and A. J. Mura, Jr., *J. Org. Chem.*, **40**, 812 (1975); (c) T. Cohen, D. Kuhn, and J. R. Falck, *J. Am. Chem. Soc.*, **97**, 4749 (1975). Recently the selective 1,4 addition of $RCu \cdot BF_3$ to ethyl sorbate was reported: (d) Y. Yamamoto and K. Maruyama, *ibid.*, **100**, 3240 (1978).

(8) In ether 1,4- and 1,6-addition products were isolated in 58 and 8% yields, respectively, while in THF containing 2 equiv of HMPT the ratio of the isolated yields changed to 46:28.

(9) Freshly dried and distilled solvent (methanol or ethanol) should be used; otherwise amides are produced as byproducts.

(10) The similar results were obtained with 4 equiv of MeI.

(11) (a) R. N. Hurd and G. DeLaMater, *Chem. Rev.*, **61**, 45 (1961); (b) G. E. Lienhard and T. Ch. Wang, *J. Am. Chem. Soc.*, **90**, 3781 (1968); (c) R. Mukherjee, *Chem. Commun.*, 1113 (1971).

(12) Details of procedure to convert thioamides to esters, ketones, and aldehydes will be reported in due course. Thioamides which do not possess the protons α to thiocarbonyl group are converted to the corresponding ketones by treatment of the onium salts with Grignard reagents: T. Yamaguchi, Y. Shimizu, and T. Suzuki, *Chem. Ind. (London)*, 380 (1972).

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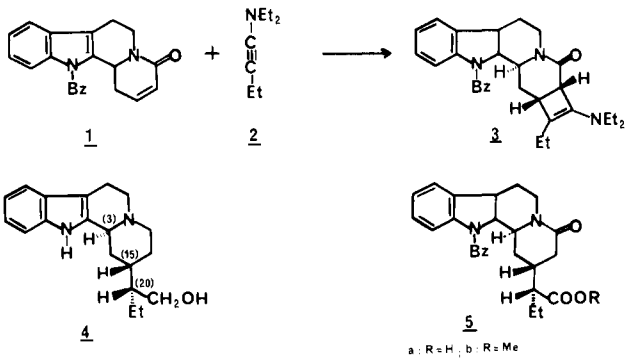
Stereoselective Synthesis of (±)-Dihydroantirhine

Sir:

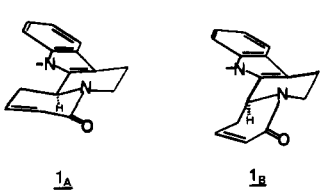
We describe here a new route to indole alkaloids which leads specifically to the less stable anti relationship of the centers at C_3 and C_{15}.[1] The first stereoselective synthesis of (±)-dihydroantirhine (**4**)[2,3] will serve to illustrate our synthetic approach. It is noteworthy not only because of its complete stereoselectivity (all three asymmetric centers of dihydroantirhine are rigorously controlled) but also by its efficiency; the overall yield of (±)-dihydroantirhine is 40% starting from lactam **1** (20% based on tryptamine).



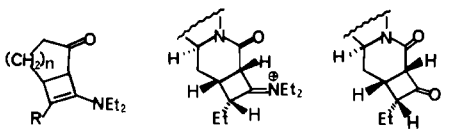
The two key steps on which this new approach is based are the cycloaddition of the ynamine **2**[4] with the unsaturated lactam **1**[5] (**1** + **2** → **3**) and the hydrolysis of the enamine system of the resulting cycloadduct **3** (**3** → **5a**).

The initial cycloaddition of ynamines with α,β-unsaturated lactams was made possible, as we described in the case of unsaturated nitriles,[6] by the addition of magnesium bromide.

The first stereochemical problem was that of establishing the correct anti relationship of C_3 and C_{15} which is characteristic of the antirhine alkaloids. The cycloaddition[7] of ynamine **2** with **1** offers a solution to this problem because perpendicular attack[8] of **2** at C_{15} would be expected to involve a transition state in which the lactam is in a half-chair conformation (cf. $\mathbf{1}_A$) leading to **3** rather than in a half-boat conformation (cf. $\mathbf{1}_B$) which would have led to a syn relationship of the relevant centers.



The second problem involves the control of the relative configuration of the centers at C_{15} and at C_{20} in dihydroantirhine. This control of a center in a flexible chain adjacent to a ring can be achieved during the hydrolysis of the cycloadduct (**3** → **5a**). Treatment of **3** with 10% hydrochloric acid for 1 h at 20 °C gave the acid **5a**, mp 186–187 °C (acetonitrile–ethanol).[9] The methyl ester **5b** (diazomethane, 50% overall yield from **1**; IR ($CDCl_3$) 1650–1730 cm^{-1}; ^1H NMR δ 0.9 (t, 3 H), 3.5 (s, 3 H)), was clearly a single isomer as shown by its ^{13}C NMR spectrum.[10] This result shows that the same very high stereoselectivity is observed in the hydrolysis of the cyclobutane enamine **3** which is fused to a lactam, as is observed when the fusion is to a cyclanone as in the previously studied case of **6**.[11]



Under the kinetic control involved in the conditions described above, the β-ketolactam **8** is formed via the immonium ion **7** by addition of the proton on the more accessible exo face. Irreversible cleavage of the β-ketolactam **8** is more rapid under these conditions than equilibration of **7** or **8**, and thus leads directly to the acid **5a** in which the crucial center at C_{20} in the side chain is maintained in the correct configuration.

Reduction of the ester **5b** with an excess (3 equiv) of lithium aluminium hydride (THF, reflux, 2 h), followed by debenzylation of the indole nitrogen (Na, NH_3),[12] then gave (±)-dihydroantirhine (**4**) in 80% yield. The synthetic substance and its acetate proved identical (IR, mass, ^1H NMR, ^{13}C NMR)[13] with samples prepared starting from natural antirhine.[14]

References and Notes

(1) For the biogenetic nomenclature of indole alkaloids, see J. Le Men and W. I. Taylor, *Experientia*, **21**, 508 (1965). This nomenclature is used here in the case of the intermediates which are nonalkaloidal.

(2) For the structure of dihydroantirhine, see S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Aust. J. Chem.*, **20**, 1463 (1967); Y. K. Sawa and H. Matsumura, *Tetrahedron*, **25**, 5319 (1969).

(3) For previous syntheses, see (a) E. Wenkert, P. W. Sprague, and R. L. Webb, *J. Org. Chem.*, **38**, 4305 (1973); (b) L. Chevolot, H. P. Husson, and P. Potier, *Tetrahedron*, **31**, 2491 (1975).

(4) Prepared according to J. Ficini and C. Barbara, *Bull. Soc. Chim. Fr.*, 2787 (1965).

(5) Lactam **1** (^1H NMR ($CDCl_3$) 6.09 (d, d, 1 H), 6.55 (m, 1 H); mp 162 °C after chromatography on silica gel (1/1 CH_2Cl_2—ether)) was prepared according to the method of H. J. Reich, I. L. Reich, and J. M. Renga (*J. Am. Chem. Soc.*, **95**, 5813 (1973)) and K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi (*ibid.*, **95**, 6137 (1973)), with an overall yield of 65% (3 equiv of lithium diisopropylamine, THF, 2 h, −78 °C, then 3 equiv of C_6H_5SeCl, 15 min, −78 °C, and then $NaIO_4$, 4 equiv in aqueous methanol, 30 min, 25 °C) from the corresponding saturated lactam (mp 189 °C) which is obtained after benzylation of the indole nitrogen (HNa, Me_2SO, benzyl chloride, 60 °C, 2 h, 95% yield) of the known saturated lactam (mp 250 °C): S. Corsano and S. Algieri, *Ann. Chim. Rome*, **50**, 75 (1960).

(6) J. Ficini and A. M. Touzin, *Bull. Soc. Chim. Fr.*, 2385, 2388 (1972); J. Ficini, A. Eman, J. d'Angelo, and A. M. Touzin, *Tetrahedron Lett.*, 683 (1976); J. Ficini and J. d'Angelo, *ibid.*, 687 (1976); J. O. Madsen and S. O. Lawesson, *Tetrahedron*, **30**, 3481 (1974).

(7) Ynamine **2** (8.2×10^{-3} mol) was added, under nitrogen, at room temperature to a THF solution of lactam **1** (2.74×10^{-3} mol) containing $MgBr_2$ prepared from 4.1×10^{-3} mol of Mg and 4.1×10^{-3} mol of dibromoethane in THF. After refluxing for 1.5 h, the reaction mixture was cooled and poured onto a saturated solution of ammonium chloride and ammonia. The crude cycloadduct **3** (IR (neat) 1665, 1635, 1585 cm^{-1}) obtained after distillation of the solvents was used without purification.

(8) E. Toromanoff, *C.R. Acad. Sci.*, **286**, 385 (1978); *Top. Stereochem.*, **2**, 162 (1967).

(9) The crude acid **5a** was used without purification in the esterification with diazomethane to give **5b**.

(10) The ^{13}C NMR spectrum of **5b** was taken on a Bruker WP 80 apparatus for which we thank J. P. Genêt (Université P. et M. Curie, Paris) ($CDCl_3$): δ 174.3, 170.0, 138.2, 137.6, 134.4, 128.8, 127.4, 126.8, 125.8, 122.3, 119.9, 118.5, 110.8, 109.9, 51.4, 50.7, 47.5, 40.3, 35.8, 33.4, 31.8, 23.2, 21.3, 11.8 ppm.

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(11) For a recent review, see J. Ficini, *Tetrahedron*, **32**, 1449 (1976).
(12) Y. Oikawa and O. Yonemitsu, *J. Chem. Soc., Perkin Trans. 1*, 1479 (1976).
(13) The ^{13}C NMR of the dihydroantirhine acetate was taken on a Bruker WP 80 apparatus by Dr. J. P. Genêt ($CDCl_3$): δ 172.2, 136.3, 132.4, 127.6, 121.7, 119.6, 118.1, 111.1, 107.3, 63.0, 54.5, 51.1, 46.0, 43.6, 31.6, 31.4, 28.9, 21.2, 17.4, 11.6 ppm.
(14) We thank Professor P. Potier and Dr. H. P. Husson (Gif sur Yvette) for a sample of natural antirhine.

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Received October 23, 1978

Benzenesulfonylnitrile Oxide: a Useful Intermediate for the Syn-Cyanohydroxylation of Alkenes

Sir:

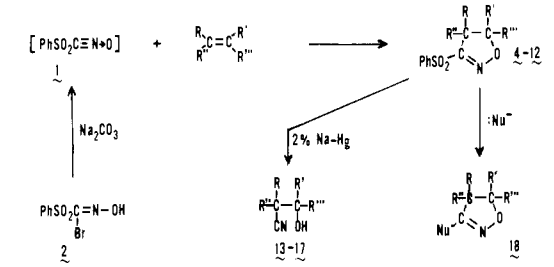
Several synthetic transformations have been reported which permit the stereospecific syn attachment of carbon and oxygen to the double bond of alkenes.[1-3] Typically, a heterodiene,[1] 1,3 dipole,[2] or ketene[3] is reacted with the alkene, followed by elaboration of the resulting cycloadduct. Nitrile oxides are among the 1,3 dipoles successfully employed for this transformation. The range of alkenes which react well with typical nitrile oxides is, however, somewhat limited owing to competition from nitrile oxide dimerization.[2a] Certain unconjugated alkenes do not work well, notably six-membered cyclic and tri- and tetrasubstituted ones.

We report here two new general synthetic procedures based on an improved version of the nitrile oxide cycloaddition process. The first of these permits the syn-cyanohydroxylation[4] of alkenes, while the second introduces an efficient indirect way to obtain 3-substituted isoxazolines. Central to both procedures is the cycloaddition of benzenesulfonylnitrile oxide (**1**) to alkenes (Scheme I). The resulting cycloadducts undergo reductive ring fragmentation to complete the syn-cyanohydroxylation process. Alternatively, nucleophilic substitution of the benzenesulfonyl group leads to a number of 3-substituted isoxazolines which would be difficult at best to prepare by direct cycloaddition.

The bromo oxime **2** has proven a convenient precursor to the nitrile oxide **1**. It is readily prepared from benzenesulfonylnitromethane (**3**)[5] in 30–40% overall yield (Scheme II).[6] Sequential bromination and O-methylation of α-nitro sulfone **3** affords an unstable nitronic ester rapidly converted in refluxing methylene chloride to bromo oxime **2**.

Slow addition (syringe pump technique) of a solution containing the bromo oxime **2** to a mixture of excess alkene and aqueous sodium carbonate[7] results in fair to excellent yields

Scheme I



Scheme II

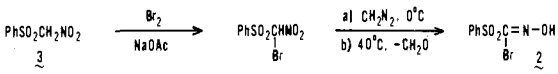
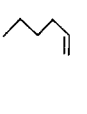
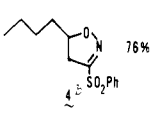
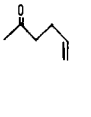
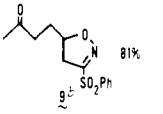
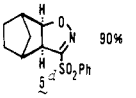
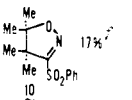
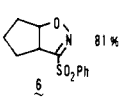
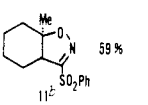
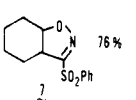
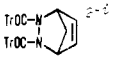
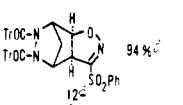
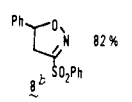


Table I. Cycloadducts Obtained from Benzenesulfonylnitrile Oxide

ALKENE	CYCLOADDUCT[a]	ALKENE	CYCLOADDUCT[a]
	 76% 4[b]		 81% 9[b]
 [c]	 90% 5[d]	 [e]	 17% [f] 10
	 81% 6	 [e]	 59% 11[b]
	 76% 7	 [g]	 94% [h] 12[c]
	 82% 8[b]		

[a] Using an ~50-fold excess of alkene unless otherwise stated. Yields are based on the nitrile oxide precursor **2** and refer to pure, isolated products. [b] NMR indicated only this regioisomer. [c] A 1.5-fold excess of alkene was employed. [d] NMR indicated the exo isomer; for the endo and bridgehead H, $J \leq 2$ Hz in all cases. [e] Distilled (spinning band) to remove isomers and passed through silica gel. [f] The major product (61% yield) was dibenzenesulfonylfurazan oxide. [g] We thank Dr. K. C. Nicolaou for a research sample. [h] A 1.5-fold excess of the alkene was used. [i] TrOC = Cl_3CCH_2OCO. [j] Based on the alkene.

of the cycloadducts **4–12** (Table I). It is noteworthy that the normally sluggish cyclohexene reacts very well. Cycloaddition also occurs readily with 1-methylcyclohexene, an alkene not previously reported to react with nitrile oxides. The limit of this procedure is reached with tetramethylethylene;[8] reaction does occur to give a 17% yield of cycloadduct **10** but the major product, obtained in 61% yield, is dibenzenesulfonylfurazan oxide (nitrile oxide dimer).

We attribute the high reactivity of benzenesulfonylnitrile oxide to synergistic electronic and steric factors. Electron-attracting substituents are known to increase the reactivity of other 1,3 dipoles[9,2f] toward alkenes and presumably this is one function of the benzenesulfonyl substituent. Also, its large size is expected to retard the dread nitrile oxide dimerization.[8]

Our syn-cyanohydroxylation process is completed by treatment of the cycloadduct with 2% sodium amalgam. The resulting expulsion of the benzenesulfonyl group with concommitant nitrogen–oxygen bond cleavage affords vicinal cyanohydrins in excellent yield[10] (Table II). For those cases where there is a stereochemical choice, only the cis isomer is obtained. Thus, the cyanohydrin **15** clearly differs in spectral and physical properties from its trans isomer obtained by treating cyclohexene oxide with potassium cyanide.

Arenesulfonyl groups are well-known one-electron acceptors.[11] Presumably the first step in fragmentation of cycloadducts **5–9** involves electron transfer from sodium amalgam to the benzenesulfonyl group. However, the conditions employed here (2% Na–Hg at 20 °C) are exceptionally mild for such a process. Consequently, the cyano group of the products is unaffected,[12] nor is the carbonyl group of cycloadduct **8** reduced during ring fragmentation.

The syn-cyanohydroxylation of cyclohexene is a typical example of the general procedure. A solution containing bromo

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