A NEW REARRANGEMENT OF α-AZO ALCOHOLS INTO N-SUBSTITUTED BRIDGED BICYCLIC LACTAMS. A POSSIBLE MODEL FOR CONFORMATION-DEPENDENT REARRANGEMENT

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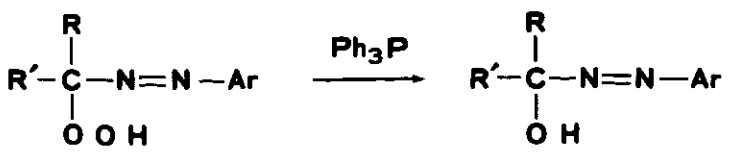
Abstract — A new thermal rearrangement of sterically crowded α-azo alcohols (2 and 4) into bridged bicyclic lactams (9 and 11) is reported. A mechanism for this rearrangement is proposed.

The rearrangement into lactam has been an interesting topic not only from mechanistic but also from synthetic points of views.[1] We wish to report a new rearrangement of sterically crowded α-azo alcohol into lactam. The rearrangement is strongly controlled by a steric hindrance effect.

α-Azo alcohols (2 - 7) were prepared from the corresponding α-azohydroperoxides (1) by the reduction with triphenylphosphine.[2,3] The structures of the endo- and exo-alcohols (2 and 3)(oils) were assigned by comparing their nmr spectra,[4] and the chemical shift of the methyl signal with that of the reference compounds such as borneol, isoborneol[5] and m-chlorobenzoates of 2 and 3.[6] In the ^{1}H nmr spectra, the signal of C_{10}-methyl hydrogens of 2 appeared at a higher field (δ 0.52) compared with that of 3, indicating that the C_{10}-methyl group of 2 is located just above an anisotropic shielding zone of the -N=N- bond of the arylazo group. The C_8-methyl group of 2, on the other hand, is out of this shielding zone.[7] The ^{1}H nmr spectrum



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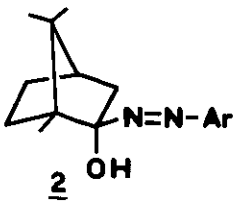

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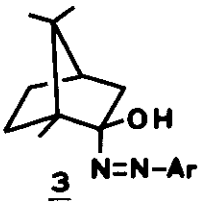

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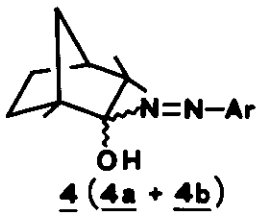
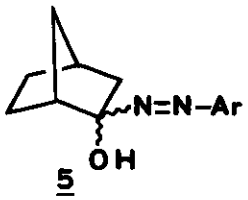


4 (4a + 4b)



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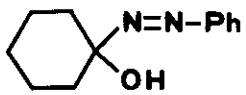

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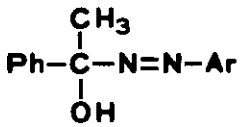

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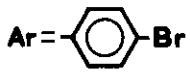
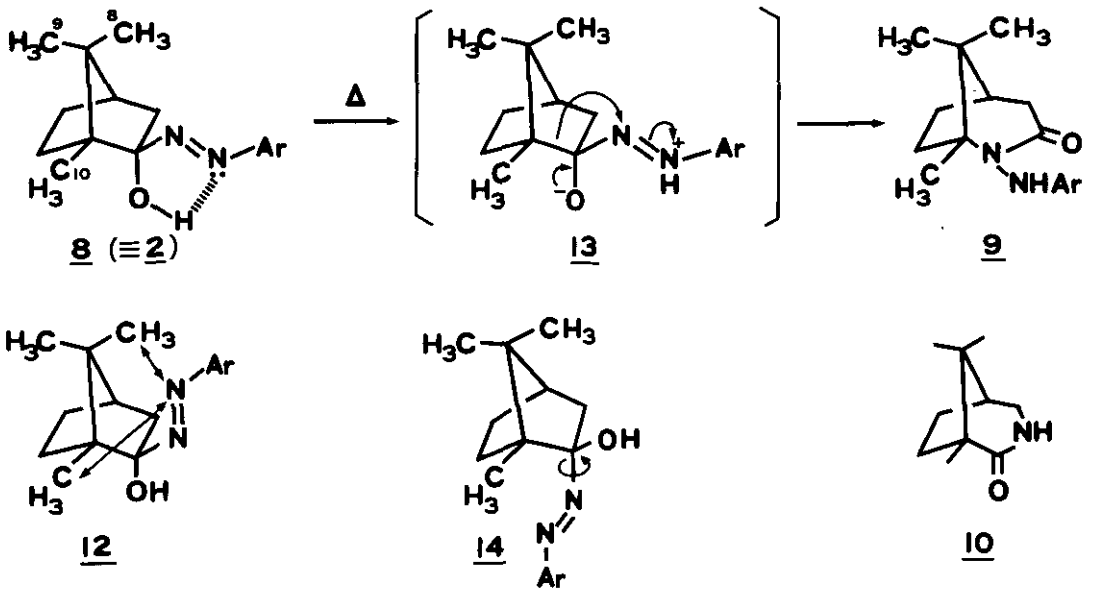


of the m-chlorobenzoates of 2 and 3 also supported the assignments of these structures.[6] The azo alcohol (4) is a 2:5 mixture of the endo- (4a) and exo-alcohols (4b). This was assigned by comparison of the intensity of methyl and/or hydroxy signals in the ^{1}H nmr spectrum.[8] The differentiation of 4a from 4b was made on the basis of the ^{1}H nmr spectra. Two methyl signals of 4a (δ 0.75 and 0.88) appeared at a relatively higher field compared with the methyl signals of 4b, indicating that both the C_8- and C_{10}-methyl groups are located by the azo π-bond shielding zone in 4a. Similarly, the inspection of the ^{1}H nmr spectrum of 5 indicated that this is a mixture of the isomeric azo alcohols.[9]

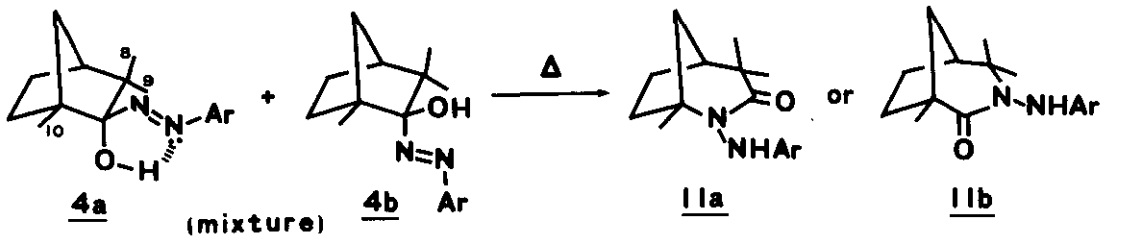
When a benzene solution of the endo-alcohol 2 (10^{-2} M) was stirred at room temperature for a couple of weeks, or heated under reflux for several hours, a new lactam (9), mp 209 °C, was formed in 80 - 88% yields (Scheme 1). The structure of the lactam 9 was established by elemental analysis and the ir (ν_{CO} (KBr) 1660 cm^{-1}), mass (m/z 337, 335, 187, 185, and 108), and nmr spectra.[10,11] The comparison of the chemical shift of the C_4-methylene hydrogens of 9 (δ 2.25 and 2.82) with those of 10 (δ 3.01 and 3.48), which was prepared by the method reported in the literature,[12] has revealed that the C_4 methylene carbon of 9 is connected to the carbonyl carbon. The comparison of the ^{13}C-chemical shift of the bridgehead C_1-carbon of 9 (δ 74.0) with that of 10 (δ 52.1) indicates that the bridgehead of 9 is connected to the amide nitrogen. The lactam 9 was unsucceptible to acid and base hydrolysis even when heated under reflux in dioxane.

Similarly, when a benzene solution of 1,3,3-trimethylnorbornyl azo alcohols (4: a

Scheme 1.



Scheme 2.

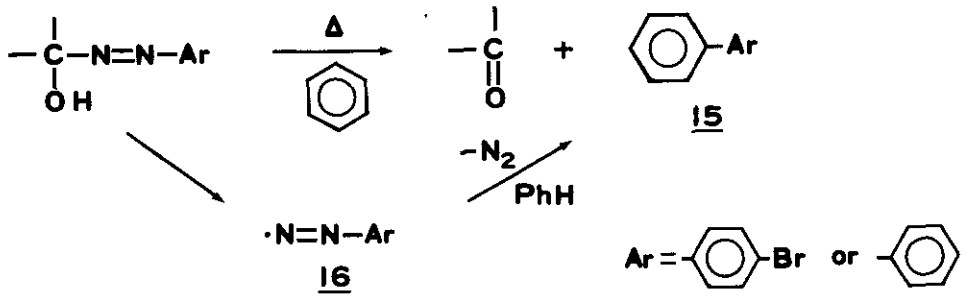


mixture of 4a and 4b (2:5)) was heated under reflux, a bridged lactam (11), mp 170 °C, was formed in 29% yield. The lactam structure was assigned by elemental analysis and spectral data.[10,13] However, the differentiation of the isomeric structures of 11a from 11b could not be made (Scheme 2).

On the other hand, when a benzene solution of bornyl exo-alcohol (3), norbornyl (5: a mixture of endo- and exo-alcohols), cyclohexyl (6), or methyl-phenyl (7) derivative was heated under reflux, the rearrangement into the corresponding lactam did not occur, but the decomposition took place to give camphor (99%), norcamphor (71%), cyclohexanone (99%), or acetophenone (90%), respectively, together with diphenyls (15) (32 - 40%). Diphenyls (15) arise from the reaction of aryl radicals,

which are formed from diazenyl radicals (16) arising from the homolytic decomposition of the azo alcohols, with benzene (Scheme 3).[14,15]

Scheme 3.



The mechanism for the rearrangement into lactams (9 and 11) is of great interest. To account for the rearrangement, we propose a mechanism in which the immobilization of the arylazo group due to the steric hindrance of the methyl groups plays an important role (Scheme 1). The fact that the more sterically crowded α-azo alcohols such as 2 and 4 gave lactams, but lactams were not formed from 3, 5, 6, and 7, suggests that the lactam formation is strongly controlled by the steric hindrance effect.

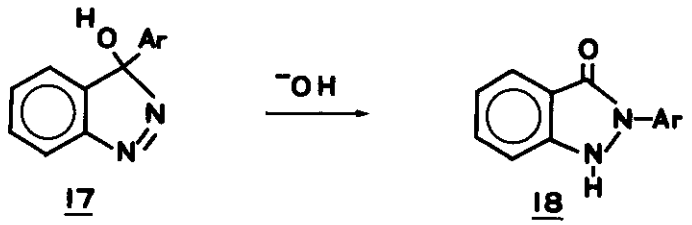
The Dreiding model implies that the free rotation of the arylazo group is restricted by the steric hindrance of the C_8- and C_{10}-methyl groups in 2 (see Scheme 1). In a conformer (12), for example, the arylazo group receives strongly a steric hindrance from both the C_8- and C_{10}-methyl groups, and this conformer is of higher energy. On the other hand, a conformer (8) does not receive the steric hindrance from the C_8- and C_{10}-methyl groups, and is further stabilized by intramolecular hydrogen bonding between the hydroxy hydrogen and the lone pair electrons of azo β-nitrogen.[16] These effects fix the arylazo and hydroxy groups in the conformation indicated in 8. This is a most favorable conformational arrangement for the hydroxy group to transfer its proton to the azo-nitrogen, generating a N-protonated species (13). This species brings about the formation of a nitrenium ion at the azo α-nitrogen and simultaneously the 1,2-shift of the bridgehead C_1-carbon onto the azo α-nitrogen,[17] giving rise to the formation of lactam (9). The transformation occurs in a concerted manner via an immobilized conformer[18,19] at a sterically protected reaction center by the surrounding methyl groups.

In contrast, in the exo-alcohol (3), the free rotation of the arylazo group is not

restricted by the steric hindrance of the methyl groups, and so the conformational flexibility of the arylazo group in 3 is high as indicated in 14. This does not allow for the arylazo group to be arranged in a manner described in 8, giving no conformational preference for 3 to rearrange into lactam. Similarly, the conformational flexibility of the arylazo group in norbornyl derivetive (5) and others (6 and 7) is so high that lactam formation in 5 - 7 is unfavorable.

The observed lactam formation from 4 (a mixture of 4a and 4b) to 11 (11a or 11b) is consistent with the proposed mechanism. The model indicates that the free rotation of the arylazo group is restricted by the steric hindrance of the methyl groups in both 4a and 4b. The restriction, however, is stronger in 4a than 4b. Therefore, the formation of lactam (11) from 4a is highly expected.[20]

Finally it should be noted that a related 1,2-shift of the aryl group in azo alcohol (17) has been reported.[21,22] Although a base treatment of the alcohol (17) yielded indazoline (18), the specific lactam formation reported in this paper has no precedent.



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The bridged bicyclic lactam bearing the amide nitrogen neighboring to the bridgehead carbon could not be made by usual Beckmann reaction in camphor oxime.[1] From this point of view, the rearrangement of α-azo alcohol into lactam found by this study is of synthetic interest.

REFERENCES AND NOTES

1. G. R. Krow, Tetrahedron, 1981, 37, 1283, and references cited therein.
2. Von M. Schulz, U. Missol, and H. Bohm, J. Prakt. Chem., 1974, 316, 47.
3. Y.-M. Chang, R. Profetto, and J. Warkentin, J. Am. Chem. Soc., 1981, 103, 7189.
4. ^{1}H nmr spectra (C_6D_6) of 2: δ 0.52 (s, 3H), 0.95 (s, 3H), 1.41 (s, 3H), 1.25 - 2.72 (m, 7H), 5.45 (broad s, OH), 7.23 (4H, aromatic protons); 3: δ 0.73 (s, 3H), 0.91 (s, 3H), 1.42 (s, 3H), 1.19 - 2.42 (m, 7H), 5.53 (broad s, OH), 7.20 (4H, aromatic protons).
5. K. Tori, Y. Hamashima, and A. Takamizawa, Chem. Pharm. Bull., 1964, 12, 924.
6. Benzoates of 2 and 3 were not formed by the reaction of 2 and 3 with benzoyl chlorides, and so the m-chlorobenzoates of 2 and 3 were prepared by the

reaction of camphor p-bromophenyl hydrazone with m-chloroperbenzoic acid (cf. B. T. Gillis and K. F. Schimmel, J. Org. Chem., 1967, 32, 2865). The ^{1}H nmr chemical shift (C_6D_6) of CH_3 of m-chlorobenzoate of 2: δ 0.63, 0.85, 1.31, and of m-chlorobenzoate of 3: δ 0.80, 0.98, 1.08.

7. This was confirmed by inspection of the Dreiding model.
8. ^{1}H nmr spectrum (C_6D_6) of 4 (a mixture of 4a and 4b (2:5)): δ 0.75 (s, CH_3 for 4a), 0.88 (s, CH_3 for 4a and 4b), 1.01 (s, CH_3 for 4b), 1.06 (s, CH_3 for 4a), 1.15 (s, CH_3 for 4b), 1.20 - 2.78 (m), 5.07 (s, OH for 4a), 5.12 (s, OH for 4b), 7.25 (aromatic protons).
9. ^{1}H nmr spectrum (C_6D_6) of 5 (an endo-exo mixture): δ 1.22 - 2.32 (m, 10H), 5.23 (broad s, 1H, OH), 7.25 (4H, aromatic protons).
10. Satisfactory elemental analysis was obtained.
11. Spectral data of 9: ^{1}H nmr ($CDCl_3$) δ 1.02 (s, 3H), 1.22 (s, 3H), 1.28 (s, 3H), 1.37 - 2.15 (m, 5H), 2.25 (dd, J = 18, 1.5 Hz, 1H), 2.82 (dt, J = 18, 3 Hz, 1H), 6.54 (broad s, NH), 6.64 (d, J = 8 Hz, 2H), 7. 24 (d, J = 8 Hz, 2H). ^{13}C nmr ($CDCl_3$) δ 15.4 (q), 18.5 (q), 25.0 (q), 27.7 (t), 37.0 (t), 39.3 (t), 42.6 (d), 45.0 (s), 74.0 (s), 112.6 (s), 115.5 (d), 131.7 (d), 148.5 (s), 172.6 (s).
12. G. R. Krow and S. Szczepanski, Tetrahedron Lett., 1980, 21, 4593.
13. Spectral data of 11: ir ν_{CO}(KBr) 1650 cm^{-1}. ^{1}H nmr ($CDCl_3$) δ 1.25 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.38 - 2.28 (m, 7H), 6.17 (broad s, NH), 6.58 (d, J = 9 Hz, 2H), 7.25 (d, J = 9 Hz, 2H). ^{13}C nmr ($CDCl_3$) δ 20.5 (q), 24.2 (q), 25.6 (t), 26.5 (q), 37.0 (t), 37.9 (t), 46.0 (s, d), 64.7 (s), 112.1 (s), 114.9 (d), 131.6(d), 148.4 (s), 177.4 (s).
14. S. G. Cohen and J. Nicholson, J. Org Chem., 1965, 30, 1162; P. C. Huang and E. M. Kosower, J. Am. Chem. Soc., 1968, 90, 2367.
15. T. Tezuka, T. Otsuka, P. C. Wang, and M. Murata, Tetrahedron Lett., 1986, 27, 3627; T. Tezuka and M. Iwaki, ibid, 1983, 24, 3109.
16. G. Büttner and S. Hünig, Chem. Ber., 1971, 104, 1088.
17. P. G. Gassman and R. L. Cryberg, J. Am. Chem. Soc., 1969, 91, 5176.
18. Conformation-dependent intramolecular reactions were reported.[19]
19. M. Oki, Acc. Chem. Res., 1984, 17, 154; S. Murata, T. Sugawara, and H. Iwamura, J. Am. Chem. Soc., 1985, 107, 6317; H. R. Sonawane, B. S. Nanjundiah, S. I. Rajput, and M. Udaya Kumar, Tetrahedron Lett., 1986, 27, 6125.
20. Studies for confirming this and on the mechanism of the reaction are in progress: T. Tezuka and T. Otsuka, to be published.
21. A. J. Boulton, J. S. Khosrowshahi, and T. Kan-Woon, J. Chem. Soc., Chem. Commun., 1978, 1052.
22. T. Kametani, K. Sota, and M. Shio, J. Heterocyclic Chem., 1970, 7, 815.

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