Tetrahedron Letters No. 40, pp 3797 - 3800.

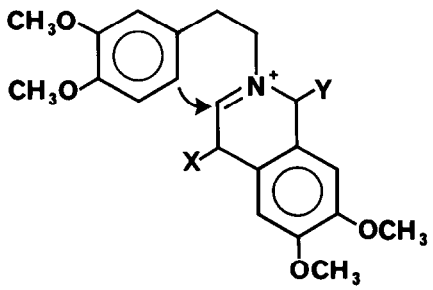
0040-4039/79/1001-3797$02.00/0

IMINIUM ION CYCLIZATIONS. HIGHLY STEREOSELECTIVE SYNTHESIS OF SUBSTITUTED TETRAHYDROISOQUINOLINE DERIVATIVES

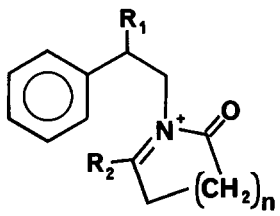
Bruce E. Maryanoff* and David F. McComsey
Chemical Research Department
McNeil Laboratories
Fort Washington, Pennsylvania 19034

Abstract: Cationic cyclizations of acyliminium ions 2 (R_1 = phenyl) occur with high stereoselectivity, which is suggested to originate in the intermediate arenium ions.

Stereoselective syntheses of substituted alkaloid ring systems are important to synthetic methodology. In this regard, Dean and Rapoport recently reported cyclizations of methyl-substituted iminium salts (1), which afford 8- and 13-methylberbines with high stereoselectivity.[1] In their work the substituent stereocenters (X or Y) were situated 1,2 and 1,3 to the incipient stereocenter of ring closure. We have been studying the stereochemical influence of substituents R_1 on ring closures of acyliminium ions 2 to isoquinoline derivatives, a process which exemplifies stereocontrol between 1,4 stereocenters, and have found that cyclizations of a variety of aryl-substituted acyliminium species (2, R_1 = Ar) occur with high stereoselectivity (>90%).

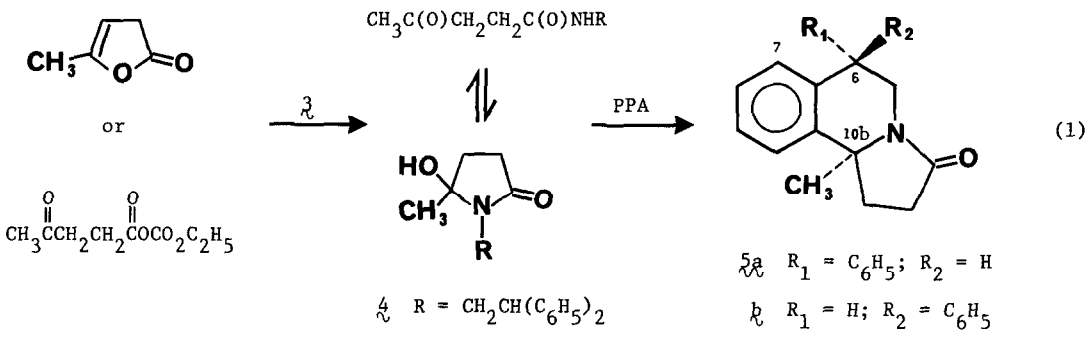


1a X = CH_3; Y = H
b X = H; Y = CH_3



2 n = 1 or 2

Reaction of 2,2-diphenylethylamine (3) with α-angelicalactone[2] or the mixed carbonic anhydride of levulinic acid[3] gave acyliminium ion precursor 4 (tautomeric mixture by ^1H and ^{13}C NMR; ir), which was treated with polyphosphoric acid (PPA) at 100° (3-15 hr) to effect cyclization (65-85% yield overall from angelicalactone; 37% via the mixed anhydride) (eq 1). The crude cyclized product consisted largely (ca. 95%) of one diastereomer, as determined by glc and ^1H NMR [the two diastereomers (5a and 5b), in ca. 16:1 ratio, were identified by glc/mass spec]. Structure 5a (6α,10bα relative configuration), having pseudoequatorial phenyl and



4 R = $CH_2CH(C_6H_5)_2$

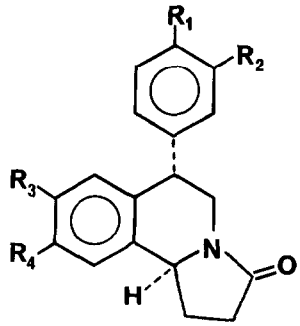
5a $R_1 = C_6H_5$; R_2 = H

b R_1 = H; $R_2 = C_6H_5$

pseudoaxial methyl groups on a half-chair ring, was assigned by ^{1}H NMR spectroscopy (proton coupling constants, confirmed by homonuclear decoupling and INDOR experiments; shift experiments with $Eu(fod)_3$; and a benzene ASIS study).[4,5]

In addition, nearly exclusive (>95%) stereoselectivity was observed in the analogous syntheses of 6a, 7, and 8.[5-8] The intramolecular α-amidoalkylations giving 6b and 6c, which occurred rapidly (10 min) in refluxing ethanol with a small amount of HCl, were slightly less stereoselective; mixtures of 6α and 6β diastereomers were formed in ca. 9:1 ratio, respectively.[9] Clearly, the stereoselectivity is independent of structural features surrounding the lactam portion of the molecules (ring size, angular substituent).

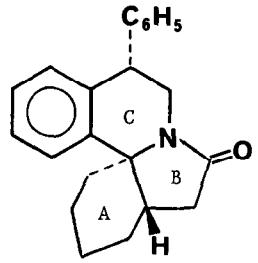
In the case of 6c, the two diastereomers were separated by tlc, assigned by ^{1}H NMR[10] and mass spec, and individually subjected to the cyclization conditions by which they were



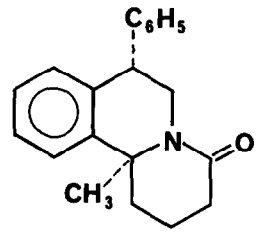
6a $R_1 = R_2 = R_3 = R_4$ = H

b $R_1 = R_2$ = H; $R_3 = R_4 = OCH_3$

c $R_1 = R_2 = R_3 = R_4 = OCH_3$



7

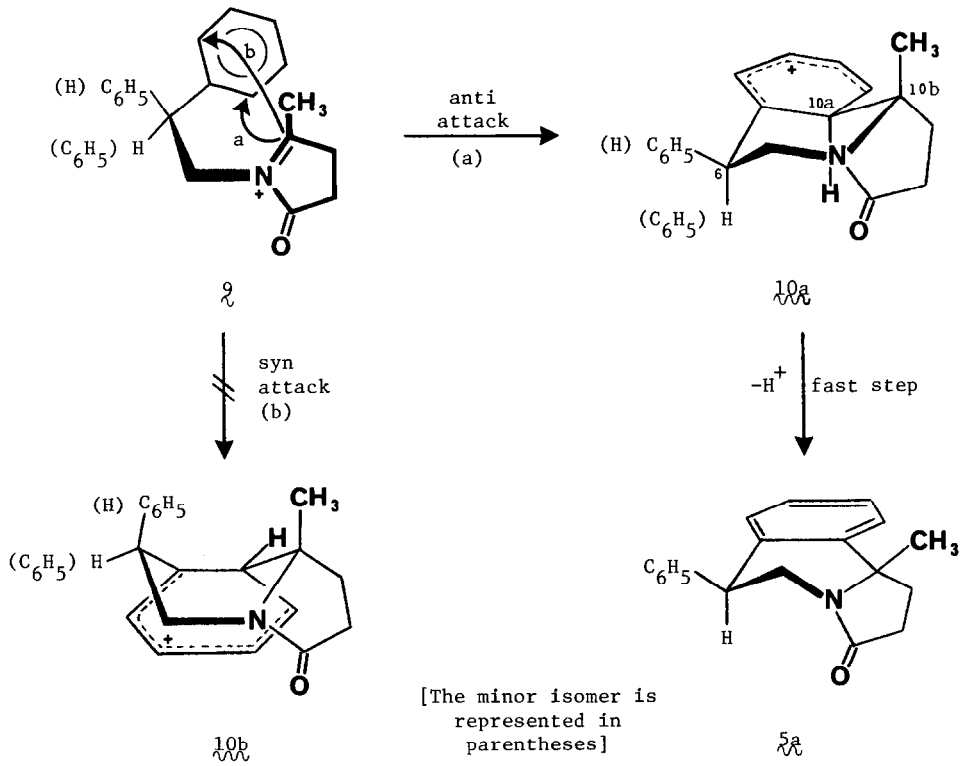


8

originally produced. No interconversion of isomers was detected, indicating that the ring closure reaction did not involve equilibration of product lactams.

The cyclization process is depicted in eq 2. Attack of the acyliminium ion in 9 on the benzene ring to generate intermediate arenium ions 10a and 10b, is probably the rate-determining step.[11] "Syn" pathway (b) involving ion 10b is unlikely to be significant because of severe strain in the boat-like structure (Dreiding molecular models; planar amide nitrogen), so "anti" pathway (a) involving chair-like ion 10a is critical for explanation of the observed stereo-

selectivity. In ion 10a, the equatorial aromatic substituent would be strongly preferred to avoid 1,3 syn-axial interaction between it and the 10a-proton, which is subsequently lost in the fast aromatization step (molecular models). If the transition state leading to 10a is assumed to be product-like, the above interactions can govern the stereochemical course of the cyclization, whereas an early, reactant-like transition state will not result in a substantial stereochemical preference (molecular models). Thus, the substituent 1,4 to the incipient 10b



(2)

chiral center exerts a strong, product-determining influence on the ring closure during the formation of arenium-ion intermediate 10a.[12] The minor reduction in stereodifferentiation for the very reactive dimethoxybenzene cyclizations may be attributed to more reactant-like transition states (Hammond postulate).[13]

The stereoselectivity in our work is induced by an aromatic substituent exocyclic to the ring containing the electrophilic carbon, but located on the newly formed ring (1,4 from the other chiral center). A cationic cyclization in the terpenoid area stereochemically related to ours was reported to proceed with high stereoselectivity, and with the same relative stereochemistry of 1,4 substituents.[14] In cyclizations studied by Dean and Rapoport,[1] the steric guidance was provided rather by a methyl substituent on the ring containing the electrophilic carbon center, situated either 1,2 or 1,3 from the new chiral center. Certainly, cationic cyclizations of the type described by us and others[1,14] are very sensitive to steric control, a characteristic conducive to useful synthetic applications.

References and Notes

1. R. T. Dean and H. Rapoport, J. Org. Chem., 43, 4183 (1978).
2. A. G. Terzyan, L. V. Khazhakyan, N. A. Arutyunyan, and G. T. Tatevosyan, Chem. Abstr., 75, 20163g (1971).
3. W. J. Houlihan and R. E. Manning, US Patent 3,502,679 (1970); 3,635,984 (1972); 3,383,388 (1968).
4. Data on purified 5a: mp 135-135.5° (corr.); ^{1}H NMR ($CDCl_3$, TMS) δ 1.65 (s, CH_3), 2.0-2.8 (m, CH_2CH_2), 3.07 (d of d, H_{5a}), 4.05-4.25 (d of d, H_6, sharpened by irradiation of aromatic region), 4.35-4.55 (d of d, H_{5e}), 6.8-7.5 (m, 9 arom H), $^3J(5a,6)$ = 11.5 Hz, $^3J(5e,6)$ = 6.5 Hz, $^2J(5e,5a)$ = -13.0 Hz; ir ν(CO) 1670 cm^{-1}. Satisfactory C,H analysis.
5. Details of the structural assignment(s) will appear in a full paper.
6. Iminium ion precursors to 6 (5-ethoxypyrrolidin-2-ones) were prepared from succinimides by selective reduction of one carbonyl group with $NaBH_4$ in acidic ethanol [J. C. Hubert, J. B. P. A. Wijnberg, and W. N. Speckamp, Tetrahedron, 31, 1437 (1975)].
7. Iminium ion precursors to 7 and 8 were obtained by methodology similar to that used for 5a.
8. The cis A/B stereochemistry for erythrinane 7 was confirmed by ^{1}H NMR proton coupling constants in Eu(fod)$_3$-shifted spectra. Cyclization reactions of this type give cis A/B erythinanes [R. K. Hill, in "The Alkaloids," R. H. F. Manske, ed., Academic Press, New York, 1967, pp. 483-515].
9. The two products in each reaction were separated by preparative tlc and confirmed as isomers by mass spectrometry (virtually identical spectra for each isomeric pair).
10. ^{1}H NMR data for the 6α,10bα isomer (6c): δ ($CDCl_3$) 1.7-2.1 (m, 1H), 2.3-3.1 (m, 4H, d of d for H_{5a} at δ 2.98, J = 12, 12 Hz), 3.6-4.6 [m, 14H, s for OCH_3 at δ 3.61, 3.82, 3.88 (2 OCH_3); d of d for H_6 (partly concealed) at δ 4.10, J = 6, 12 Hz; d of d for H_{5e} at δ 4.42, J = 5, 12.5 Hz]; 4.88 (d of d, 1H, H_{10b}, J = 7, 7.5 Hz), 6.36 (s, 1H, H_7) 6.6-7.0 (m, 4 arom H); ^{1}H NMR data for the 6β isomer (corresponding to 6c): δ ($CDCl_3$) 1.7-2.1 (m, 1H), 2.2-2.8 (m, 3H) 3.35 (d of d, 1H, H_{5a}, J = 4, 12.5 Hz), 3.6-4.4 [m, 14H, s for OCH_3 at δ 3.77 (2 OCH_3), 3.81, 3.90; d of d for H_6 (partly concealed) at δ 4.08, J = 1, 4 Hz; d of d for H_{5e} at δ 4.08, J = 2, 12.5 Hz], 4.77 (d of d, 1H, H_{10b}, J = 6.5, 9 Hz), 6.45-6.9 (m, 5 arom H). The shielding observed for H_7 in 6c supports the assigned configuration [H. P. Weber, T. J. Petcher, and H. R. Loosli, Helv. Chim. Acta, 60, 2886 (1977); W. Oppolzer, R. Achini, E. Pfenninger, and H. P. Weber, ibid., 59, 1186 (1976)].
11. J. March, "Advanced Organic Chemistry", 2nd edit., McGraw-Hill, New York, 1977, Chapter 11.
12. It is interesting to note that in cyclizations (5, 6a, 6c, 7, 8) where both aromatic rings are initially the same (enantiotopic), two chiral centers are developed simultaneously.
13. In other words, $\Delta\Delta G^{\neq}$ for a process involving diastereomeric transition states will be smaller for a reaction having a lower free energy of activation ($\Delta G^{\neq}$).
14. A. A. Macco, R. J. deBrouwer, and H. M. Beck, J. Org. Chem., 42, 3196 (1977). Their examples are not strictly analogous to ours, since the "exocyclic" methyl or t-butyl substituents were located both 1,3 and 1,4 to other centers of chirality in the new ring formed by aromatic substitution (of a thiophene nucleus).

(Received in USA 16 May 1979)