R. Hoffmann, R. Gleiter, and F. B. Mallory, *J. Am. Chem. Soc.*, **92**, 1460 (1970); (f) Th. A. J. W. Wajer and Th. J. deBoer, *Recl. Trav. Chim. Pays-Bas*, **91**, 565 (1972); (g) E. J. Burrell, Jr., *J. Phys. Chem.*, **66**, 401 (1962); (h) L. Batt and B. G. Gowenlock, *J. Chem. Soc.*, 376 (1960).
(4) Ogloblin and his co-workers investigated the addition of nitrosyl chloride to certain enol ethers in ether as a solvent: K. A. Ogloblin and D. M. Kunovskaya, *J. Org. Chem. USSR (Engl. Transl.)*, **4**, 897 (1968); (b) J. K. Mahajan, G. A. L. Ferreira, and H. C. Araujo, *Chem. Commun.*, 1078 (1972).
(5) M. M. Rogić and J. Vitrone, *J. Am. Chem. Soc.*, **94**, 8642 (1972).
(6) Generally, dimerization of a chiral nitroso compound can lead to a mixture of diastereoisomeric nitroso dimers: M. M. Rogić, T. R. Demmin, R. Fuhrmann, and F. W. Koff, *J. Am. Chem. Soc.*, **97**, 3241 (1975). A detailed discussion of the dimerization of α-nitroso ketone acetals, structures, and ^{13}C NMR spectra of the corresponding dimers will be published subsequently.
(7) All α-oximino ketone acetals in this work were single diastereoisomers. No particular effort was made to establish whether the configuration of the oxime hydroxyl group was *E* or *Z* in the isolated compounds. Consequently, while in the structural formulas throughout this paper the oxime group (and some derivatives thereof) is represented in one particular configuration, this is done for convenience in writing and it does not imply one given configuration, see also ref 23.
(8) B. G. Gowenlock, J. Trotman, and L. Batt, *Chem. Soc., Spec. Publ.*, **10**, 75 (1957).
(9) For a general discussion of fragmentation reactions see, e.g., C. A. Grob in "Theoretical Organic Chemistry", Report on the Kekule Symposium, London, 1958, p 114; *Angew. Chem., Int. Ed. Engl.*, **8**, 535 (1969). In principle, the transformation of **2** to **20** is not a fragmentation but a ring cleavage reaction. However, a similar transformation of open chain analogues affords indeed fragmented products. For this reason, as well as for the fact that even cyclic α-oximino acetals de facto provide at least two products, the general term Beckmann fragmentation will be maintained.
(10) A. Werner and A. Piguet, *Chem. Ber.* **37**, 4295 (1904); (b) A. Werner and T. Detscheff, *ibid.*, **38**, 69 (1905); (c) A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934); (d) R. L. Autrey and P. W. Scullard, *ibid.*, **87**, 3284 (1965); (e) R. A. Hill, *J. Org. Chem.*, **27**, 29 (1962); (f) M. Ohno, N. Naruse, S. Torimitsu, and I. Teresawa, *J. Am. Chem. Soc.*, **88**, 3168 (1966); (g) C. W. Shoppe and S. K. Roy, *J. Chem. Soc.*, 3774 (1963); (h) A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, **25**, 496 (1960); (i) A. Hassner and N. A. Wentworth, *Chem. Commun.*, 44 (1965), and references therein.
(11) It is of interest to note that certain oximes undergo reaction with liquid sulfur dioxide at room temperature. For example, cyclohexanone oxime reacts with sulfur dioxide to give among other products ammonium hydrogen sulfate. M. M. Rogić and K. P. Klein, unpublished observations.
(12) Nitrosolysis reaction is carried out in sulfur dioxide solution containing a substantial excess of ethanol.[1] From the discussion of the mechanism of the cleavage of α-oximinocyclohexanone acetal that follows, it is clear that an excess of alcohol does suppress the cleavage reaction.
(13) R. F. Borch, *J. Am. Chem. Soc.*, **90**, 5303 (1968).
(14) These tetrafluoroborates were prepared from the corresponding ortho esters according to the procedure of ref 13.
(15) I. Fleming and R. B. Woodward, *J. Chem. Soc., Perkin Trans 1*, 1653 (1973), and references cited therein.
(16) Nitrosation of cyclohexanone in various solvents and with various nitrosating reagents generally leads to 2,6-dioximinocyclohexanone: O. Touster, *Org. React.*, **7**, (1953); A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, **25**, 496 (1960).
(17) F. M. Jaeger and J. A. Van Dijk, *Proc. Acad. Sci. Amsterdam*, **39**, 384 (1936); (b) J. Toul, J. Pedrta, and A. Okoe, *J. Chromatogr.*, **57**, 107 (1971).
(18) After completion of this work, a partially successful preparation of α-oximinocyclohexanone was reported by the low temperature, low conversion nitrosation of cyclohexanone in the presence of a large excess of hydrogen chloride: M. Katooka and M. Ohno, *Bull. Chem. Soc. Jpn.*, **46**, 3474 (1973).
(19) V. Schmidt and P. Grafen, *Justus Liebigs Ann. Chem.*, **656**, 97 (1962).
(20) A. D. Allen, *J. Chem. Soc.*, 1968 (1954).
(21) W. L. Semon and V. R. Damerell, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 204.
(22) Only one diastereoisomer was formed. The implication regarding the stereochemistry of dimerization of chiral nitroso compounds will be discussed in a subsequent paper.
(23) ^{13}C NMR assignments of the methylene carbon atoms adjacent to the oxime and acetal functions are consistent, but remain tentative at this time.

Isoquinolines. 8. Ethylene Oxide Mediated Conversion of Isoquinolines to Isoquinolones and Oxazolidines. Its Extension to Related Nitrogen Heterocycles[1]

Crist N. Filer,*[2] Felix E. Granchelli,[2] Peter Perri, and John L. Neumeyer*[3]

Department of Medicinal Chemistry and Pharmacology, College of Pharmacy and Allied Health Professions, Northeastern University, Boston, Massachusetts 02115

Received July 14, 1978

Treatment of 1-(3-methoxy-2-nitrobenzyl)isoquinoline (**1b**) with ethylene oxide in acetic acid afforded stable 10b-(3-methoxy-2-nitrobenzyl)oxazolo[2,3-*a*]isoquinoline (**3b**). Similarly, 1-cyanoisoquinoline (**1c**) yielded *N*-(2-hydroxyethyl)-1-isoquinolone (**6a**) and *N*-(2-acetoxyethyl)-1-isoquinolone (**6b**). In the latter instance no competitive formation of lactone **4** was observed. When quinoline was treated with ethylene oxide in acetic acid, novel labile 10b*H*-oxazolo[3,2-*a*]quinoline (**7**) was obtained, but similar treatment of 2-methylquinoline gave no reaction.

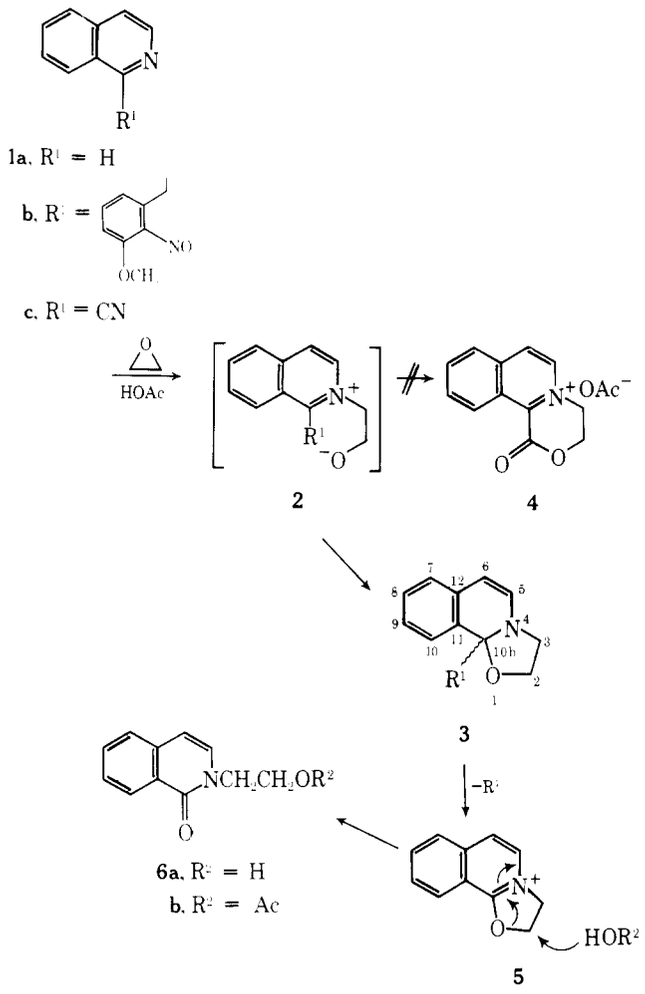
In an earlier communication[4] we reported that isoquinoline **1a** reacts with ethylene oxide in acetic acid at room temperature to afford after workup oxazolidine **3a** (Scheme I). Supporting the intermediacy of zwitterion **2a** in this conversion was the known cyclization of *N*-(2-hydroxyethyl)-3,4-dihydroisoquinolinium salts with bases to 5,6-dihydro analogues of **3a**[5a-e] and the reported synthesis of 2,3-disubstituted analogues of **3a** by treating *N*-benzylisoquinolinium halides with aldehydes and base.[6a,b] Herein we report further on the scope of this reaction with other isoquinolines and its partially successful extension to several related nitrogen heterocycles.

A possible explanation for the previously observed instability of oxazolidine **3a**[4] was the presence of an oxidizable 10b position. To test this explanation and probe the possible steric limitations of the ethylene oxide insertion reaction with isoquinolines, 1-(3-methoxy-2-nitrobenzyl)isoquinoline (**1b**) was treated with ethylene oxide in acetic acid to afford after workup an oxazolidine (69%) whose spectral data and combustion analyses are compatible with structure **3b** (for ^{13}C NMR consult Table I). In contrast to labile oxazolidine **3a** (where R^1 = H), 10b-substituted oxazolidine **3b** was isolated as a stable crystalline substance, mp 139–142 °C. Ethylene oxide mediated oxazolidine formation in the isoquinoline series appears to be a facile reaction even with appreciable steric hindrance in the isoquinoline 1 position.

The observation[4] that bromine substitution in the 1 position of isoquinolines facilitated ethylene oxide mediated isoquinolone conversion (presumably via oxazolidine **3** and oxazolinium salt **5** intermediates of Scheme I) prompted us to investigate whether putative cyano intermediate **2c** functioned similarly or underwent intramolecular ring closure to afford lactone **4** (Scheme I). Treatment of **1c** with ethylene oxide in acetic acid yielded after chromatography a mixture of isoquinolones **6a** (48%) and **6b** (34%). Basic hydrolysis of crude mixture **6a** and **6b** immediately after reaction of **1c** with

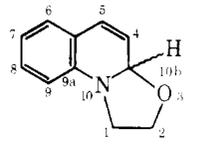
0022-3263/79/1944-0285$01.00/0

Scheme I



ethylene oxide afforded **6a** in essentially quantitative yield. No competitive formation of lactone **4** was noted.[7] Good leaving groups such as bromide or cyanide in the 1 position of isoquinolines appear to exclusively promote ethylene oxide mediated isoquinolone conversion.

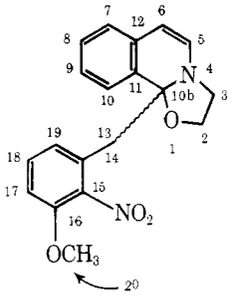
The extension of this addition reaction to several related bicyclic nitrogen heterocycles was briefly explored. Quinoline reacted with ethylene oxide in acetic acid to yield novel oxazolidine ring system **7** in quantitative crude yield.[8] The assigned structure of **7** is well supported by IR and ^{1}H NMR spectra.[9] In particular, both the chemical shift and coupling constant values for the 10b, 4, and 5 position protons of oxazolidine **7** are in excellent agreement with published ^{1}H NMR values for the analogous protons in several 1-alkyl-2-alkoxy-1,2-dihydroquinolines.[10] Oxazolidine **7** is even more labile than its structural isomer **3a**. Whereas **3a** was stable in $CDCl_3$ solution for >4 days at room temperature as monitored by ^{1}H NMR, the originally colorless $CDCl_3$ solution of oxazolidine **7** became dark red after being allowed to stand for several hours at ambient temperature and its initially clean and assignable ^{1}H NMR resonances became intermingled with extraneous peaks.



7

In contrast to quinoline, when 2-methylquinoline was treated with ethylene oxide in acetic acid at room temperature, it was quantitatively recovered from the reaction.

Table I. ^{13}C NMR Spectrum of Oxazolidine 3b[a]



3b

carbon assignment[b]	chemical shift[c]
2	63.7
3	50.6
5	131.3
6	100.2
10b	94.2
13	42.0
16	151.0[d]
20	56.4

[a] In $CDCl_3$. [b] Based in part on gated spectra and by analogy to the ^{13}C spectrum of **3a**.[4] [c] Chemical shift values are expressed in parts per million downfield from internal $(CH_3)_4Si$. [d] The remaining aromatic resonances appeared as a pattern of ten (one signal hidden due to overlap) lines between 110.8 and 129.9 ppm, but could not be rigorously assigned without ambiguity.

Experimental Section

General Methods. General methods were as previously described.[4]

10b-(3-Methoxy-2-nitrobenzyl)oxazolo[2,3-*a*]isoquinoline (3b). A solution of 1.0 g (3.40 mmol) of **1b**[11] and 10 mL (200 mmol) of ethylene oxide in 50 mL of acetic acid was allowed to sit at room temperature overnight. The clear colorless solution was then cooled to 0 °C and basified with excess 20% aqueous NaOH and extracted with $CHCl_3$. Drying (Na_2SO_4), filtration, and evaporation yielded 1.20 g of a red glass. Trituration with cold ether afforded 790 mg (69%) of **3b** as a yellow solid: mp 139–142 °C; NMR ($CDCl_3$) δ 7.40–6.45 (m, 7), 6.25 (d, 1, J = 7 Hz, H-5), 5.45 (d, 1, J = 7 Hz, H-6), 3.80 (s, 3, OCH_3), 3.80–2.80 (m, 6); IR ($CHCl_3$) 3000, 2900, 1600, 1580, 1530, 1470, 1450, 1370, 1350, 1280, 1085, 1020, 855 cm^{-1}; UV (EtOH) λ_{max} 219 (log ϵ 4.38), 236 (4.45), 331 (3.54) nm. Anal. (molecular ion) Calcd for $C_{19}H_{18}N_2O_4$: 338.12665. Found: 338.12621.

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.28; H, 5.39; N, 8.19.

1-Cyanoisoquinoline (1c). Isoquinoline **1c**, mp 87–89 °C, was prepared using the morpholine elimination procedure of George[12] on 1-cyano-1,2-dihydro-2-(phenylsulfonyl)isoquinoline[13] in 82% yield.

***N*-(2-Hydroxyethyl)-1-isoquinolone (6a) and *N*-(2-Acetoxyethyl)-1-isoquinolone (6b).** A solution of 600 mg (3.90 mmol) of **1c** and 6 mL (120 mmol) of ethylene oxide in 30 mL of acetic acid was allowed to sit at room temperature overnight. The clear colorless solution was then worked up in the usual fashion to yield 900 mg of a crude tan semisolid. Preparative TLC (silica gel eluted with EtOAc) yielded 351 mg (48%) of alcohol **6a** (R_f 0.40) as a white crystalline solid: mp 115–116 °C (lit.[14] 117–117.5 °C); NMR ($CDCl_3$) δ 8.30 (m, 1, H-8), 7.60–7.10 (m, 3), 7.00 (d, 1, J = 7 Hz, H-3), 6.40 (d, 1, J = 7 Hz, H-4), 4.25–3.70 (m, 4), 3.65 (s, 1, OH, D_2O exchanges); IR ($CHCl_3$) 3400, 3000, 1640 (lactam C=O), 1620, 1600 cm^{-1}; UV (EtOH) λ_{max} 209 (log ϵ 4.47), 224 (4.27), 279 (3.96), 286 (3.96), 325 (3.78) nm; MS *m/e* (rel intensity) 189 (67, M$^+$), 171 (62, M$^+$ – H_2O).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.97; N, 7.35.

Acetate **6b** (R_f 0.77) was isolated as an oil (307 mg, 34%): NMR ($CDCl_3$) δ 8.30 (m, 1, H-8), 7.60–7.20 (m, 3), 7.00 (d, 1, J = 7 Hz, H-3), 6.40 (d, 1, J = 7 Hz, H-4), 4.50–4.00 (m, 4), 2.00 (s, 3, $COCH_3$); IR ($CHCl_3$) 3000, 1740 (acetate C=O), 1645 (lactam C=O), 1630, 1600 cm^{-1}; UV (EtOH) λ_{max} 209 (log ϵ 4.41), 224 (4.24), 279 (3.90), 286 (3.90), 325 (3.64) nm; MS *m/e* (rel intensity) 231 (64, M$^+$), 172 (54, M$^+$ – CO_2CH_3).

Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found: C, 67.64; H, 5.71; N, 6.04.

Treatment of 1.0 g (6.5 mmol) of **1c** with ethylene oxide in acetic acid as described above followed immediately by basic hydrolysis (1 equiv of NaOH in aqueous CH_3OH at room temperature for 2 h) yielded directly after workup 1.22 g (99%) of alcohol **6a**, mp 113–115 °C.

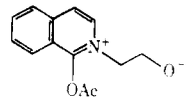
10b*H*-Oxazolo[3,2-*a*]quinoline (7). A solution of 1.0 g (7.70 mmol) of quinoline and 10 mL (200 mmol) of ethylene oxide in 50 mL of acetic acid was allowed to sit at room temperature overnight. Workup in the usual fashion yielded 1.34 g (100%) of **7** as a mobile yellow oil: NMR ($CDCl_3$) δ 7.30–6.40 (m, 5, including H-5), 5.75 (dd, 1, J = 3 and 9 Hz, H-4), 5.50 (d, 1, J = 3 Hz, H-10b), 3.50 (br s, 4, NCH_2CH_2O); IR ($CHCl_3$) 3000, 2900, 1650, 1600, 1500, 1465 cm^{-1}.

Acknowledgments. We thank Dr. Catherine Costello (MIT) for the aquisition and interpretation of the high resolution mass spectrum for **3b**, Professor Arthur C. Watterson (University of Lowell) for assistance in interpreting the ^{13}C NMR spectrum of **3b**, and Professor Jack E. Baldwin (MIT) for an invaluable discussion regarding the mechanisms of the transformations discussed herein. This investigation was supported in part by the National Cancer Institute, Contract 1-CM-53741.

Registry No.—**1b**, 53055-08-6; **1c**, 1198-30-7; **3b**, 68152-19-2; **6a**, 68152-20-5; **6b**, 68152-21-6; **7**, 68152-22-7; ethylene oxide, 75-21-8; quinoline, 91-22-5; 1-cyano-1,2-dihydro-2-(phenylsulfonyl)isoquinoline, 1035-19-4.

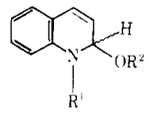
References and Notes

(1) Presented in part at the Eighth Northeast Regional Meeting of the American Chemical Society, Boston, Massachusetts, June, 1978, Abstract ORGN-57.
(2) New England Nuclear, Boston, Massachusetts 02118.
(3) Author to whom correspondence should be addressed.
(4) C. N. Filer, F. E. Granchelli, A. H. Soloway, and J. L. Neumeyer, *J. Org. Chem.*, **43**, 672 (1978).
(5) (a) W. Schneider and B. Müller, *Arch. Pharm. (Weinheim)*, **294**, 360 (1961); (b) *ibid.*, **294**, 645 (1961); (c) *ibid.*, **295**, 571 (1962); (d) W. Schneider and E. Kämmerer, *ibid.*, **299**, 817 (1966); (e) G. Habermehl, *Chem. Ber.*, **96**, 2029 (1963).
(6) (a) H. Ahlbrecht and F. Kröhnke, *Tetrahedron Lett.*, 967 (1967); (b) *ibid.*, 3653 (1967).
(7) Professor Jack E. Baldwin.(MIT) has kindly pointed out to us that, although these results do suggest the intermediacy of **2c**, they do not unambiguously implicate intermediate **3c** [formed from a 5-endo-trig ring closure: (J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976)] in the conversion of **1c** to **6a** and **6b**. Intermolecular attack of solvent on **2c** could compete with intramolecular ring closure (either 5-endo-trig yielding **3c** or 6-exo-dig yielding lactone **4**) to give intermediate i shown below. Our results do not exclude the intermediacy of i in the conversion of **1c** to mixture **6a** and **6b**, but do show that the formation of these isoquinolones through whatever mechanism is more favored than lactone **4**.



i

(8) Although several alcohols (R^2 = H) and ethers (R^2 = alkyl) of general structure ii, a quinoline pseudobase, have been described (N. Campbell in "Rodd's Chemistry of Carbon Compounds", 2nd ed, Vol. IV, Part F, S. Coffey, Ed., Elsevier, Amsterdam, 1976, p 271, and references cited therein), the preparation of **7** represents the first example of a cyclic derivative of ii.



ii

(9) The lability of oxazolidine **7** precluded aquisition of a combustion analysis, high-resolution mass spectrum, or ^{13}C NMR.
(10) R. Bramley and M. D. Johnson, *J. Chem. Soc.*, 1372 (1965).
(11) J. L. Neumeyer, F. E. Granchelli, K. Fuxe, U. Ungerstedt, and H. Corrodi, *J. Med. Chem.*, **17**, 1090 (1974).
(12) T. George, D. V. Mehta, and D. A. Dabholkar, *J. Org. Chem.*, **39**, 1965 (1974).
(13) J. M. Wefer, A. Catala, and F. D. Popp, *Chem. Ind. (London)*, 140 (1965).
(14) W. Schneider and B. Müller, *Chem. Ber.*, **93**, 1579 (1960).

Transannular Cyclizations of 1-Aza-4-cyclooctene[1]

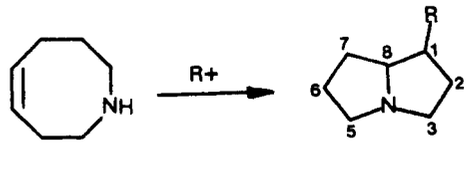
Stephen R. Wilson* and Robert A. Sawicki

Department of Chemistry, Indiana University, Bloomington, Indiana 47401

Received August 28, 1978

The stereospecific, transannular cyclizations of 1-aza-4-cyclooctene (1) are described. Compound **1** reacts with electrophiles (Br_2, I_2, $HgCl_2$, PhSBr, PhSeBr) to produce 1-substituted pyrrolizidines **6**. The stereochemistry of the bromine-induced cyclization was determined by X-ray crystallography. The reaction proceeds via transannular reaction of the nitrogen with the corresponding "onium" ion. There is no evidence of through-space (transannular) interaction of the amine and the double bond by PES.

Most naturally occurring pyrrolizidine alkaloids[3] contain substitution at the C-1 position. Thus, an approach to this bicyclic ring system which would enable simultaneous substitution at the 1 position would allow for the greatest flexibility in the synthesis of these natural products (eq 1). The

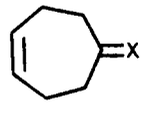


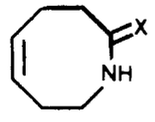
(1)

1 2

synthetic pathway described herein results in the stereospecific formation of C-1 substituted pyrrolizidines via transannular cyclization. Intramolecular cyclizations of medium ring systems are common.[4,5] We have reported recently our results in the azacyclononene series.[6]

Preparation of 1-Aza-4-cyclooctene (1). Amine **1** was prepared by the following series of reactions. Formation of oxime **3** of 4-cycloheptenone[7] followed by treatment with *p*-toluenesulfonyl chloride and pyridine yielded tosylate **4**. Tosyl oxime **4** underwent a facile Beckmann rearrangement[8] to give lactam **5**. Compound **5** was a white crystalline material





3 X = NOH **5** X = O

4 X = NOTs **1** X = H_2

0022-3263/79/1944-0287$01.00/0