would have been detected. Inspection of molecular models reveals that 1 should be considerably overcrowded and that the dynamic process may become feasible only by literally geared rotation around the bridgehead-to-oxygen bonds. Then rotation by 15° will produce without difficulty the transition state which has C_2 symmetry and is again degenerate sixfold.

In order to form an estimate of the barrier height for the degenerate conformational change, we investigated the low-temperature NMR measurements in dichloromethane-d_2. Even at −94 °C, no spectral change was noted both in ^1H and ^{13}C NMR. Some lowering of the peak height due to the tertiary carbons relative to the quaternary carbons was found. The phenomenon is, however, nothing more than diminution of the nuclear Overhauser effect, since no appreciable line broadening accompanied it. The magnetic environment of ^1H and ^{13}C nuclei in the benzene rings will be different, depending on whether they are flanked by the two benzene rings of the other triptycene moiety or they are situated outside. According to molecular models and the ring current models of Johnson and Bovey,[8] the difference in chemical shifts of the corresponding nuclei on different benzene rings is estimated to be 1–3 ppm. The above results that the chemical-shift difference of this magnitude may still be averaged out at −94 °C appear to indicate that the barrier height, if present, is not greater than ca. 8 kcal mol^{-1}. This low barrier should be taken as quite a contrast to the usually high barrier associated with triptycenes carrying more or less axially symmetric substituents.[1] Note that interaction between the opposing peri substituents is so significant that there is a substantial barrier even in 1,2-bis(1-triptycyl)acetylene.[9] It is interesting that, once the alignment is lost and the correlated rotation becomes possible, the barrier can get extremely low.

One may attribute the observed rapid conformational change in 1 to a possible inversion at the oxygen. The inversion at the divalent oxygen is, however, predicted by the Walsh rule to be unlikely,[10] and has been ruled out.[11] We also add that, just as in 1, 2 showed no change in its NMR spectrum at −94 °C and therefore is conformationally flexible.

Registry No. 1, 73611-45-7; 2, 73611-46-8; 3, 73597-15-6; 4, 73597-16-7; benzyne, 462-80-6; bis(9-anthryl)methane, 15080-14-5; diethyl ether, 60-29-7; 1-triptycyllithium, 59239-90-6; 1-triptycenecarbonyl chloride, 73597-17-8; triptycene, 477-75-8.

(8) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(9) P. K. T. Mew and F. Vögtle, *Angew. Chem., Int. Ed. Engl.*, **18**, 159 (1979).
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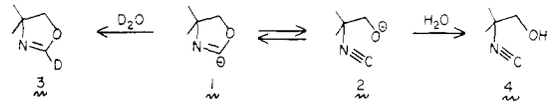
Oxazoles in Organic Chemistry. 2. Application to the Synthesis of Benzylisoquinoline Alkaloids.

Summary: A conceptually new route to the benzylisoquinoline alkaloids has been devised. The reaction of 2-lithiooxazoles with aromatic aldehydes to generate the thermodynamically favored 2-substituted oxazoles constitutes the key step in this process. A single-pot two carbon–carbon bond-joining reaction leading to an oxazoline suitable for further transformation to a phenethylamide is also described.

Sir: In continuation of our studies on the use of oxazoles for the construction of therapeutically important alkaloids,[1] we were led to explore the chemistry of the 2-metalated derivatives of this class of heterocycles. It was our desire to introduce specific carbon electrophiles at the 2-position of the oxazole nucleus, for we had envisioned that achievement of this goal would engender a new route to the benzylisoquinoline alkaloids.

Our work was guided by several observations recorded by previous workers on the metalation of oxazolines and oxazoles. Meyers and Collington had shown that *n*-butyllithium effectively deprotonates C-2 of 4,4-dimethyloxazoline by quenching with deuterium oxide to obtain the 2-deuterooxazoline **3**.[2] This oxazoline anion **1** was further



shown to be in equilibrium with its open-chain isomer **2**, since careful hydrolysis of the reaction mixture afforded β-hydroxyethylisocyanide **4**, in addition to the starting oxazoline.

The existence of the same type of mobile equilibrium between open-chain tautomer and oxazole has been recorded by Schöllkopf and co-workers; when 4,5-diphenyloxazole was metalated and then treated with chlorotrimethylsilane, the α-isocyano enolate anion **6** was ki-

netically trapped as the open-chain enol ether **8** (85%, *E* and *Z* isomers). In contrast, when benzaldehyde was added as the trapping agent, the thermodynamically favored 2-substituted oxazole **7** was generated (68%).[3] The formation of this product constitutes to our knowledge the sole literature example of the reaction of a 2-metalated oxazole with an electrophilic agent to produce a new substituted oxazole.[4]

These observations, in conjunction with the known ease of preparation of 5-aryl-substituted oxazoles from aromatic aldehydes by employment of van Leusen's reagent, tosylmethyl isocyanide,[5] and the reported facile hydrogenolytic cleavage of 2-aryloxazoles,[6] suggested a simple scheme for the preparation of the benzylisoquinoline alkaloids. Since these alkaloids and their synthetic analogues

(1) For part 1, a synthesis of ellipticine by the Diels–Alder reaction of an oxazole, see A. P. Kozikowski and N. M. Hasan, *J. Org. Chem.*, **42**, 2039 (1977).
(2) A. I. Meyers and E. W. Collington, *J. Am. Chem. Soc.*, **92**, 6676 (1970).
(3) R. Schröder, U. Schöllkopf, E. Blume, and I. Hoppe, *Justus Liebigs Ann. Chem.*, 533 (1975).
(4) The 4- and 5-lithio derivatives of oxazoles have also been prepared but generally through a metal–halogen exchange process. J. H. Bowie, P. F. Donaghue, H. J. Rhodda, and B. K. Simons, *Tetrahedron*, **24**, 3965 (1968).
(5) A. M. van Leusen, G. J. M. Boerma, R. B. Helmhod, H. Siderius, and J. Strating, *Tetrahedron Lett.*, 2367 (1972); A. M. van Leusen, B. E. Hoogenboom, and H. Siderius, *ibid.*, 2369 (1972).
(6) C. Tanaka and H. Asai, *Yakugaku Zasshi*, **91**, 436 and 485 (1971); *Chem. Abstr.*, **75**, 35847*g* and 35848*h* (1971). A. Dornow and H. Eicholtz, *Chem. Ber.*, **86**, 384 (1953). For examples of oxazoles that resist hydrogenation, see C. Tanaka, *Yakugaku Zasshi*, **87**, 10 (1967); *Chem. Abstr.*, **66**, 94929*x* (1967).

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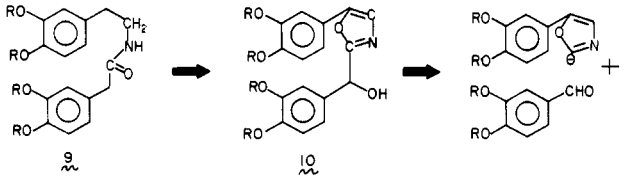
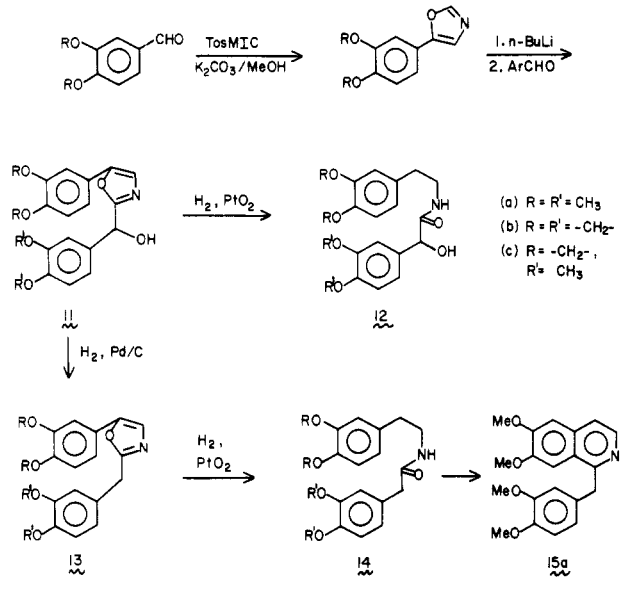
Scheme I



Scheme II

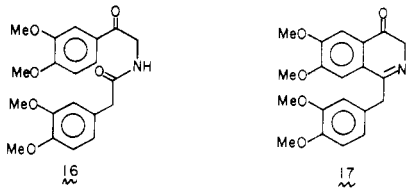


are important pharmacological agents[7] (smooth-muscle relaxants, coronary and peripheral vasodilators, etc.) the development of a new, efficient route to these products from readily available alkoxy-substituted benzaldehydes was deemed worthy of pursuit.

Schematically, the synthesis entailed the generation of a phenethylamide **9**, the standard precursor to these natural products, by the linkage of two benzylic units with a C–N–C fragment. This conceptually unique approach, the success of which was dependent on the generality of C–C bond formation with metalooxazoles, thus utilizes an oxazole as a synthetic template for further molecular elaboration (Scheme I).

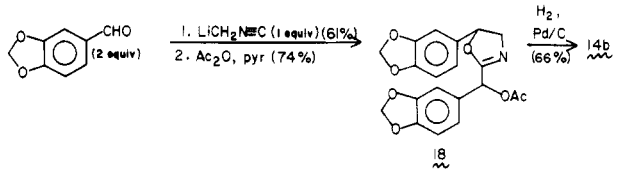
Our strategy was realized experimentally with veratraldehyde and piperonal as the starting aldehydes (Scheme II). Conversion into their respective oxazoles with tosylmethyl isocyanide proceeded in high yield (≥90%) as described by van Leusen. Subsequent metalation with either *n*-butyllithium or LDA/HMPA in tetrahydrofuran (−70 °C, 30 min)[8] gave deep red solutions which generally became amber in color on addition of the second aldehyde component and stirring overnight with gradual warming to room temperature. The efficiency of the addition reactions was readily ascertainable from ^{1}H NMR analysis by disappearance of the singlet at δ 7.70–7.90, which is attributable to the low-field C-2 hydrogen of the starting 5-aryloxazole. The crude reaction products were purified by silica gel chromatography to afford the generally crystalline 2,5-disubstitued oxazoles **11a–c** in 50–90% yield. These compounds were then subjected to hydrogenation over palladium or platinum catalysts in acetic acid using a hydrogen-filled balloon. The products generated in nearly quantitative yield for all cases at this stage were, not unexpectedly, found to be catalyst controlled. Hydrogenation of compounds **11a–c** over Adam's catalyst furnished the hydroxyphenethylamides **12a–c**, whereas hydrogenation over 5% palladium on carbon led to hydrogenolysis of the hydroxyl group (**11–13**). Continued hydrogenation of these latter products (**13a–c**) over Adam's catalyst effected scission of the oxazole ring with generation of the phenethylamides **14a–c**. Since the conversion of these products to the corresponding isoquinolines is well-documented, only the amide **14a** was carried on further. Cyclodehydration of this product with an eightfold excess of phosphorus oxychloride in refluxing toluene followed by dehydrogenation with palladium oxide in refluxing tetralin yielded papaverine (**15a**), a constituent of opium whose hydrochloride salt finds use as a smooth-muscle relaxant.[9]

It is interesting to note here that in 1930, Buck reported a several step synthesis of papaverine from the keto amide **16**.[10] Robinson and Young, reinvestigating this chemistry



in 1933, found that the product of the reaction of **16** with phosphorus oxychloride was not compound **17** as originally formulated by Buck, but the oxazole **13a**.[11] In order to then explain Buck's synthesis of papaverine, Robinson and Young thus recognized that oxazole **13a** was catalytically reducible to the phenethylamide **14a**. They further proposed at that time that this chemistry might well indicate "a general method which may have many useful applications".

While perhaps such oxazole-based strategies to the benzylisoquinolines may be more notable for their novelty than their practicality, it did occur to us that our particular scheme could be made more efficient by using an unactivated isocyanide in the opening step. We believed that it should be possible to effect in a single reaction vessel a two carbon–carbon bond-joining reaction which would produce an oxazoline suitable for further transformation to a phenethylamide bearing aryl groups of the same functionality. This notion derived support from the observation recorded by Schöllkopf and collaborators that 2-(hydroxyalkyl)-2-oxazolines are byproducts in the synthesis of 2-unsubstituted oxazolines from aromatic aldehydes and lithioalkyl isocyanides.[12] Indeed, simply reacting lithiomethyl isocyanide with 2 equiv of piperonal followed by acetylation[13] of the isolated hydroxy compound with acetic anhydride led to the oxazoline **18** via presum-



ably in the first stage the intermediate 2-lithiooxazoline. Hydrogenation of **18** over palladium on carbon afforded

(7) M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology", Academic Press, New York, 1972.
(8) Deuterium-quenching studies revealed that the metalation reactions were generally complete within 15 min at these temperatures.
(9) V. R. Shrinivasan and F. Turba, *Biochem. Z.*, **327**, 362 (1956).
(10) J. S. Buck, *J. Am. Chem. Soc.*, **52**, 3610 (1930).
(11) P. C. Young and R. Robinson, *J. Chem. Soc.*, 275 (1933).
(12) U. Schöllkopf, F. Gerhart, I. Hoppe, R. Harms, K. Hantke, K.-H. Scheunemann, E. Eilers, and E. Blume, *Justus Liebigs Ann. Chem.*, 183 (1976).
(13) Conversion to the acetate was required to effect hydrogenolysis of the hydroxyl group in this case.

in three steps the same phenethylamide **14b** generated previously in four steps by Scheme II. Other examples of this double-joining reaction should be equally feasible.

The work described herein thus offers a conceptually new route to benzylisoquinoline alkaloids. The generality of the reaction of 2-lithiooxazoles and oxazolines with aromatic aldehydes as carbon electrophiles has been substantiated, and the hydrogenolytic dismantling of these heterocyclic rings has been demonstrated to be a process of routine applicability.[14]

Acknowledgment. We gratefully acknowledge the Health Research and Services Foundation (HRSF) of Pittsburgh, PA, and the National Institutes of Health (Grant No. R01 HL20579-03) for support of these investigations.

Registry No. **11a**, 73663-56-6; **11b**, 73680-43-0; **11c**, 73663-57-7; **13a**, 73663-58-8; **14a**, 139-76-4; **14b**, 42971-27-7; **15a**, 58-74-2; **18** (isomer 1), 73663-59-9; **18** (isomer 2), 73663-60-2; 5-(3,4-dimethoxyphenyl)oxazole, 73663-61-3; 3,4-dimethoxybenzaldehyde, 120-14-9; methyl isocyanide, 593-75-9; (*R**,*R**)-2-[(3,4-methylenedioxyphenyl)acetoxymethyl]-5-(3,4-methylenedioxyphenyl)-4,5-dihydrooxazole, 73663-62-4; (*R**,*S**)-2-[(3,4-methylenedioxyphenyl)acetoxymethyl]-5-(3,4-methylenedioxyphenyl)-4,5-dihydrooxazole, 73663-63-5.

Supplementary Material Available: Experimental procedures for compounds **11a**, **13a**, **14a**, **14b**, and **18** (5 pages). Ordering information is given on any current masthead page.

(14) All new compounds reported had spectral properties and high-resolution mass spectral data for the molecular ion fully compatible with the assigned structures.

(15) Fellow of the Alfred P. Sloan Foundation.

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Remarkable Solvent Control of Functional Group Selectivity in Complex Metal Hydride Reductions

Summary: Lithium aluminum hydride in ethyl ether reduces alkyl tosylates to the corresponding alkanes rapidly and selectively in the presence of alkyl iodides and bromides without concurrent attack on halogen, whereas in diglyme the reactivity order is reversed, alkyl iodides and bromides being reduced selectively without significant attack on alkyl tosylates.

Sir: Since the discovery of sodium borohydride[1] and lithium aluminum hydride[2] ($LiAlH_4$), a number of modified and highly selective reducing agents have evolved, largely by the introduction of various substituents in the parent complex ion.[3] Unfortunately, very little attention[4] has been devoted to the study of using solvents to control the reactivity as well as the functional group selectivity of complex metal hydrides. The lack of such data is mainly attributed to the high reactivity associated with the complex metal hydrides, which severely limits the choice of possible solvents for such explorations.[3] As a part of an extensive study of the reactivity of various complex metal hydrides toward alkyl halides and tosylates,[5] it was of interest to explore the influence of solvents on the reactivity of hydride reagents.

Table I. Reaction of Lithium Aluminum Hydride with *n*-Octyl Derivatives in Representative Ethereal Solvents at 25 °C[a]

compd	solvent	% reduction[b] 0.25 h	0.5 h	1.0 h	6.0 h	24.0 h
n-octyl tosylate	EE	88	96	98		
	THF	79	85	96		
	MG	60	69	78	100	
	DG	39	61	72	91	
n-octyl iodide	EE		9	22		90
	THF	99	100			
	MG	94	99	99		
	DG	97	98	98		
n-octyl bromide	EE		8	16	53	77
	THF	84	97	99		
	MG	84	97	100		
	DG	92	100			
n-octyl chloride	EE	0	0	0	4	20
	THF	0	0	4	37	73
	MG	0	4	9	35	70
	DG	0	7	15	58	87

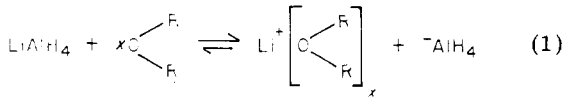
[a] Solutions were 0.25 M in both $LiAlH_4$ and compound. [b] Monitored by GLC by measuring the *n*-octane formed, with *n*-nonane as the internal standard.

Lithium aluminum hydride was chosen as the test reagent. The rates of reduction of *n*-octyl derivatives (tosylate, iodide, bromide, and chloride) with lithium aluminum hydride in representative ethereal solvents of different solvating power (ethyl ether, THF, monoglyme, and diglyme) were examined. Reactions were run with clear solutions of the reagent in the respective solvents under identical reaction conditions (0.25 M each in $LiAlH_4$ and RX, 25 °C). The results are summarized in Table I.

Lithium aluminum hydride in ethyl ether (EE) reduced *n*-octyl iodide sluggishly, requiring 24 h for 90% reduction. Changing the solvent to tetrahydrofuran (THF) dramatically enhanced the rate, the reduction being essentially complete in 0.25 h! In monoglyme (MG) and diglyme (DG) the rates of reduction of *n*-octyl iodide were still faster. A similar order of solvent influence (DG > MG > THF ≫ EE) on the reactivity of $LiAlH_4$ toward alkyl bromides and chlorides was realized.

In contrast, the solvent influence on the rates of reduction of alkyl tosylates follows the order EE > THF > MG > DG, which is exactly the reverse of the order observed for alkyl halide reductions. Thus, in ethyl ether *n*-octyl tosylate was rapidly (0.5 h) and quantitatively reduced to *n*-octane. In diglyme, the corresponding reaction was sluggish, requiring 12 h for completion.

In ethereal solvents, lithium aluminum hydride can be represented as an "ion pair"[6] (eq 1). In solvents such as



(1)

(1) Schlesinger, H. I.; Brown, H. C.; Hoekstra, H. R.; Rapp, L. R. *J. Am. Chem. Soc.* **1953**, *75*, 199–204.

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(3) For a detailed review and discussion on this subject see: (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607; (b) Brown, H. C.; Krishnamurthy, S. *Aldrichimica Acta* **1979**, *12*, 3–11.

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