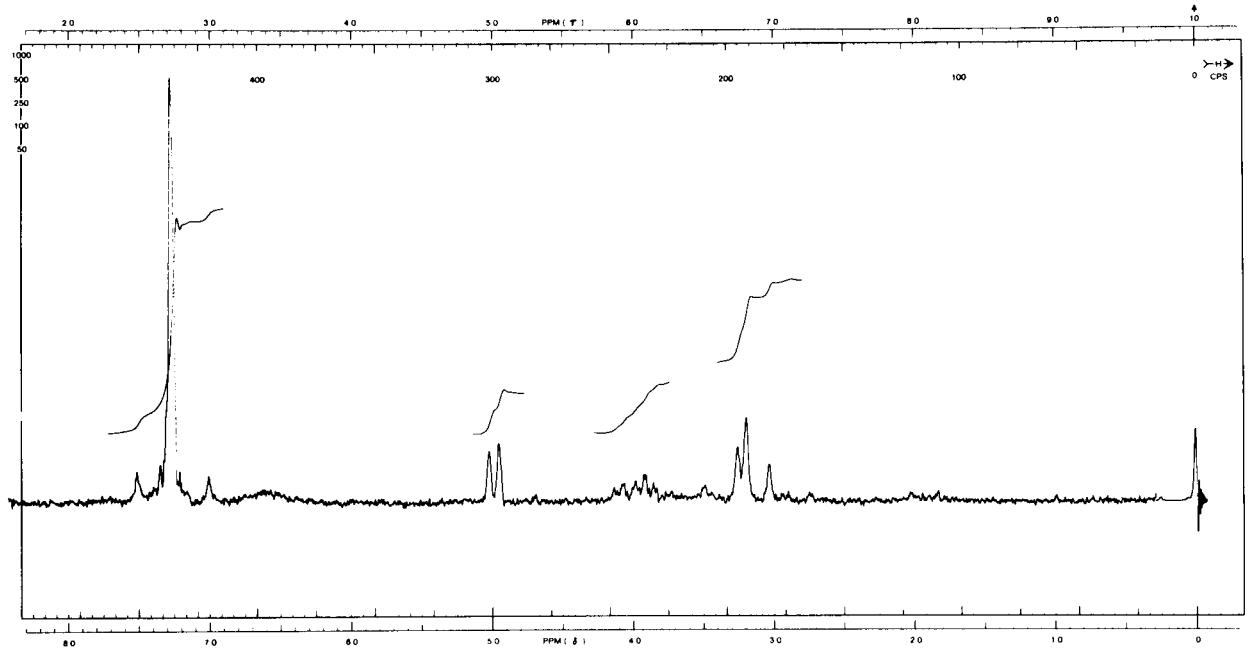


Figure 1. The nmr spectrum of β-lactam **8**.

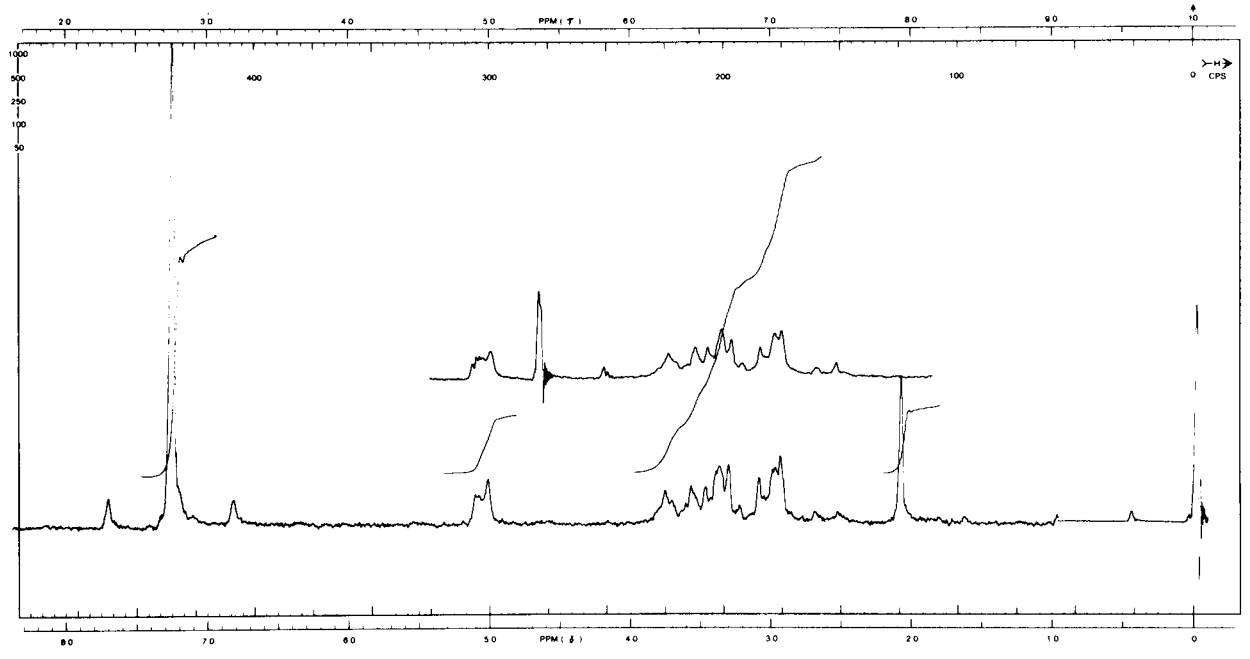


Figure 2. (a) The nmr spectrum of bicyclic azetidine **1**. (b) Deuterium oxide added.

spectrum of **8** is clearly indicative of the β-lactam structure with NH and C=O absorptions at 3410 and 1760 cm^{-1}, respectively, in chloroform. The nmr spectrum of **8** is also consistent with the assigned structure (Figure 1). The low yield of the azetidinone formed may be attributed to the method employed in which yields of 30-40% are not uncommon (5) and the fact that only the *cis* isomer would be expected to form the *cis*-fused azetidinone. Reduction

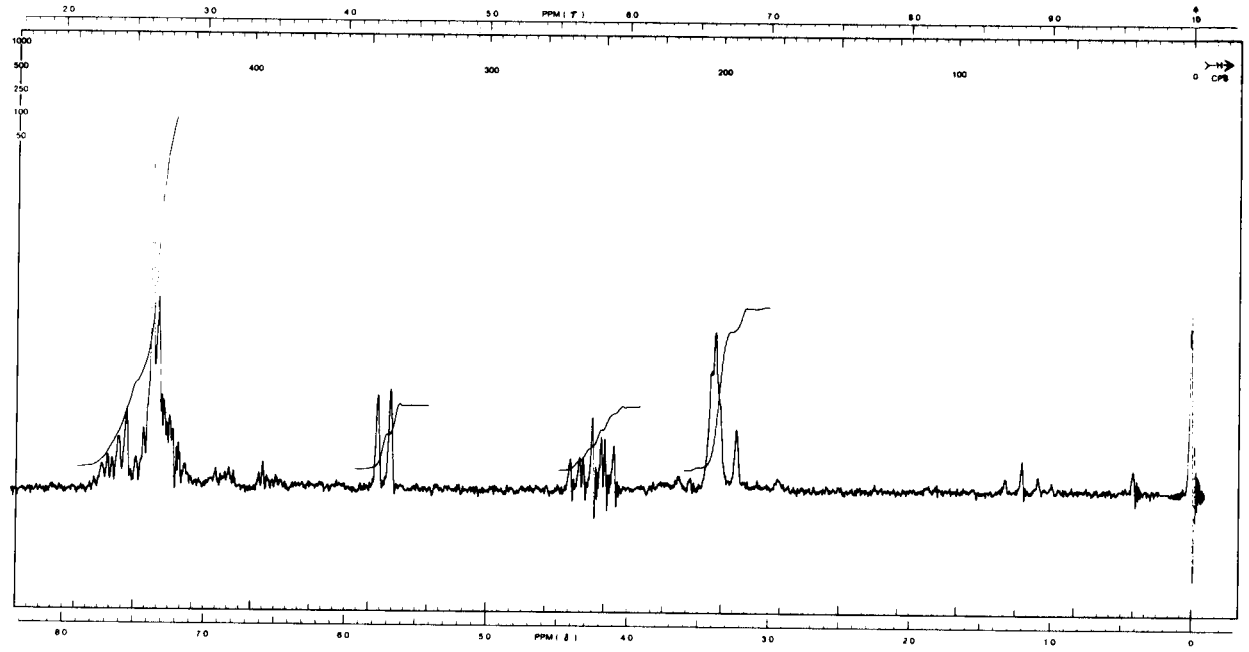


Figure 3. Nmr spectrum of the *N*-sulfonyl chloride β-lactum **9**.

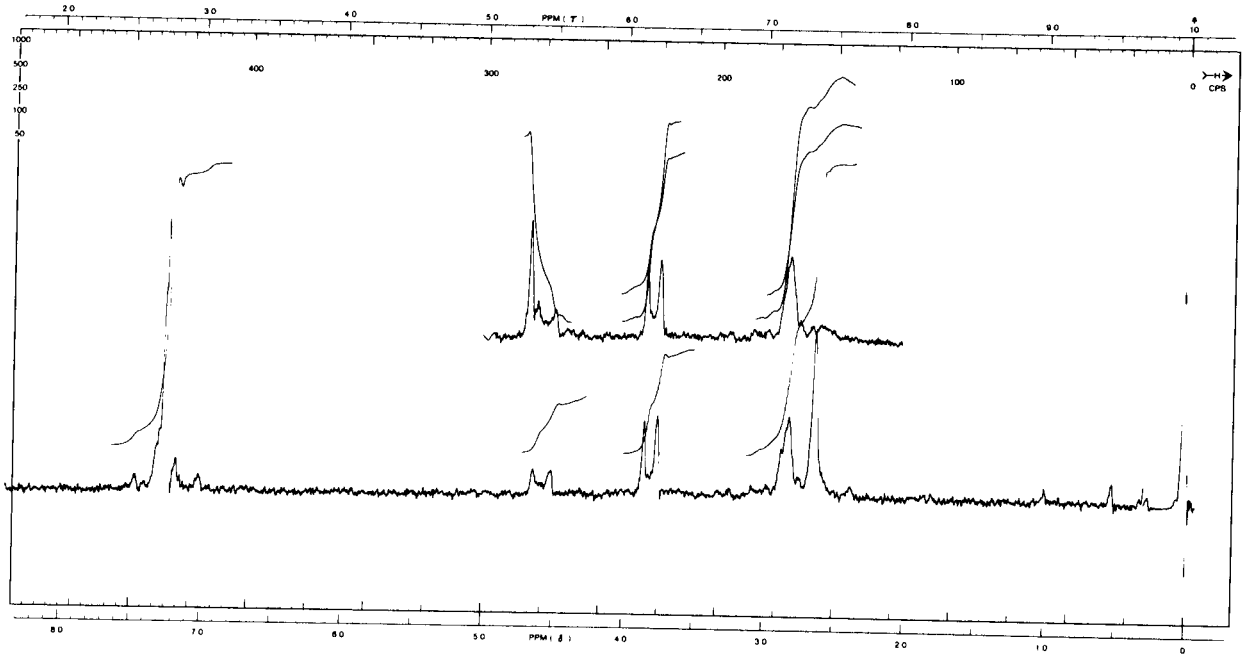


Figure 4. (a) The nmr spectrum of *cis*-1-amino-2-indanmethanol (**11**). (b) Deuterium oxide added.

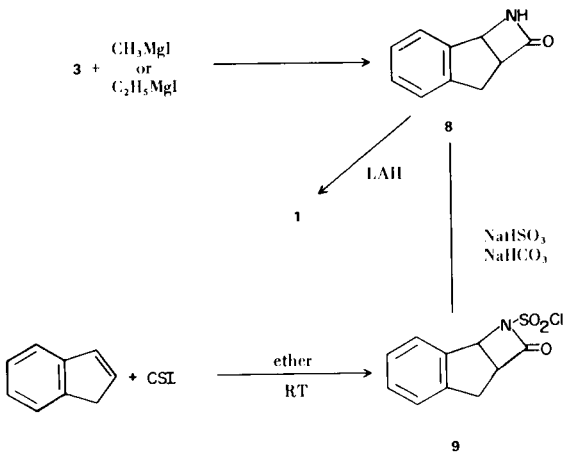
of **8** with excess lithium aluminum hydride gave the parent heterocycle **1** as a colorless oil in 50% yield (nmr Figure 2).

Since the ring closure to β-lactam **8** occurred in such low yield and consequently the overall yield of **1** was poor an alternative synthesis was devised as outlined in Scheme I. Contrary to the report of Graf (6), indene was found to react with *N*-chlorosulfonylisocyanate (CSI) in ether at *room temperature* to form the *cis*-*N*-chlorosulfonyl β-

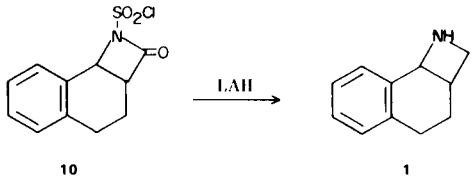
lactam **9** in 72% yield. Its infrared spectrum exhibited a carbonyl band at 1790 cm^{-1} reflecting the combined effects of a strained β-lactam ring containing a strong electron withdrawing substituent on the amide nitrogen. The *cis* geometry in **9** is suggested by Graf's (6) pioneering work on the reaction of CSI with simple olefins. The nmr spectrum (Figure 3) is very similar to that of β-lactam **8** except for the absence of the amide NH signal and a shift downfield of the protons in the vicinity of the nitrogen, especially C_5.

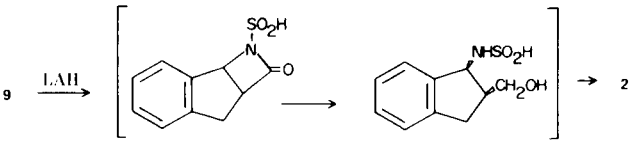
Reductive cleavage of the sulfonyl chloride nitrogen bond in **9** according to the method of Shaviv (7) yielded a colorless crystalline compound identical in all respects with β-lactam **8** prepared by the ring closure of **3** with Grignard reagent. As stated previously, **8** could be reduced with lithium aluminum hydride to the fused azetidine **1** in 50% yield. The availability of starting materials and the greater overall yield of this second method makes it the method of choice for the synthesis of **1**.

Scheme I



Further effort to improve upon the yield of azetidine **1** involved the attempted direct reduction of the *N*-sulfonyl chloride β-lactam **9** with lithium aluminum hydride. It was found however that instead of obtaining an azetidine as Moriconi (8) had observed on the reduction of 7-chlorosulfonyl-8-keto-benzo[*d*]-*cis*-7-azabicylo[4.2.0]octane (**10**) with LAH, a new compound **11** resulted. Based upon infrared, nmr (Figure 4) and mass spectral data as well as elemental analysis **11** is believed to be *cis*-1-amino-2-indanmethanol (**2**), apparently resulting from the reductive decomposition of **9** or its sulfinic acid derivative as pictured below.





EXPERIMENTAL (9)

2-Carbomethyl-1-indanone (**4**).

This compound was prepared by the method of House and Hudson (2) in 67% yield, m.p. 52-59° (lit. (2) m.p. 51-60°).

2-Carbomethoxy-1-indanone Oxime (**5**).

A solution of 20.0 g. (0.105 mole) of 2-carbomethoxy-1-indanone (**4**) in 60 ml. of methanol was added to a solution of 14.4 g. (0.207 mole) of hydroxylamine hydrochloride and 14.4 g. (0.175 mole) of sodium acetate in 20 ml. of water. The resulting mixture was heated on a steam bath for 4 hours and then allowed to stand at room temperature overnight. The cloudy solution was extracted with ether (3 x 100 ml.) and the ethereal extracts were washed with dilute sodium bicarbonate solution (2 x 50 ml.), dried over magnesium sulfate and evaporated. The crystalline residue (20.1 g.) was recrystallized from a methanol-water mixture to yield 16.1 g. (74.9%) of **5** as colorless crystals, m.p. 126-138°; ir (chloroform): 3250 (s, OH), 3240 (broad OH), 1735 cm^{-1} (C = O); 1640 cm^{-1} (C = N); nmr (deuteriochloroform): δ 7.86-7.65 (m, 1H, C_7 proton), 4.21 (m, 1H, C_2 proton), 3.73 (s, 3H, $-OCH_3$), 3.30 (t, J = 4 Hz, 2H, C_3 proton).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.48; H, 5.55; N, 6.79.

1-Amino-2-indanmethanol (**2**).

A 3.2 g. (0.0156 mole) sample of oxime **5** dissolved in 150 ml. of dry ether was added to 1.44 g. (0.0379 mole) of lithium aluminum hydride in 50 ml. of dry ether, then the mixture was refluxed with stirring for 72 hours. The solution was cooled in an ice bath and excess lithium aluminum hydride was neutralized by the dropwise cautious addition of water; the inorganic solids were filtered off and washed well with ether. The combined filtrates were dried over magnesium sulfate, and evaporated at reduced pressure to afford a colorless semi-solid. Recrystallization from a hexane chloroform mixture yielded 0.80 g. (31.5%) of **2** as colorless crystal, m.p. 89-93°; nmr (deuteriochloroform): δ 7.20 (bs, 4H, aromatic protons), 4.13 (d, J = 9 Hz, 1H, C_1 proton), 3.92 (d, 6 Hz, 2H, $-CH_2OH$), 3.01-2.28 (m, 3H, C_2 and C_3 protons), 2.38 (bs, 3H, OH and NH_2; removed on treatment with deuterium oxide).

N-Tosyl-1-amino-2-indanmethanol (**7**).

To an ice cold (-3°) solution of crude amino alcohol **2** (1.92 g., 0.0128 mole) in 65 ml. of pyridine, previously dryed over barium oxide, was added 1.17 g. (0.0061 mole) of freshly recrystallized tosyl chloride in portions, keeping the temperature below 5°. The solution immediately assumed a yellow-orange color. It was stirred at 0° for 16 hours, and then let stand at 0° until precipitation was complete (three days). The red solution was decanted into 600 ml. of ice water and then refrigerated for 36 hours. The resulting yellow crystals were filtered, washed well with cold water, and recrystallized from chloroform hexane to yield 1.32 g. (32.6%) of **7** as colorless crystals, m.p. 144-146°; ir (potassium bromide): 3450 (OH), 3200 (NH), 1350 (SO_2), 1160 cm^{-1} (SO_2); nmr (deuteriochloroform): δ 7.78 (d, J = 9 Hz, 2H, aromatic protons *ortho* to the SO_2 group), 7.26 (d, J = 9 Hz, 2H,

aromatic protons *ortho* to the CH_3 group), 7.19 (m, 4H, indane aromatic protons), 4.77 (m, 1H, C_1 proton), 3.75 (m, 2H, $-CH_2-OH$), 3.27-2.27 (m, 3H, C_2 and C_3 protons), 2.37 (s, 3H, CH_3); mass spectrum: m/e 317 (parent), 286 (m-31, loss of $-CH_2OH$), 162 (m-155, loss of $C_7H_7SO_2-$).

Anal. Calcd. for $C_{17}H_{19}NO_3S$: C, 64.35; H, 5.99; N, 4.42; S, 10.09. Found: C, 64.32; H, 6.17; N, 4.39; S, 10.11.

Attempted Tosylation of **7**.

To 0.5 g. (0.0016 mole) of monotosylate **7** in 150 ml. of dry ether was added 0.038 g. (0.0016 mole) of sodium hydride. The resulting suspension was stirred under reflux for 2 hours, then cooled to 0° and 0.35 g. (0.0018 mole) of tosyl chloride dissolved in 50 ml. of ether was added. It was stirred at 0° for 30 minutes and then at room temperature for 2.5 hours. Tlc on the reaction showed only the presence of unreacted starting alcohol and tosyl chloride. The ether was evaporated to cryness at room temperature and the crude product recrystallized from chloroform-hexane to yield 0.42 g. (85% recovery) of colorless crystals m.p. 143-145°, nmr same as **7**.

The same results were obtained when attempts were made to react tosyl chloride with **7** in pyridine at 0°.

2-Carbomethoxy-1-indanamine (**3**).

A solution of the oximino ester **5** (10.0 g., 0.0487 mole) in 200 ml. of absolute ethanol was placed in a Paar hydrogenation flask, the air was displaced with nitrogen and 2.0 g. of 10% palladium on charcoal was added, followed by 50 ml. of 1*M* ethanolic hydrogen chloride. The resulting mixture was then hydrogenated at 45 psi for 16 hours. The catalyst was filtered off, and the colorless solution was evaporated to give a nearly white solid. Recrystallization from ether-chloroform gave 0.8 g. (72%) of the hydrochloride of **3** as colorless crystals m.p. 185-190° dec.; ir (potassium bromide): 1735 cm^{-1} (C = O). Neutralization of the amine salt with triethylamine, gave the free base as a colorless oil, b.p. 110-112°/0.5 mm: nmr (deuteriochloroform): δ 7.45-7.06 (m, 4H, aromatic protons), 4.80 (d, J = 7 Hz, 1/2 H, C_1 proton in the *cis* isomer), 4.78 (d, J = 5 Hz, 1/2 H, C_1 proton in the *trans* isomer), 3.95-2.82 (m, 3H, C_2 protons and C_3 protons), 3.73 (s, 3H, $-OCH_3$), 1.58 (s, 2H, $-NH_2$). Elemental analysis was obtained for the hydrochloride salt.

Anal. Calcd. for $C_{11}H_{14}NO_2Cl$: C, 58.02; H, 6.15; N, 6.15; Cl, 15.60. Found: C, 57.75; H, 6.33; N, 6.09; Cl, 15.48.

7-Ketobenzo[*c*]*cis*-6-azabicyclo[3.2.0.]heptane (**8**) from **3**.

To the Grignard reagent prepared from 0.36 g. (0.0148 mole) of magnesium and 1.62 g. (0.0148 mole) of ethyl bromide in 50 ml. of absolute ether was added, over 30 minutes, 1.40 g. (0.0073 mole) of amino ester **3** dissolved in 75 ml. of dry ether. The mixture was refluxed for 2 hours with stirring, cooled to 0° and treated dropwise with 30 ml. of 5% ammonium chloride solution. The ether layer was separated, the aqueous layer extracted with 100 ml. of additional ether, and the combined ethereal extracts washed with dilute hydrochloric acid solution (2 x 100 ml.) and water (2 x 50 ml.). The ether solution was dried over magnesium sulfate and evaporated at reduced pressure. The resulting crude product was recrystallized from ether-petroleum ether to yield 0.15 g. (12.1%) of **3** as colorless plates, m.p. 184-186° (lit. (7) m.p. 182-183°); ir (chloroform): 3410 cm^{-1} (NH), 1760 cm^{-1} (C = O); nmr (deuteriochloroform): δ 7.25 (br, s, 4H, aromatic protons), 6.58 (br, s, 1H, amide NH), 5.00 (d, J = 5 Hz, 1H, C_5 proton, 4.18-3.83 (m, 1H, C_1 proton), 3.28-3.00 (m, 2H, C_2).

6-Chlorosulfonyl-7-ketobenzo[*c*]-*cis*-6-azabicyclo[3.2.0]heptane (**9**).

To 5.5 g. (0.0474 mole) of freshly distilled indene dissolved in 150 ml. of dry ether was added rapidly a solution of 10.0 g. (0.0707 mole) of *N*-chlorosulfonylisocyanate in 50 ml. of ether. The resulting colorless solution was then stirred at room temperature for 2 hours. The addition of 100 ml. of hexane and refrigeration caused the precipitation of the adduct. Recrystallization of the crude product from ether gave 9.0 g. (72.2%) of **9** as nearly colorless crystals, m.p. 82-85° dec., (lit. (7) m.p. 84-85°); ir (potassium bromide): 1790 cm^{-1} (C = O), 1380 and 1150 cm^{-1} (SO_2); nmr (deuteriochloroform): δ 7.78-7.13 (m, 4H, aromatic protons), 5.72 (d, J = 5Hz, 1H, C_5 proton), 4.23-4.10 (m, 1H, C_1 proton), 3.33 (m, 2H, C_2 protons).

Preparation of β-Lactam **8** from the Reduction of **9**.

The general procedure of Dunkelblum and Shaviv (7) was employed without variation. To an ice cold mixture of 12.5 g. of sodium bisulfite and 93 g. of sodium bicarbonate in 40 ml. of of water and 60 ml. of methylene chloride was added, in portions, 36.5 g. (0.150 mole) of **9**. After the addition was complete, the flask was allowed to warm to room temperature and then was stirred an additional 2 hours. The layers were separated, the aqueous layer was washed with methylene chloride (3 x 200 ml.). and the combined methylene chloride extracts were dried over magnesium sulfate. Removal of solvent gave 14.2 g. of crude product. Recrystallization from benzene-hexane afforded 9.0 g. (37.5%) of colorless crystals m.p. 182-184°, Ir and nmr data were identical with those of the product obtained from the ring closure of amino ester **3** with ethylmagnesium bromide, compound **8**.

Preparation of Benzo[*c*]-6-azabicyclo[3.2.0]heptane (**1**) by the Lithium aluminum Hydride Reduction of (**8**).

Into a suspension of 4.0 g. (0.105 mole) of lithium aluminum hydride in 300 ml. of dry ether was extracted, from the thimble of a Soxhlet, 4.0 g. (0.025 mole) of β-lactam **8** over the course of 4 hours. The resulting mixture was then refluxed for an additional 16 hours. After cooling, the excess lithium aluminum hydride was decomposed by the dropwise addition of a saturated solution of ammonium chloride. The inorganic salts were filtered and washed well with 150 ml. of 1:1 methanol-ether. The combined filtrates were washed with four 50 ml. portions of 10% hydrochloric acid. The acid washings were saturated with solid potassium hydroxide under a layer of ether and extracted with four 50 ml. portions of ether. The combined ether extracts were dried over magnesium sulfate, and evaporated at reduced pressure to yield a colorless oil which discolored on standing. Distillation at reduced pressure afforded a clear oil, b.p. 70-72°/0.1 mm; ir (potassium bromide): 3450 (broad, NH), 1580 cm^{-1} (Ar); nmr (deuteriochloroform): δ 7.27 (s, 4H, aromatic protons), 5.08 (m, 1H, C proton), 3.87-3.28 (m, 3H), 3.11-2.90 (m, 2H), 2.10 (s, 1H, NH; lost on shaking with deuterium oxide); mass spectrum: m/e 145.

Compound **1** gave a strong positive test for secondary amines with nickel chloride-carbon disulfide-ammonium hydroxide (10).

The phenylurea derivative of **1**, was obtained in the usual manner as a white solid m.p. 148-150°, after two recrystallizations from ethanol-petroleum ether.

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.27; H, 6.06; N, 10.61. Found: C, 77.04; H, 6.20; N, 10.56.

cis-1-Amino-2-indanmethanol (**11**).

The procedure described above was used without variation. From 8.4 g. (0.033 mole) of *N*-sulfonyl chloride β-lactam **9** and

8.4 g. (0.221 mole) of lithium aluminum hydride, there was obtained 1.6 g. of a colorless oil, b.p. 108-110°/0.1 mm, which solidified on standing. Recrystallization from chloroform-hexane yielded 1.1 g. (21.0%) of **11** as colorless needles, m.p. 81-83°; ir (potassium bromide): 3340 (sharp, OH), 3260 (sharp, NH); 1560 cm^{-1} (Ar); nmr (deuteriochloroform): δ 7.24-7.08 (m, 4H, aromatic), 4.53 (d, J = 7 Hz, 1H, C_1 proton), 3.78 (d, J = 7 Hz, 2H, CH_2-OH), 2.78-2.50 (m, 3H, C_2 and C_3 protons), 2.68 (s, 3H, -NH_2 and OH; lost on shaking with deuterium oxide); mass spectrum: m/e 163.

Compound **11** gave a negative test for secondary amines with nickel chloride-carbon disulfide-ammonium hydroxide (10).

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.84; H, 8.10; N, 8.55.

Acknowledgement.

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