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TOTAL SYNTHESIS OF ASPIDOSPERMINE*1

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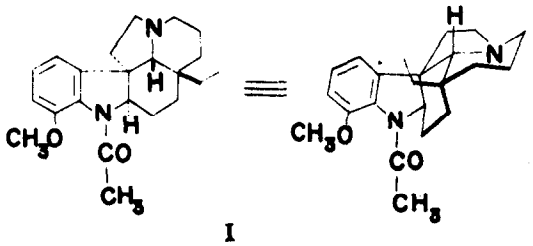
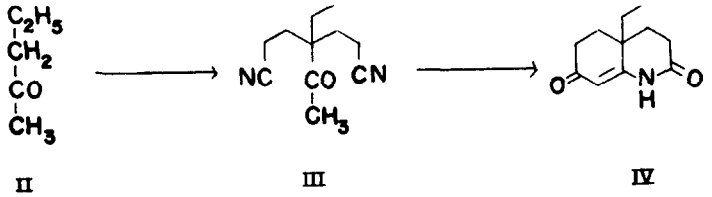
The structures of a large number of aspidosperma alkaloids have been recently elucidated mainly by mass and n.m.r. spectra.[1] All of them have the similar basic skeletons to that of aspidospermine(I),[2] a representative alkaloid of this family, which was synthesized by Stork and Dolfini in 1963.[3]

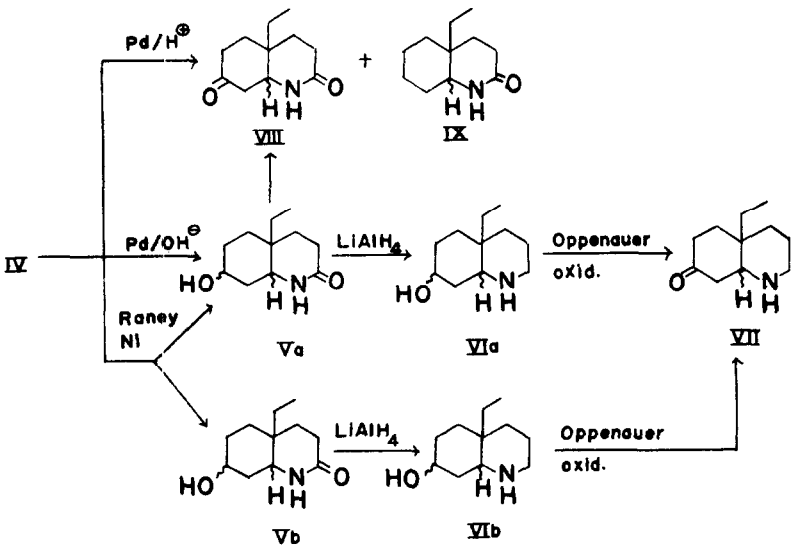


I

*1 The outline of this communication was read at the International Symposium on the Chemistry of Natural Products held in Kyoto(April 17, 1964).



II III IV



Independently from their brilliant work, several possible routes for a synthesis of this alkaloid had been investigated in this laboratory. One of them reached the intermediate(VII) which has the same planar structure as the corresponding one of Stork's synthesis. Physico-chemical properties of ours(VII), however, are quite different from those of Stork's

one, where we propose that they are diastereomeric based upon the following results.

The condensation of methyl n-propyl ketone(II) with 2 molar equivalents of acrylonitrile gave III(m.p. 110-112.5°)[4] as colorless plates(n.m.r. singlet at 7.25 τ(3H, $-CO-CH_3$)), which was heated with 80% sulfuric acid at 150-160° for 5 min. to yield IV*2 as pale yellow needles, m.p. 188-189° in 80% yield. This lactam(IV) was hydrogenated with palladium in an alkaline medium to afford Va, colorless needles, m.p. 211-212.5°, (i.r. ν_{max}^{nujol} 3370, 3180, 1645 cm^{-1}), as a single product in 79.2% yield, which in turn was reduced with $LiAlH_4$ in tetrahydrofuran at 75° for 20 hrs. to afford VIa as colorless needles, m.p. 145-147°, in 81.1% yield. This was subjected to the Oppenauer oxidation with potassium t-butoxide and cyclohexanone to yield VII in 74% yield as a pale yellow oil, $b.p._2$ 116°, which solidified on standing. M.p. 32-35° of this compound(VII, i.r.

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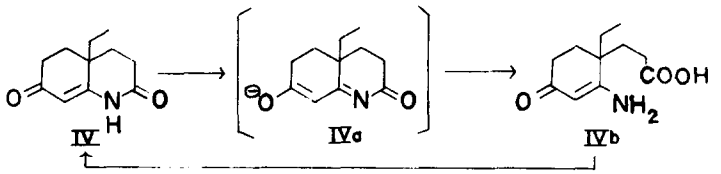
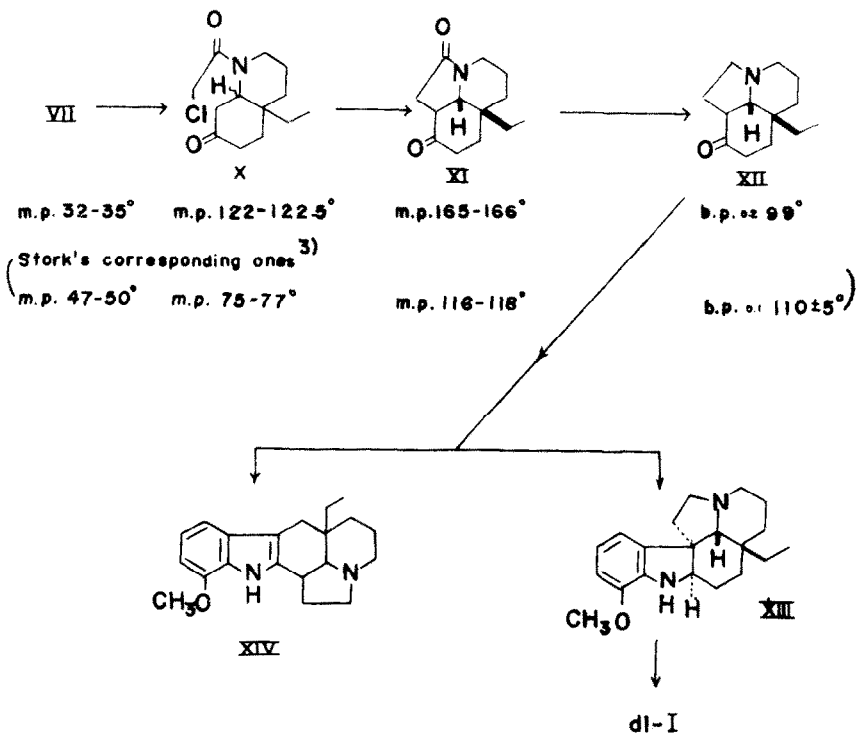
*2 It is noteworthy that the ultraviolet absorption($\lambda_{max}^{H_2O}$ 284 mμ(ε : 36,830)) of IV changes into 334 mμ(ε :33,700) in 3 min. after it is dissolved in 0.1N NaOH at a room temperature, and becomes constant at 293 mμ(ε :37,030) in this solution after 30 min. This solution is acidified to pH 3.0 with 0.4N HCl to deposit the crystal which is recrystallized from acetone to give IVb as pale yellow needles, m.p. 159-160°(decomp.), $\lambda_{max}^{0.4N\ HCl}$ 282 mμ(ε :29,780). The last product(IVb) is reconverted to the starting material on fusion at melting point until the cease of effervescence. This conversion could be interpreted as follows:



ν_{max}^{film} 3330, 1715 cm^{-1}) is different from m.p. 47-50° of Stork's corresponding intermediate.[3] Therefore, the Stork's synthesis from this compound was followed to confirm the validity of our synthetic route.

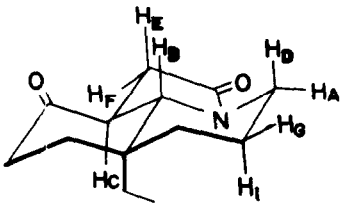
Prior to this persuit, hydrogenations of IV in various solutions were investigated. The compound(VII) was also prepared in a similar way via VIb(m.p. 130-132°) from one(Vb, colorless amorphous powder, m.p. 120-130°) of the two products(the other is identical with Va, m.p. and m.m.p. 211-212.5°) on hydrogenation of IV with Raney Ni under an initial 70 atm. pressure of hydrogen. Thus, it is clear that the inconsistency between Va and Vb is only due to the different conformations of hydroxyl groups at C-7. When hydrogenated with palladium in an acidic medium, IV gave the ketolactam(VIII, mp. 180-182°) and the lactam(IX, m.p. 139-140°), the former of which was also obtained by the oxidation of Vawith sodium dichromate. These correlations indicated that IV on the above hydrogenations yields compounds consisting of only one kind of ring system that is possibly cis-decahydroquinoline.

The compound(VII) was reacted with chloroacetyl chloride to afford the acylamide(X) as colorless needles, m.p. 122-122.5°(Stork's corresponding one,[3] m.p. 75-77°) which was cyclized with potassium t-butoxide to the ketolactam(XI), m.p. 165-166°(Stork's one, m.p. 116-118°). The o-methoxyphenylhydrazone(m.p. 163-164°) derived from the ketone(XII), a pale yellow viscous oil, $b.p._{0.2}$ 99°(Stork's one,[3] $b.p._{0.1}$ 110 ± 5°), prepared from the above lactam(XI) was subjected to the Fischer indole synthesis in acetic acid at 90-95° for 30 min., followed by $LiAlH_4$ reduction in tetrahydrofuran

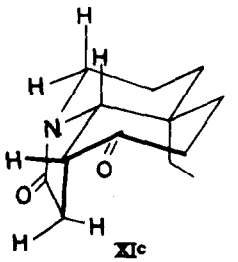


to yield a brownish oil which was purified by chromatography on alumina. A fraction eluted by hexane-benzene(10 : 3) gave a pale yellow gum, whose u.v., i.r. in $CHCl_3$ and Rf values on thin layer chromatography are identical with those of an authentic sample of deacetylaspidospermine(XIII) derived from the natural aspidospermine. Another fraction eluted by benzene and benzene-ether(1 : 1) afforded a yellow oil which solidified on standing, m.p. 85-88°. The formula(XIV) should be assigned to this compound, as

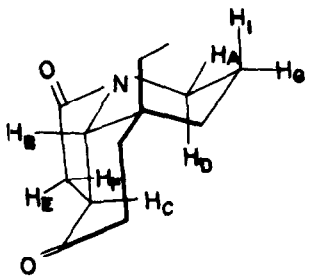
FIG.1



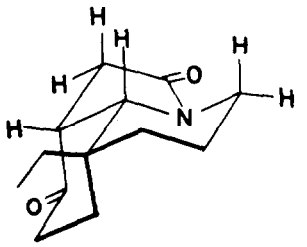
XIa



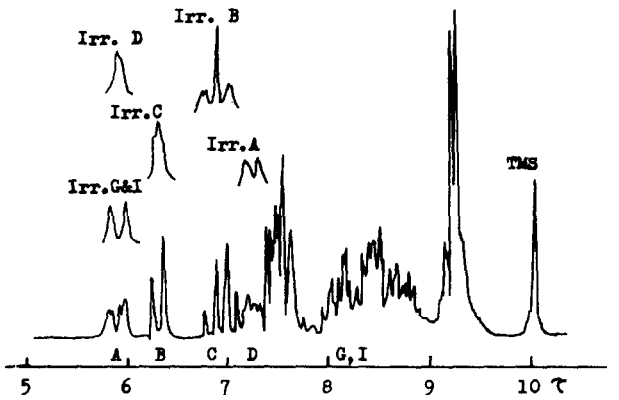
XIc



XIb



XId



its u.v. spectrum is similar to that of 7-methoxyindole and the mass spectrum showed a molecular ion peak at m/e 310. The rest of the fragmentation patterns is reasonable for this assignment. The synthetic dl-deacetylaspidospermine(XIII) was acetylated with acetic anhydride in pyridine to afford dl-aspidospermine, m.p. 185-195°(Stork[3] m.p. 195-195.5°) whose u.v., i.r. in $CHCl_3$, Rf values on thin layer chromatography and mass spectrum are identical with those of the natural alkaloid, establishing the validity of our synthetic path through the other diastereoisomers of intermediates of Stork's synthesis.*3

For conformational analyses of these intermediates, Professor Stork generously supplied necessary data(i.r., n.m.r. spectra and samples) at our request, enabling us to compare directly our results with theirs.

FIG. 1 shows the n.m.r. spectrum of XI, whose possible conformations are delineated by XIa, b, c and d. In the spectrum, there are observed the quartet(A) centered at 5.86 τ(1H due to H_A, J_{AD}= 13 cps), the doublet (B) at 6.27 τ(1H due to H_B, J_{BC}= 10 cps), the quartet(C) centered at 6.91 τ (1H, due to H_C, J_{CB}= J_{CE}= J_{CF}= 10 cps), and the multiplet(D) centered at 7.23 τ(1H due to H_D). These assignments were confirmed by double resonance operations(See inserted patterns in FIG. 1), and are compatible with XIa or XIb, alternatively.*4 Considering that the o-methoxyphenyl-

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*3 Satisfactory elemental analyses were obtained for all new compounds described.

*4 The spectra were obtained on a Varian HR-100 spectrometer euipped to accomplish proton-proton spin-decoupling.

hydrazone of XII and XII itself involve no or very weak absorptions in the range of 2700-2800 cm^{-1},[5] and further the former(XIa) was assigned by Stork to his compound,[3] we propose XIb for our intermediate(XI).

Thus, the fact that dl-deacetylaspidospermine(XIII) is synthesized from either XIa or XIb, supports the plausible mechanism for cyclization to the indolenine proposed by Stork.[3]

The present synthetic scheme will be extended to syntheses of the other alkaloids of this family.

We wish to thank Professor G. Stork for supplies of his unpublished data and samples, Dr. G. F. Smith for generous gifts of deacetylaspidospermine and aspidospermine, Dr. T. Hino and Miss Y. Shibanuma for the measurements of n.m.r. spectra, and Mrs. T. Toma and Miss A. Maeda for microanalyses. We are also grateful for support of this work by the National Institutes of Health, the United States Public Health Service, under grant MH 08187.

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