Hydrogenation was continued until the originally dark orange mixture became a pale yellow solution. At this point 120–130% of the calculated amount of hydrogen had been absorbed. The catalyst was filtered and the ethanolic filtrate was evaporated *in vacuo*. The yellow residual solid was dissolved in 10 ml. of benzene and the solution was placed on a ¾″ × 18″ alumina column. The column was eluted with petroleum ether (b.p. 30–60°) (100 ml.), 100 ml. of 20% benzene in petroleum ether (b.p. 30–60°), and finally with 100 ml. of 50% benzene in petroleum ether (b.p. 30–60°). The first fraction was cut at the first sign of yellow coloration in the eluate. A strongly yellow colored second fraction was obtained by further elution with benzene. The second fraction was concentrated *in vacuo* to give a yellow solid, which was recrystallized from ethanol to give 0.3 g. of yellow plates; m.p. 186–195°. An infrared spectrum indicated this material was mostly recovered I-b.

The first fraction was concentrated *in vacuo* to give 1.7 g. of an almost colorless residue, m.p. 80–83° after recrystallization from aqueous ethanol. The colorless crystals were sublimed at 78° and 0.3 mm. to give a small amount of sublimate, m.p. 97–100°. The melting point of this sample was not depressed by mixture with 10,11-dihydro-5H-dibenz[b,f]azepine. The material which did not sublime was recrystallized from aqueous ethanol to give 1.55 g. of colorless crystals, m.p. 84.5–86°. (III-c.)

Anal. Calcd. for $C_{14}H_{12}NCl$: C, 73.20; H, 5.27. Found: C, 72.73, 72.62; H, 5.39, 5.28.

3-Chloro-10,11-dihydro-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (III-d). Alkylation was accomplished essentially as described above for the preparation of 5-(3-dimethylaminopropyl)dibenz[b,f]azepine. Toluene was used as the solvent, and the crude free base was not chromatographed, but was distilled; b.p. 160–170° at 0.3 mm. The hydrochloride was recrystallized from acetone-ether and then from methanol-ether to give a 75% yield of colorless crystals; m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{22}ClN\cdot HCl$: C, 64.93; H, 6.89. Found: C, 64.66; H, 6.96.

3-Chloro-5-(3-dimethylaminopropyl)-5H-dibenz[b,f]azepine (I-d). Alkylation of 3-chloro-5H-dibenz[b,f]azepine was carried out as described above for the alkylation of 5H-dibenz[b,f]azepine. Toluene was used as the solvent, and instead of chromatography, distillation was used to purify the free base of the product; b.p. 168–176° at 0.4–0.5 mm. The maleate was formed in ethyl acetate and was recrystallized three times from acetone-ether to give a 45% yield of yellow crystals; m.p. 124.5–125.5°.

Anal. Calcd. for $C_{19}H_{22}ClN_2\cdot C_4H_4O_4$: C, 64.40; H, 5.88. Found: C, 64.01; H, 6.01.

10,11-Dihydro-5-[3-(4-methyl-1-piperazinyl)propyl]-5H-dibenz[b,f]azepine (IIIe). The alkylation differed from that described above for the alkylation of 5H-dibenz[b,f]azepine as follows. Toluene was used as the solvent, and the alkylation required 12 hr. The free base was purified by distillation; b.p. 199–212° at 0.2–0.3 mm. The dihydrochloride was recrystallized from methanol-ether three times to give a 63% yield of colorless crystals; m.p. 245–246.5°. The infrared spectrum indicated that a trace of water was present.

Anal. Calcd. for $C_{22}H_{29}N_3\cdot 2HCl$: C, 64.70; H, 7.16. Found: C, 62.90; H, 7.82.

Anal. Calcd. for hemihydrate: C, 63.30; H, 7.73.

Addendum. Subsequent to the original preparation of this paper, two papers have appeared in which the preparation of Ia is reported.[14,15]

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. V. Azetidines[1,2]

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The problem of azetidine synthesis is reviewed, several unsuccessful approaches are described, and a relatively convenient method for the preparation of certain azetidines is reported. Cyclization to the azetidine system is considered as a conformational problem.

Although azetidine (I) and its derivatives have been known since the latter part of the nineteenth century,[4] comparatively little work has been done on methods of preparation, which in general appears to be inherently difficult, azetidine or an azetidine derivative often being but a minor constituent of the reaction products.

The present work was undertaken because of the potential relationship between azetidine and ethylenimine as regards "alkylating action," which in the latter has generally been credited with its effectiveness in certain anticancer agents.[5] To this end it was proposed to prepare azetidine analogs of various ethylenimine derivatives of known clinical use in the control of neoplastic disease.

It rapidly became apparent that the major barrier to such a program was the lack of convenient syntheses affording a good yield of azetidine itself or of its carbon-substituted derivatives. Potential approaches are from 2-azetidinones (*e. g.*, β-lactams) by reduction or from acyclic 3-functionally substituted (*e. g.*, halogen, *O*-sulfonate) amines.

(1) Previous paper in this series, R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, 25, 1583 (1960).

(2) This work supported by a Research Grant (CY-2961) from the National Cancer Institute to The University of Michigan.

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Reduction of 2-azetidinones. In spite of the report in 1954[6] that 1,4-diphenyl-2-azetidinone undergoes lithium aluminum hydride reduction to give 3-anilinodihydrocinnamyl alcohol, this reaction was reinvestigated, but with substantially the same results under a variety of conditions. The results are of use only as a potential source of 3-aminoalcohols for cyclization studies. Hydride reductions of 1,4-diphenyl-3,3-dimethyl-2-azetidinone[7] also afforded only the analogous acyclic alcohol, while high pressure hydrogenation over Raney nickel afforded 2,2-dimethyl-3,*N*-dicyclohexylpropionamide, which could be recovered unchanged after fifteen hours refluxing with 25% sodium hydroxide.

Our experience with 1,4-substituted 2-azetidinones has been confirmed recently by others.[8a,b] However, it is of considerable interest to note that successful reduction of 2-azetidinones to azetidines by lithium aluminum hydride is possible, providing there is no substituent on nitrogen.[8a]

Cyclization procedures. Four general methods purporting to yield azetidines by cyclization have been reported: (1) dehydrohalogenation of 3-haloalkylamines[9-13]; (2) reaction of 1,3-dihaloalkanes with amides[14-18]; (3) reaction of 3-aminoalkyl hydrogen sulfates with base[19-21]; (4) pyrolysis of diamines and related compounds.[22]

We have attempted to adapt the dehydrohalogenation of 3-haloalkylamines to the preparation of azetidine itself by way of *N*-benzylazetidine, which proved to be readily debenzylated. The necessary starting material, 3-*N*-benzylaminopropanol (II) is readily available by catalytic reduction of the Schiff base of commercially available 3-aminopropanol. Subsequent conversion of II to the *O*-tosylate (III) was realized by the procedure of Cope and Burg[23] for the mesylation of amino alcohols, but the product was difficultly separable from accompanying pyridine hydrochloride. The hydrochloride of III was cyclized using two equivalents of sodium hydroxide in the general manner for this method, and a 26% yield of *N*-benzylazetidine (V), isolated as the picrate, was obtained. This represents a reasonable yield for an otherwise unsubstituted *N*-alkylazetidine. Hydrogenolysis afforded azetidine.

We have also applied the cyclization of 3-aminoalkyl hydrogen sulfates to the synthesis of *N*-benzylazetidine (V) and obtained but a 5% yield. Almost twice the yield was obtained when 3-*N*-benzylaminopropanol was treated with concentrated sulfuric acid followed by alkali, but variations in concentrations did not improve the yield.

In view of the previous results it appeared to us that the most favorable conditions for constructing the azetidine ring system involved either cyclization of a suitable 3-substituted amine (secondary) or reaction of a 1,3-dihaloalkane with a sulfonamide in the presence of base. Consequently, we turned attention to a combination of the best features of both procedures. Thus 3-(*p*-toluenesulfonamido)-propyl *p*-toluenesulfonate (VI) provides an ideal starting point. This substance can be prepared in 95% yield from commercially available 3-aminopropanol, and the analogous 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate (VII) can be prepared in 66% yield from the corresponding aminoalcohol. Under appropriate conditions VI and VII were cyclized to IV (*p*-toluenesulfonazetidide)[15] and *p*-toluenesulfon-2-methylazetidide (VIII) in yields of 80–93% and 68% respectively. In addition *N*-(3-chloropropyl)methanesulfonamide (IX) was cyclized to methanesulfonazetidide (X) in 67% yield. This is appreciably better than the 55% yield of IV from *N*-(3-chloropropyl)-*p*-toluenesulfonamide reported by Searles.[15]

The chief problems in cyclization are competing

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eliminations and dimerization to bisazacyclo-octane sulfonamides. The former was negligible in the case of the primary tosylates, although recovery of the theoretical quantity of sodium chloride from the reaction of IX suggested that appreciable dehydrohalogenation may have occurred. Dimerization during the cyclization of VII became appreciable when the concentration of VII was increased above 0.097*M*; and with VIII appreciable dimerization occurred at lower concentrations, best yields being obtained using high dilution addition technique.

Having in hand acceptable syntheses of sulfonazetidides, we turned our attention to the previously discouraging problem of converting them to azetidines. Basic cleavage was found ineffective (*e. g.*, potassium ethoxide in toluene[24] as was high pressure hydrogenolysis (Raney nickel). With lithium aluminum hydride IV afforded a 10% yield of I, but X failed to react. Accordingly, we determined to reinvestigate the early report of almost quantitative conversion by sodium and amyl alcohol[16] in spite of later failures to duplicate this result.[10,17]

In the initial report[16] no special precautions were noted, and subsequent investigators gave no explicit details. However, since azetidine boils at 62° and amyl alcohol at 140°, and since a stream of hydrogen gas is constantly escaping, it seemed only prudent to trap any azetidine which might be carried out of the reaction. To this end the exit gases were passed through dilute sulfuric acid; and whether or not this acid was subsequently used to extract the free base from the amyl alcohol, I and 2-methylazetidine (XI) were obtained in excellent yield, while X afforded I in 42% yield. Thus the problem seems to have been largely mechanical; the free flow of hydrogen entrained the volatile azetidine, while forcing the gas through a trap served to mitigate such loss.

DISCUSSION

The substance of this investigation is the emergence of a comparatively convenient route from 3-aminopropanols to *N*-unsubstituted azetidines which is in principle limited only by the character of the hydroxyl: *i.e.*, with a tertiary alcohol, solvolysis would be expected and the resultant carbonium ion will then stabilize *via* solvent capture, deprotonation or "fragmentation" as with the analogous 3-aminopropyl halides.[25] It is perhaps surprising, though gratifying, that the anions derived from the 3-sulfonamidopropyl sulfonates do not fragment, since the gross conformation appropriate for cyclization, as well as conformations derived from it by rotation about the C_3–C_4 bond, are all sterically ideal for such a reaction. Failure to observe fragmentation with primary tosylates is in large part attributable to the greater energy requirement for heterolytic cleavage of a primary carbon-oxygen bond, but failure to observe it where this bond is secondary (VI) must be attributed to a stereoelectronic situation arising from the great bulk of the sulfonyl group which tends to place it conformationally staggered with respect to the substituents on C_3 (Fig. 1). Thus it occupies the position required of an electron pair if the latter is to participate effectively in the fragmentation process, which is the dominant if not exclusive reaction when stereoelectronic conditions are fulfilled.[25]

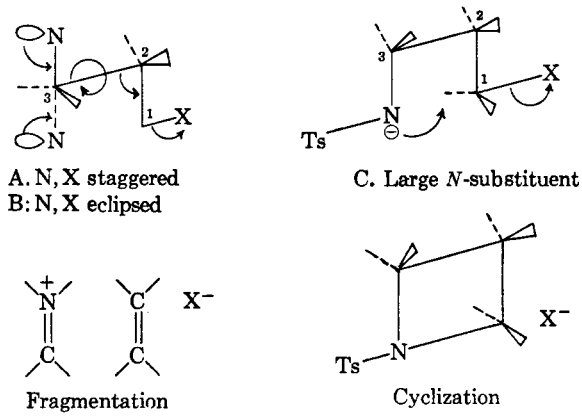

Fig. 1. Conformations during cyclization and fragmentation

By applying Grob's stereoelectronic requirements for fragmentation, one may account for previous failures to obtain satisfactory yields of azetidines from *N*-unsubstituted 3-halo- or 3-*O*-sulfonoylpropylamines and for the improvement in yield when the nitrogen is substituted. When the nitrogen is unsubstituted the conformations A and B (Fig. 1), with the π-electrons of nitrogen directed as indicated, are comparatively readily realized, and fragmentation is to be expected as a serious competitor to cyclization. When the nitrogen is substituted, the extent to which the substituent suffers non-bonded interaction with other substituents will be reflected in a stereoelectronic situation which is progressively less favorable to fragmentation with increasing substituent bulk; and while the rate of cyclization may be unfavorably affected, the rate of fragmentation will be more seriously depressed owing to its great sensitivity to stereoelectronic factors.[25]

The most favorable situation for effective cyclization to the azetidine system, then, will be found in a 3-aminopropyl system in which there are no substituents on any of the carbons and a (large) substituent on nitrogen. Symmetrical *gem*-substitution on C_2 (provided the groups are not too large) with no substituents on C_1 and C_3, or on C_3 with none on C_1 and C_2 should be approximately as good, and *threo*-substituents on C_1 and C_2 or C_2 and C_3 (or on

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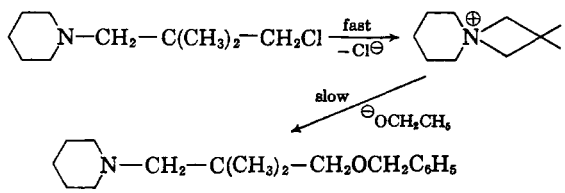
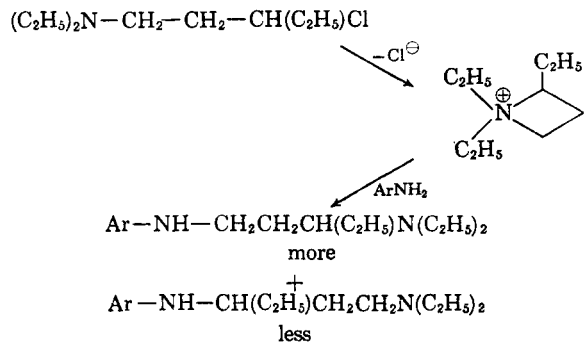
all three carbons) should not interfere with cyclization.

The effectiveness of *N*-substitution as a means of promoting cyclization is to be seen not only in the data of Table I but also in the following. It has been reported that 3-*N*-piperidyl-2,2-dimethylpropyl chloride undergoes a displacement reaction with sodium benzyloxide at a much faster rate than expected for a neopentyl-type chloride.[26] The authors explain this in terms of a fast conversion to an azetidinium ion which is then cleaved by benzyloxide ion in a slower step:



The reaction of 6-methoxy-8-aminoquinoline with 1-diethylamino-3-chloropentane to give both 6-methoxy-8-(1-diethylamino-3-pentylamino)quinoline and 6-methoxy-8-(3-diethylamino-1-pentylamino)quinoline (more) would appear to involve an azetidinium ion also.[27]



One is now in a position to predict in any given case whether cyclization will be a reasonably satisfactory reaction. Neither fragmentation nor E_2 elimination may be expected to interfere if the "leaving group" on C_1 is primary; only dimerization, which can be controlled by appropriate dilution, need be considered. When the leaving group is secondary, conditions should be selected which favor Sn_2 reactions over Sn_1; and the nitrogen should be substituted by a bulky group to inhibit fragmentation. Again suitable dilution should control the relative rates of E_2 or dimerization and cyclization. The data of Table I support these generalizations.

Strain factors arising from the size of the four-membered ring assuredly need not interfere with cyclization *per se*, although they just as assuredly do contribute to ring instability, though to a lesser extent than in the ethyleneimine system. Their chief deleterious effects are to be seen in the relatively slow rate at which cyclization occurs (slowest of the series of 3-, 4-, 5- and 6-membered nitrogen heterocycles[28]), which gives competing reactions a better chance. More serious, and also contributory to slow cyclization, are conformational effects due to substituents on the carbons of the propyl chain. The transition state for cyclization, requires that substituents on carbons 2 and 3 be eclipsed; thus large substituents *erythro* to each other (Fig. 2) will both diminish the rate of cyclization and decrease the stability of the ring once it is formed. The same may be said of large, *erythro* substituents on carbons 1 and 2, but eclipsing here is serious only in the transition state (and product) whereas on C_2 and C_3 the substituents must be eclipsed in the conformation leading to the transition state, thus materially decreasing the probability of cyclization which must proceed from an energetically unfavorable ground state.

TABLE I

EFFECT OF SUBSTITUTION ON CYCLIZATION

3-Halopropylamines	Azetidine, %	Reference
$Br(CH_2)_3NH_2$	6–26	10
$X(CH_2)_3NH_2$	poor	11
3-Bromo-*N*-methylpropylamines		
$BrCH_2C(CH_3)_2CH_2NHCH_3$	80	11
$BrCH(CH_3)CH_2CH(CH_2CH(CH_3)_2)$-$NHCH_3$	79	12a
$BrCH(CH_3)CH_2CH(CH(CH_3)_2)$-$NHCH_3$	50	12b
N-Alkyl-3-propylsulfonate ions		
$[^-OSO_2(CH_2)_3NH_2]$	[1.7]	21
$^-OSO_2(CH_2)_3NHCH_3$	8	15
$^-OSO_2(CH_2)_3NHC_2H_5$	13	22
$^-OSO_2(CH_2)_3NHCH_2C_6H_5$	9[a]	
$^-OSO_2(CH_2)_3NH$-*n*-C_4H_9	30	19
$^-OSO_2(CH_2)_3NH$-*t*-C_4H_9	47	20
3-Chloropropyl-*N*-sulfonamide ions		
$Cl(CH_2)_3N^-SO_2$-*p*-$C_6H_4CH_3$	55[b]	15
$Cl(CH_2)_3N^-SO_2CH_3$	67	
3-(4-Toluenesulfonoxy)-propyl-*N*-sulfonamide ions	55[b]	15
p-$CH_3C_6H_4SO_3(CH_2)_3N^-SO_2$-*p*-$C_6H_4CH_3$	80–93	
p-$CH_3C_6H_4SO_2CH(CH_3)(CH_2)_2N^-SO_2$-*p*-$C_6H_4CH_3$	68	

[a] This appears to be out of line. The 26% yield from 3-*N*-benzylpropyl *p*-toluenesulfonate suggests the proper value. [b] This value is probably not high enough as the intermediate shown was formed *in situ* from trimethylene chlorobromide and sodium *p*-toluenesulfonamide.

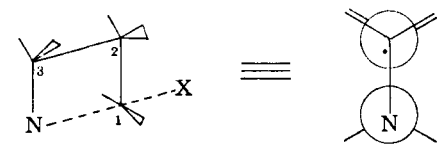


Fig. 2. Conformational effects due to substituents on the propyl chain

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EXPERIMENTAL[29]

3-Anilino-3-phenyl-1-propanol. To a stirred solution of 0.30 g. (7.9 mmoles) of lithium aluminum hydride in 10 ml. of dry ether was added, dropwise, a solution of 2.2 g. (10 mmoles) of 1,4-diphenyl-2-azetidione[30] in 15 ml. of dry ether. No evolution of heat was noticed during the addition. The solution was refluxed for 0.5 hr. after which 30 ml. of a 25% sodium hydroxide solution was added. After stirring for 0.5 hr. the layers were separated and the ether layer was dried with anhydrous magnesium sulfate. Removal of the ether in a stream of air precipitated a light-yellow solid which was recrystallized from a methanol/petroleum ether (b.p. 90–100°) mixture. The yield of 3-amino-3-phenyl-1-propanol was 1.7 g. (74%), m.p. 89–90° (reported[6] m.p. 87–88°). The use of tetrahydrofuran as a solvent gave 1.9 g. (82%) of product.

1,4-Diphenyl-3,3-dimethyl-2-azetidinone. This substance was prepared by the method of Gilman and Speeter[30] from ethyl α-bromoisobutyrate, benzylideneaniline, and zinc in 38.6% yield: m.p. 149–150°, reported 148–149°.[7]

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol. Reduction of 5.0 g. (20 mmoles) of 3,3-dimethyl-1,4-diphenyl-2-azetidinone by lithium aluminum hydride (0.60 g., 15.8 mmoles) in tetrahydrofuran afforded 4.7 g. of product, 1.8 g. of which was dissolved in a mixture of 25 ml. of petroleum ether (b.p. 60–75°) and 35 ml. of benzene and chromatographed on a neutral alumina[31] column. Elution with benzene gave 1.5 g. of 3-anilino-2,2-dimethyl-3-phenyl-1-propanol (corresponds to a 93.2% reduction of the β-lactam), m.p. 105.0–105.5°.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.94; H, 8.29; N, 5.48. Found: C, 79.99; H, 8.09; N, 5.58.

The same procedure, with a recrystallization from alcohol substituted for the chromatographic procedure, was used for the reduction of the β-lactam with other metal hydrides under various conditions: (sodium borohydride, lithium borohydride, sodium borohydride–aluminum chloride, and lithium borohydride–aluminum chloride) without improvement.

3-Anilino-2,2-dimethyl-3-phenyl-1-propanol hydrochloride. The hydrochloride was made by passing dry hydrogen chloride through a dry ethereal solution of 3-anilino-2,2-dimethyl-3-phenyl-1-propanol. The salt precipitated quantitatively, m.p. 168.0–169.0°.

Anal. Calcd. for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; Cl, 12.15; N, 4.81. Found: C, 69.78; H, 7.60; Cl, 11.62; N, 4.84.

2,2-Dimethyl-N,3-dicyclohexylpropionamide. 3,3-Dimethyl-1,4-diphenyl-2-azetidinone (2.5 g., 0.01 mole) was dissolved in 70 ml. of absolute alcohol and 0.3 g. of Raney nickel catalyst (W-2) was added.

The mixture was charged with hydrogen to a pressure of 1300 p.s.i. and shaken for 11 hr. at 250°.

The catalyst was filtered and the solvent distilled from a warm water bath at reduced pressure (water-aspirator). Recrystallization of the residue from dilute alcohol gave 2.6 g. (100%) of the amide, m.p. 92.0–92.5°.

Anal. Calcd. for $C_{17}H_{31}NO$: C, 76.92; H, 11.77; N, 5.28. Found: C, 76.93; H, 11.64; N, 5.29.

The infrared spectrum possessed bands at 3340 and 1635 cm.$^{-1}$ but no absorption at 1600 or 1500 cm.$^{-1}$ The compound failed to hydrolyze when refluxed with 25% sodium hydroxide for 15 hr.

Attempted preparation of 3-aminopropyl methanesulfonate hydrochloride. An attempt to prepare this substance involved conversion of 3-aminopropanol to the hydrochloride in chloroform followed by addition of 1 equivalent each of pyridine and methanesulfonyl chloride at ~0°. However, only 38% of pyridinium methanesulfonate was obtained, m.p. 178–180°.

Anal. Calcd. for $C_4H_9NO_3S$: C, 41.14; H, 5.18; N, 8.00. Found: C, 41.08; H, 5.11; N, 8.11.

3-N-Benzylaminopropanol (II). One mole of benzaldehyde (106 g.) and one mole of 3-hydroxypropylamine (75 g.) were dissolved in 200 ml. of absolute ethanol and hydrogenated at 3 atm. over Adams' catalyst (0.5 g.). The absorption of hydrogen stopped after about 7 hr. Filtration through Celite and distillation afforded 138.2 g. (85%) of 3-benzylaminopropanol, b.p. 125–130° (2 mm.).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.80; H, 9.15; N, 8.54.

3-Benzylaminopropanol hydrochloride. A quantitative yield of 3-benzylaminopropanol hydrochloride was formed by bubbling dry hydrogen chloride through a dry ether solution of 3-benzylaminopropanol. Two recrystallizations from absolute alcohol–ether gave the analytical sample, m.p. 83.5–85.0°.

Anal. Calcd. for $C_{10}H_{16}ClNO$: C, 59.54; H, 8.00; Cl, 17.58; N, 6.94. Found: C, 59.02; H, 7.77; Cl, 18.09; N, 6.76.

N-(3-Benzoyloxypropyl)-N-benzylbenzamide. A pyridine solution of 3-benzylaminopropanol was benzoylated with a slight excess of benzoyl chloride. Three recrystallizations from an acetone-water mixture gave the analytical sample, m.p. 80.0–81.5°.

Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 76.89; H, 6.42; N, 3.73. Found: C, 77.19; H, 6.21; N, 3.75.

3-Benzylaminopropyl-p-toluenesulfonate hydrochloride. (III; *hydrochloride*). Four grams (0.02 mole) of 3-benzylaminopropanol hydrochloride was dissolved in a mixture of 6.8 g. (0.08 mole) of pyridine and 15 ml. of chloroform. The solution was cooled to −3° and 4.7 g. (0.025 mole) of *p*-toluenesulfonyl chloride was added in small portions, keeping the temperature below 3°. The solution was refrigerated (0°) for 6 days and the solvent was removed under reduced pressure. Trituration of the gummy residue with anhydrous ether gave 11.9 g. of yellow solid. Several recrystallizations from absolute ethanol–ether gave 2.0 g. (22.5%) of 3-benzylaminopropanol *p*-toluenesulfonate hydrochloride, m.p. 182–183°.

Anal. Calcd. for $C_{17}H_{22}ClNO_3S$: C, 57.36; H, 6.23; N, 3.93; S, 9.01. Found: C, 57.60; H, 6.10; N, 3.70; S, 8.65.

N-Benzylazetidine (V). *Procedure A.* Twenty-nine grams (0.25 mole) of freshly distilled chlorosulfonic acid was added dropwise to 36 g. (0.18 mole) of 3-hydroxypropylbenzylamine hydrochloride. After the initial reaction subsided, the mixture was heated on the steam bath for 30 min. and then under vacuum (water-aspirator) in an oil bath, first at 80° for 0.5 hr., then at 140° for 0.5 hr.

After cooling, the viscous oil was dissolved in 75 ml. of water and slowly added to a solution of 60 g. of potassium hydroxide in 75 ml. of water. The alkaline solution was then steam-distilled with the product coming over in the first 125 ml. of distillate.

Twenty grams of potassium hydroxide was added to the distillate, and the solution was extracted with ether. After drying and removal of solvent the product was distilled: 1.3 g. (5%) of 1-benzylazetidine, b.p. 71–75° (5 mm.). Two distillations gave the analytical sample, b.p. 78° (5.5 mm.).

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.54. Found: C, 81.48; H, 9.04; N, 9.56.

The *picrate* melted at 89–90°.

Anal. Calcd. for $C_{16}H_{16}N_4O_7$: C, 51.05; H, 4.28; N, 14.90. Found: C, 51.18; H, 4.28; N, 14.91.

(29) All melting and boiling points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. The infrared spectra of solids were recorded from Nujol mulls on a Perkin-Elmer Model 21 Infrared Spectrophotometer; liquids were recorded as thin films by the same instrument.

(30) H. Gilman and M. E. Speeter, *J. Am. Chem. Soc.*, 65, 2255 (1943).

(31) The alumina used in this and subsequent experiments was prepared from acid-washed alumina (Merck) by shaking with ethyl acetate for 12 hr. After decanting the ethyl acetate, the alumina was washed with methanol and acetone and dried in an oven (60°).

Procedure B. A solution of 33 g. of 3-hydroxypropylbenzylamine in 15 ml. of water was cooled in an ice bath and a cold solution of 25 ml. of concd. sulfuric acid in 12 ml. of water was added. The resulting solution was maintained at 50–60° while the water was removed by distillation at reduced pressure (water-aspirator). The solution was next cooled to room temperature, and 88 g. of a 40% sodium hydroxide solution was added in 10-ml. portions. A violent reaction occurred after the first few additions, and after all the base was added the solution was steam-distilled. About 250 ml. of distillate was collected, treated with 50 g. of potassium hydroxide, and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and distilled to give 2.5 g. (9%) of 1-benzylazetidine, b.p. 71–75° (5 mm.). The infrared spectrum of this compound and *N*-benzylazetidine obtained by Procedure A were superimposable.

N-Benzylazetidine (V) *(by cyclization of 3-benzylaminopropyl p-toluenesulfonate hydrochloride* (III. *hydrochloride).* A solution of 1.9 g. (5.3 mmoles) of 3-benzylaminopropyl *p*-toluenesulfonate hydrochloride in 10 ml. of water was treated with 0.42 g. (10.6 mmoles) of sodium hydroxide. The solution was refluxed for 1 hr. An oil separated during this time. The solution was extracted with ether and the ethereal solution was washed with water and dried with magnesium sulfate. Picric acid in ether (1.2 g. (5.3 mmoles)) was added to the ether solution. A small amount of oil separated and solidified on refrigeration (0°): 0.53 g. (26%), m.p. 84–89°. A mixed melting point with a sample of *N*-benzylazetidine picrate obtained from the cyclization of 3-benzylaminopropanol showed no depression.

3-(p-Toluenesulfonamido)propyl p-toluenesulfonate (VI). A solution of 19.0 g. (0.25 mole) of 3-aminopropanol in 300 ml. of dry pyridine was cooled to −6° in an ice-salt bath. *p*-Toluenesulfonyl chloride (110 g., 0.59 mole) was added in portions, keeping the temperature below 5°. After stirring for 4 hr., the white solid was filtered (28.7 g., corresponding to a 52.5% yield of pyridine hydrochloride). The filtrate was diluted with 2 l. of ice and water, whereupon a red oil precipitated. The oil slowly crystallized to an orange solid which upon recrystallization from ethanol-water yielded 90.6 g. (95%) of 3-(*p*-toluenesulfonamido)propyl *p*-toluenesulfonate, m.p. 116–119°. Recrystallization of a 16.5-g. sample from methanol afforded 15.5 g. of pure VI: m.p. 120–121° (corr.).

Anal. Calcd. for $C_{17}H_{21}NO_5S_2$: C, 53.26; H, 5.52; N, 3.65. Found: C, 53.52, 53.47; H, 5.69, 5.58; N, 3.84, 3.77.

4-(p-Toluenesulfonamido)-2-butyl p-toluenesulfonate (VII). A solution of 8.8 g. (0.10 mole) of 4-amino-2-butanol in 150 ml. of pyridine was cooled to −6° and 38.2 g. (0.20 mole) of *p*-toluenesulfonyl chloride was added slowly, keeping the temperature below 5°. After the addition the solution was refrigerated (0°) for 3 days during which time pyridine hydrochloride precipitated and the solution turned deep red. The mixture was poured into 600 ml. of ice water. A red oil separated and solidified slowly. After standing at 0° for 1 hr. the solid was filtered and washed with cold, dilute hydrochloric acid. The adsorbed water and color were removed by dissolving the solid in chloroform, separating the water layer and filtering through Norit. The chloroform solution was then dried with magnesium sulfate and diluted with petroleum ether (b.p. 30–60°) to precipitate 26.2 g. (66%) of 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate, m.p. 91.0–93.5°. Two recrystallizations from the same solvent pair gave the analytical sample, m.p. 94.0–95.0°.

Anal. Calcd. for $C_{18}H_{23}NO_5S_2$: C, 54.39; H, 5.83; N, 3.52. Found: C, 54.47; H, 5.81; N, 3.40.

N-(3-Chloropropyl)methanesulfonamide (IX). A solution of 75.1 g. (1.0 mole) of 3-hydroxypropylamine and 158 g. (2 moles) of pyridine in 300 ml. of chloroform was cooled to −10°. Methanesulfonyl chloride (229.2 g., 2 moles) was added dropwise, keeping the temperature below 0°. After the addition, the solution was stirred for 3 hr. at 0°. The solvent was removed by distillation at reduced pressure and the residue, after extraction with cold water, was distilled *in vacuo* to give *N*-(3-chloropropyl)methanesulfonate [77.2 g., b.p. 150–153° (0.3 mm.); 45% yield]. The compound gave no precipitate with aqueous silver nitrate.

Anal. Calcd. for $C_4H_{10}ClNO_2S$: C, 27.99; H, 5.90; Cl, 20.65; N, 8.16; S, 18.69. Found: C, 27.80; H, 5.56; Cl, 20.74; N, 8.48; S, 18.77.

p-Toluenesulfonazetidide (IV) (A). To a solution of 5.1 g. (0.0146 mole) of 3-(*p*-toluenesulfonamido)propyl-*p*-toluenesulfonate (VI) in 425 ml. of absolute ethanol was added a solution of 0.36 g. (0.0146 g.-atom) of sodium in 75 ml. of absolute ethanol. After refluxing for 16 hr. the solvent was distilled until the remainder amounted to about 100 ml. The latter was then diluted to 1 l. with water and on standing for a few hours *p*-toluenesulfonazetidide precipitated in short needles; yield, 2.25 g. (75.5%), m.p. 119.0–121.5° (reported[16] m.p. 120°).

(B). Cyclization of 10.2 g. (0.0292 mole) of VI using 0.72 g. (0.0292 g.-atom) of sodium in a total volume of 570 ml. of absolute ethanol gave 5.0 g. (80.7%) of *p*-toluenesulfonazetidide, m.p. 118–120°.

(C). Cyclization of 10.2 g. (0.0292 mole) of VI using 0.72 g. (0.0292 g.-atom) of sodium in a total volume of 300 ml. absolute ethanol gave 4.2 g. of a white solid, m.p. 116–150°. The solid was dissolved in benzene and chromatographed on a neutral alumina[28] column. Benzene eluted 3.5 g. (56.4%) of *p*-toluenesulfonazetidide, m.p. 119–122°. Ether eluted 0.4 g. of a white solid, m.p. 210–213° (reported[14a] for 1,5-di(*p*-toluenesulfonyl)-1,5-diazacyclooctane, 215°).

(D). To a solution of 5.1 g. (0.013 mole) of VI in 500 ml. of *t*-butyl alcohol was added 14 ml. of 1.04*M* potassium *t*-butoxide, and the mixture was refluxed for 10 hr., with stirring. The fine precipitate of potassium *p*-toluenesulfonate (2.6 g., 85%) was filtered off while hot, and the solvent was removed *in vacuo* from the filtrate. The residue was taken up in hot methanol, filtered and diluted with water, whereupon there was obtained 2.6 g. (93%) of IV, m.p. 116–120°.

2-Methyl-p-toluenesulfonazetidide (VIII). *Procedure A.* To a solution of 5.92 g. (14.6 mmoles) of 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate in 425 ml. of absolute ethanol was added, in one portion, a solution of 0.36 g. (14.6 mg.-atoms) of sodium in 75 ml. of absolute ethanol. After refluxing for 19 hr. the solvent was distilled until the remainder amounted to about 75 ml. The latter was then diluted to 1 l. with water to precipitate 1.32 g. (35.5%) of 2-methyl-*p*-toluenesulfonazetidide, m.p. 97–99°. Two recrystallizations from a chloroform/petroleum ether (b.p. (30–60°) mixture gave the analytical sample, m.p. 99–100°.

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.63; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.59; H, 6.67; N, 5.98; S, 14.19.

Procedure B. A solution of 19.8 g. (50.0 mmoles) of 4-(*p*-toluenesulfonamido)-2-butyl *p*-toluenesulfonate in 300 ml. of absolute ethanol was added in high dilution;[32] over a period of 48 hr. to a refluxing solution of 1.2 g. (50 mg.-atoms) of sodium in 350 ml. of absolute ethanol. When the addition was completed the solvent was distilled until the remainder amounted to about 150 ml. (removal of more solvent resulted in a brown product). The remainder was diluted to 1 l. with water to precipitate 8.2 g. (67.7%) of the product, m.p. 97–99°.

Methanesulfonazetidide (X). A solution of 0.5 g. (21 mg.-atoms) of sodium in 100 ml. of absolute ethanol was added in one portion to a refluxing solution of 3.4 g. (20 mmoles) of *N*-(3-chloropropyl)methanesulfonamide in 75 ml. of absolute ethanol. The resulting solution was refluxed for 48 hr. during which time sodium chloride precipitated (1.2 g., 100% yield). The solvent was distilled at atmospheric pressure and the residue was dissolved in chloroform. Concentration of the chloroform solution gave 1.8 g. of methanesulfonazetidide (66.6% yield), m.p. 81–82°.

(32) A. C. Cope and E. C. Herrick, *J. Am. Chem. Soc.*, 72, 985 (1950).

Anal. Calcd. for $C_4H_9NO_2S$: C, 35.54; H, 6.71; N, 10.36; S, 23.74. Found: C, 35.64; H, 6.77; N, 10.19; S, 23.92.

Azetidine (I) (*by reduction of sulfonazetidides.*) (A) A three-necked flask (with its side-necks stoppered) was fitted with a 400-mm. reflux condenser. To the top of the condenser was attached a glass tube which extended 1 cm. into a dilute sulfuric acid solution.

A solution of 11.4 g. (0.0845 mole) of methanesulfonazetidide in 350 ml. of *n*-amyl alcohol was refluxed in the three-necked flask. Through one of the side necks was added 20 g. (0.87 g.-atom) of sodium in 1-g. pieces. The sodium was added after the preceding piece had completely reacted with the solvent. After all of the sodium had reacted the solution was cooled to room temperature and 150 ml. of water was added. The layers were separated and the aqueous layer was distilled up to 100°. This distillate was combined with the amyl alcohol and the mixture was extracted with the dilute sulfuric acid which was used as a trap. Extraction with dilute sulfuric acid was continued until the extracts were strongly acidic. The combined acid extracts were cooled and made strongly alkaline with potassium hydroxide pellets and distilled up to 100°. The distillate was made strongly alkaline with potassium hydroxide pellets and extracted with ether. After drying with potassium hydroxide pellets, the ether solution was distilled to give 2.0 g. (42.5%) of azetidine, b.p. 61–66° (750 mm.) [reported[9] b.p. 62° (730 mm.)]. The picrate melted at 161–165° (reported[4] m.p. 166–167°).

(B). A 73.0-g. (0.35 mole) sample of IV was dissolved in 2 l. of boiling *n*-amyl alcohol, and 146.4 g. of sodium was added in portions over 3 hr., waiting for most of the effervescence to cease before each subsequent addition. The condenser was connected to a sulfuric acid trap as in the preceding experiment. The mixture was allowed to cool overnight, and 900 ml. of water was added. The lower layer was separated and distilled (about 100 ml.) until no more amyl alcohol came over. The distillate was added to the alcohol layer remaining in the separatory funnel, which was then chilled and extracted with enough of 2*N* sulfuric acid (including that from the trap) to ensure complete acidity.

The resulting acidic extract was itself ether-extracted and then freed of ether by an air stream, after which it was added to the original strongly alkaline solution. Aqueous I was distilled out and the distillate was saturated with potassium hydroxide. The dried azetidine, which separated, weighed 16.9 g. [84.7%: n_D^{22} 1.4110 (reported n_D^{20} 1.4229[15])].

Azetidine (I) (*by hydrogenolysis of 1-benzylazetidine*). To 30 ml. of absolute ethanol was added 163.2 mg. (1 mmole) of 1-benzylazetidine. Twenty milligrams of 10% palladium-on-charcoal were added and the mixture was hydrogenated under 1 atm. hydrogen pressure. One millimole of hydrogen was taken up in 3 days. The catalyst was filtered off and a solution of 229 mg. (1 mmole) of picric acid in a minimum amount of absolute ethanol was added to the filtrate. The solution was diluted with dry ether and refrigerated (0°) for 2 days. Azetidine picrate, m.p. 166–169° (reported[4] m.p. 166–167°), precipitated during this time.

2-Methylazetidine (XI). To a refluxing solution of 8.2 g. (0.036 mole) of 2-methyl-*p*-toluenesulfonazetidide in 300 ml. of *n*-amyl alcohol was added 16 g. (0.70 g.-atom) of sodium in 1-g. portions. The portions of sodium were added after the preceding portion had completely reacted with the solvent. After the addition the solution was cooled and 150 ml. of water was added. The aqueous layer was distilled up to 100° and the distillate added to the amyl alcohol layer. The mixture was extracted with dilute sulfuric acid. The acid extracts were cooled and made strongly basic with potassium hydroxide pellets. The mixture was distilled up to 100° and the distillate made strongly alkaline with potassium hydroxide pellets.

The oil, which separated, was dried with potassium hydroxide pellets and distilled to give 2.0 g. [(78.2%) of 2-methylazetidine, b.p. 72–76° (755 mm.) reported[18a] b.p. 75°]. Treatment of a pyridine solution of 2-methylazetidine with *p*-toluenesulfonyl chloride followed by dilution with water gave 2-methyl-*p*-toluenesulfonazetidide, m.p. 96–99°. A mixed melting point with an authentic sample showed no depression.

The *p*-nitrobenzamide of 2-methylazetidine melted at 42.0–43.0°.

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.80; H, 5.42; N, 12.64.

Attempted hydrogenolysis of p-toluenesulfonylazetidide. Two grams (9.5 mmoles) of *p*-toluenesulfonazetidide was dissolved in 25 ml. of dry ether. One gram of Raney nickel (W-2) was added, and the mixture was shaken at 500 p.s.i. hydrogen pressure at 100° for 11 hr. Only starting material was recovered.

Attempted reduction of 1-methanesulfonazetidide with lithium aluminohydride. To a refluxing solution of 1.28 g. (9.50 mmoles) of 1-methanesulfonazetidide in 80 ml. of dry ether was added dropwise a solution of 1.72 g. (45.2 mmol.) of lithium aluminum hydride in 100 ml. of dry ether. The solution was refluxed for 22 hr. No azetidine was obtained on alkaline work-up.

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