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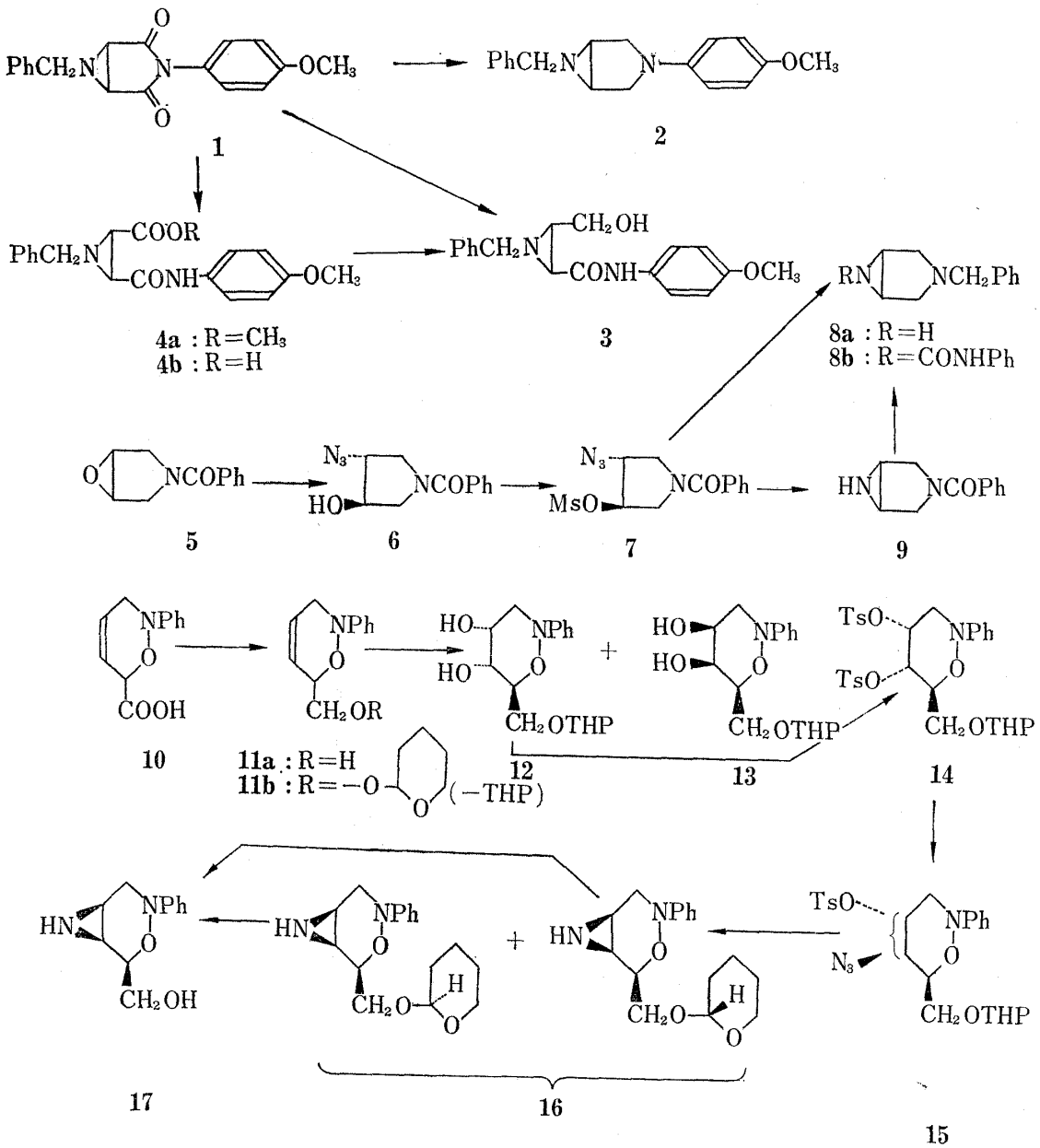
Syntheses of 3,4-Epiminopyrrolidine and 4,5-Epiminotetrahydro-1,2-oxazine

Examples of diazabicyclo compounds in which an aziridine ring is fused to another heterocyclic system are sparse.[1] We now wish to report on syntheses of new heterocyclic compounds having a 3,6-diazabicyclo[3.1.0]hexane (3,4-epiminopyrrolidine) or a 3-oxa-4,7-diazabicyclo[4.1.0] heptane (4,5-epiminotetrahydro-1,2-oxazine) skeleton. These compounds are not only of chemical interest because of their potency as synthetic intermediates,



1) *a*) For 2,4-dioxo-3,6-diazabicyclo[3.1.0]hexane, see A. Mustafa, S.M.A.D. Zayed, and S. Hattab, *J. Am. Chem. Soc.*, **78**, 145 (1956); S.J. Davis and C.S. Rondestvedt, Jr., *Chem. Ind.* (London), 845 (1956); W.I. Awad, S.M.A.R. Omran, and F. Nagiel, *Tetrahedron*, **19**, 1591 (1963); *b*) For 5-oxo-7-phenyl-1,4-diazabicyclo[4.1.0]heptane, see H. Moureu, P. Chavin, and L. Petit, *Compt. Rend.*, **143**, 910 (1956) and *Bull. Soc. Chim. France*, 1785 (1956); *c*) For 3-oxa-6-azabicyclo[3.1.0]hexane, see P.E. Fanta, and E.N. Walsh, *J. Org. Chem.*, **31**, 59 (1966); *d*) For 1,3-diazabicyclo[3.1.0]hex-3-ene, see H.W. Heine, R.H. Weese, and R.A. Looper, *J. Org. Chem.*, **32**, 2708 (1967).

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but also of pharmaceutical interest in cancer chemotherapy as one of active principles of the anti-tumor antibiotics, mitomycins.

First, we attempted a conversion of 1-benzyl-2,3-aziridine (N-*p*-anisyl) dicarboximide[2] (**1**), whose skeleton had been well characterized as one member of the 3,6-diazabicyclo[3.1.0] hexane system, into a 3,4-epiminopyrrolidine (**2**). Lithium aluminum hydride reduction of **1** in ether gave the desired pyrrolidine (**2**), mp 115—116°,[3] but the yield was quite low. Reduction of **1** with sodium borohydride in borontrifluoride etherate[4] did afford a small amount of **2** but, mainly, 1-benzyl-2-*p*-anisylcarbamoyl-3-hydroxymethylaziridine (**3**), mp 94.5—96°. The latter (**3**) was also obtained by lithium aluminum hydride reduction of a methylester (**4a**) which was prepared by saponification of **1**, followed by treatment of the resulting carboxylic acid (**4b**) of mp 171° (decomp.) with diazomethane. Many attempts at the conversion of **3** into **2** were unsuccessful.

The second approach was made, based on a stepwise synthesis of an aziridine ring on a pyrrolidine system as follows. N-Benzoyl-Δ^3-pyrroline[5] was found to be inert to ordinary peracids, but oxidized with pertrifluoroacetic acid in the presence of disodium hydrogen phosphate[6] in dichloroethane to afford N-benzoyl-3,4-epoxypyrrolidine (**5**), mp 66—68°, in a good yield. Treatment of **5** with sodium azide gave a syrupy azide-alcohol (**6**), whose mesylate (**7**) was treated with lithium aluminum hydride to give the desired 3,4-epimino(N-benzyl)pyrrolidine (**8a**), bp 106—107° (0.7 mmHg). The epimine (**8a**) was characterized as its phenylurethane (**8b**) of pm 168.5—169°. The yield of **8** from **5** was 60%. In addition, treatment of **7** with sodium borohydride/cobalt-II-tris-α,α'-dipyridyl bromide[7] in ethanol afforded 3,4-epimino(N-benzoyl)pyrrolidine of mp 98.5—100° (**9**), which was converted into **8b** on further reduction with lithium aluminum hydride, followed by treatment with phenylisocyanate.

Synthesis of a 4,5-epiminotetrahydro-1,2-oxazine was analogously carried out by formation of an aziridine moiety on a tetrahydro-1,2-oxazine ring. Lithium aluminum hydride reduction of N-phenyl-3,6-dihydro-1,2-oxazine-6-carboxylic acid (**10**), mp 113°, which was prepared by cycloaddition reaction[8] of nitrosobenzene to butadiene carboxylic acid, gave an dihydro-1,2-oxazine alcohol (**11a**) of mp 58—59.5° in 71% yield. **11a** formed its tetrahydropyranyl derivative[9] (**11b**) $bp_{0.03}$ 180° (bath temp.) quantitatively. **11b** was oxidized with osmium tetroxide, affording in 66% yield, a *cis*-glycol[9] (**12**) of mp 109—112°, accompanied by a small amount of another isomeric *cis*-glycol (**13**) of mp 155—156°. **12** formed a ditosylate[9] (**14**) of mp 141—144.5° in 80% yield. Treatment of **14** with sodium azide in dimethylformamide gave predominantly a syrupy azide tosylate (**15**), which could not be characterized well due to its unstability, along with a corresponding diazide. Without purification, **15** was treated with lithium aluminum hydride, furnishing, in 24.3% yield from **14**, an epimeric mixture (**16**) of an aziridine (major product) of mp 136—137.5° (N-benzoyl derivative, mp 111—111.5°) and another (minor product) of mp 115—117° (N-benzoyl derivative, mp 118.5—120.5°). Either of these components when treated with dilute hydrochloric acid afforded quantitatively the same 2-phenyl-4β,5β-epimino-6β-hydroxymethyl-1,2-

2) S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 764 (1968). Also see Footnote 1*a*).
3) All compounds were characterized by infrared, ultraviolet and nuclear magnetic spectra and elementary analysis.
4) G.R. Pettit, U.R. Ghatak, B. Green, T.R. Kasturi, and D.M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).
5) F. Anderlini, *Ber.*, **22**, 2512 (1889).
6) W.D. Emmons and G.B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955) and its preceding papers.
7) K. Ponsold, *J. Prakt. Chem.* **36**, 148 (1967).
8) J. Hamer, "1,4-Cycloaddition Reaction, Organic Chemistry—a series of monographs," vol. 8, Academic Press, New York and London, 1967, p. 419.
9) Compounds **11b**, **12**, **13**, and **14** were thin-layer chromatographically homogenous, and could not be separated into the corresponding epimers which arise from the asymmetric center of the tetrahydropyranyl group, as with **16**.

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oxazine (**17**) of mp 180—183°. Therefore, this suggested that these components of **16** were isomeric at the asymmetric center of the tetrahydropyranyl group. Steric configurations of these compounds (**12**—**17**) are designated as shown in Chart assuming that the predominant attack of osmium tetroxide[10] occurs at the unhindered site of the double bond of dihydro-1,2-oxazine (**11b**), followed by unequivocal displacement reactions of these substituents of the resulting *cis*-glycol (**12**). This was also supported by analysis of nuclear magnetic resonance spectra. Moreover, in the reductive displacement reaction of **15**, treatment of **15** with hydrazine hydrate and Raney Ni[11] or hydrogenation of **14** over Adams' catalyst, followed by addition of base, gave the same aziridine mixture (**16**), although the yield was lower.

These aziridine derivatives thus obtained were found to show no activity against leukemia L-1210.

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10) B. Belleau and Y. Au-Young, *J. Am. Chem. Soc.*, **85**, 64 (1963).
11) R.D. Guthrie and D. Murphy, *J. Chem. Soc.*, **1963**, 5288.

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Studies on the Chemical Structures of the New Glucans isolated from *Gyrophora esculenta* Miyoshi and *Lasallia papulosa* (Ach.) Llano and Their Inhibiting Effect on Implanted Sarcoma 180 in Mice

Recently, we have reported[1] that the ethanol-precipitates prepared by adding ethanol to the aqueous extract of a lichen, *Gyrophora esculenta* Miyoshi, had remarkable inhibiting effect against subcutaneously implanted sarcoma 180 in mice. In this communication, we wish to describe the further study on the active principle of the lichen. The ethanol-precipitates were purified by freezing and thawing method to yield ultracentrifugally homogeneous white fibrous flakes, $[\alpha]_D^{19}$ −37.5° (c=0.5, 1 N NaOH). Yield, about 90%, based on ethanol-precipitates. On complete acid hydrolysis, it gave D-glucose as a sole product. (Total glucose content determined by the anthrone method was 98.4%). Its infrared spectrum had an absorption at 910 cm^{-1}. The inhibiting effect of the glucan was tested on solid sarcoma 180 under the same conditions as described in the previous paper.[1] The inhibition ratio was 99.1% and complete regression of the tumour occurred in 8 out of 10 mice. The active glucan liberated homo series of oligosaccharides by partial acid hydrolysis or by enzymolysis with a β-1,6-

1) S. Shibata, Y. Nishikawa, M. Tanaka, F. Fukuoka and M. Nakanishi, *Z. Krebsforsch.*, **71**, 102 (1968).

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