Base-Catalyzed Reactions. XLI.[1] Novel Intramolecular Nucleophilic Cyclizations of Alkenylpyridines

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A novel cyclization reaction has been found to occur when ω-(3-pyridyl)-1-alkenes, such as 6-(3-pyridyl)-1-hexene or 7-(3-pyridyl)-1-heptene, are reacted in the presence of alkali metal catalysts. The final tricyclic products obtained from this reaction are formed by a facile intramolecular nucleophilic attack onto the electron-deficient α or γ positions of the pyridine ring. From 6-(3-pyridyl)-1-hexene (1) it is thus possible to produce both 4b,5,6,7,7a,8-hexahyropentaleno[2,1-*b*]pyridine (**5**) and 5,5a,6,7,8,8a-hexahydropentaleno[1,2-*c*]pyridine (**6**), depending if cyclization occurs in the 2 or 4 position of the pyridine ring. When ω-(4-pyridyl)-1-alkenes are subjected to the same reaction conditions, only monocyclizations occur. For example, 6-(4-pyridyl)-1-hexene (**3**) cyclizes to yield both *trans*- and *cis*-1-methyl-2-(4-pyridyl)cyclopentane (**9** and **10**). No double cyclization occurs in the case of 4-alkenylpyridines because nucleophilic attack would have to take place in the electron-rich β position of pyridine. Changing the alkali metal catalyst from potassium to sodium has no marked effect upon the course of the reaction.

During the last 15 years, we have demonstrated the use of sodium and potassium as catalysts for a number of reactions of hydrocarbons such as isomerization of olefins, dehydrogenation of olefins to aromatics, hydrogen transfer, alkylation of arylalkanes, etc.[2] Previous studies have included the alkali metal catalyzed side chain alkylation,[2] alkenylation,[3] and aralkylation[4] of 2- and 4-alkylpyridines. The formation of the majority of the products from these base-catalyzed reactions has been explained *via* a carbanion intermediate.

The present investigation has been extended to include reactions of ω-pyridyl-1-alkenes which contain both intrinsic acidic picolyl hydrogens[5] and double bonds. When 3-alkenylpyridines are reacted, intramolecular cyclizations occur to give pyrindan derivatives. However, when the 4-pyridylalkenes are subjected to the same reaction conditions, no intramolecular cyclization onto the pyridine ring is noticed. Although pyridines are known to undergo facile nucleophilic substitution in the α and γ positions, intramolecular nucleophilic cyclizations have not been reported until recently. The only example found in the literature was the cyclization of a 2-substituted 3-(3-pyridyl)-propylamine to a tetrahydro-1,8-naphthyridine in a 54% yield,[6] a reaction similar to a Chichibabin reaction in that an amine is the attacking nucleophile. A preliminary report from our laboratory appears to be the first cited example of an intramolecular cyclization where a carbanion is the attacking species.[7]

Even though alkali metals are known to disperse quite readily in 4-alkenylpyridines,[3a] it was found in this study that sodium dispersed very sluggishly in 3-alkenylpyridines under the reaction conditions used. So that all reactions could be performed under the same conditions, *o*-chlorotoluene was used as a chain initiator.[8] The *o*-chlorotoluene reacts readily with the alkali metal to give an organoalkali metal complex which then initiates the reaction. It has been reported previously[9] that potassium and cesium initiate cyclizations reactions onto benzene, but that sodium and lithium are ineffective as catalysts for the same nucleophilic cyclizations. Consequently, the present study examines the catalytic effect of both sodium and potassium on the intramolecular cyclizations onto the pyridine ring.

Results and Discussion

Intramolecular cyclization reactions were found to occur when ω-pyridyl-1-alkenes, in an inert solvent such as *sec*-butylcyclohexane, were heated to 160° in the presence of an organoalkali metal catalyst. The degree of cyclization was found to be dependent upon which position of the pyridine ring carried the substituent.

When 6-(3-pyridyl)-1-hexene (1) was allowed to react under the conditions described, two tricyclic products, **5** and **6**, were isolated from the reaction mixture in better than 30% yield (Table I, expt 1–4). The ratio greatly favors the formation of product **5**, where cyclization onto the pyridine ring occurs in the 2 position. Scheme I outlines a reaction mechanism that can explain the products formed. In the initial step the alkenylpyridine loses the picolyl proton, the most acidic one in the compound, to form intermediate **1a**. Owing to the close proximity of the picolyl carbon to the terminal double bond, intermediate **1a** will cyclize in such a way as to form the most stable carbanion, giving intermediate **1b**. (The formation of **1b** is favored over a cyclohexylpyridine intermediate which would necessitate the formation of a less stable secondary carbanion.) The next step of the reaction is intramolecular alkylation (cyclialkylation) of the anion onto the pyridine nucleus. The most common nycleophilic attack on pyridine is addition across the azomethine linkage; when this occurs, compound **5** is formed. The 4 position of pyridine is also susceptible to nucleophilic attack, and addition here forms compound **6**. The pronounced reactivity of the 2 and 4 positions can be attributed to the fact that addition at these sites permits the negative charge to reside partially on the electronegative nitrogen atom, as shown for intermediates **1c** and **1d**.

(1) (a) For paper XL, see S. V. Kannan and H. Pines, *J. Org. Chem.*, **36**, 2304 (1971). (b) Paper XII of the series Alkylation of Heteroaromatics; for paper XI, see ref 1a.

(2) H. Pines and L. A. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(3) (a) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 415 (1970); (b) H. Pines and J. Oszczapowicz, *ibid.*, **32**, 3183 (1967).

(4) N. E. Sartoris and H. Pines, *ibid.*, **34**, 2119 (1969).

(5) Picolyl hydrogens throughout the paper are defined as those hydrogens on the α-carbon atom of an alkyl group on pyridine.

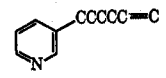
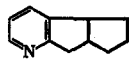
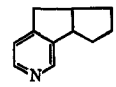
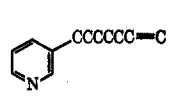
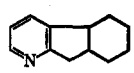
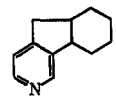
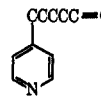
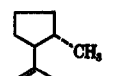
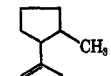
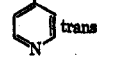
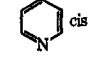
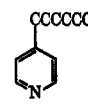
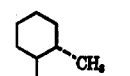
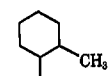
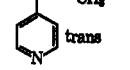
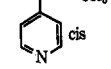
(6) E. M. Hawes and D. G. Wibberley, *J. Chem. Soc. C*, 315 (1966).

(7) H. Pines and S. V. Kannan, *Chem. Commun.*, 1360 (1969).

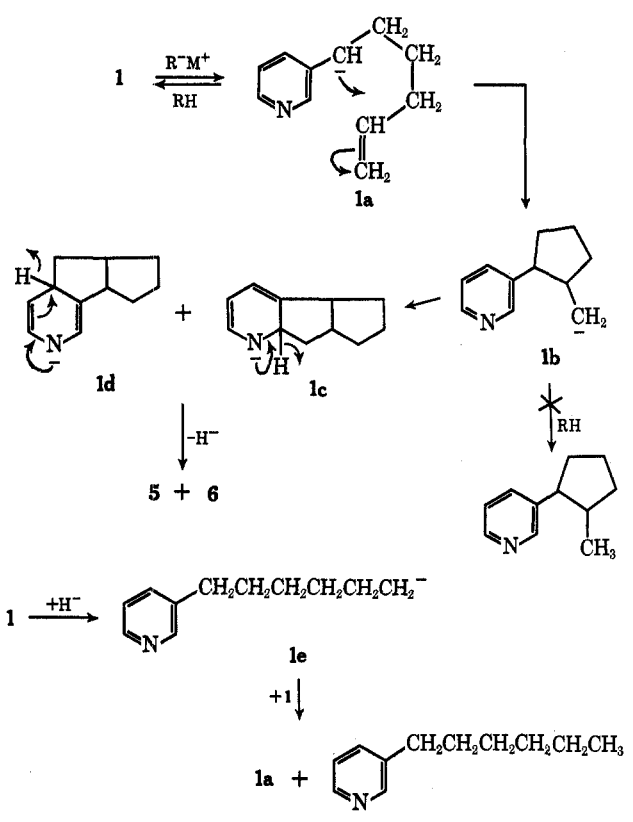
(8) H. Pines, J. A. Vesely, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **77**, 554 (1955).

(9) H. Pines, N. C. Sih, and T. Lewicki, *J. Org. Chem.*, **30**, 1457 (1965).

TABLE I
PRODUCTS OF CYCLIZATION OF ω-PYRIDYL-1-ALKENES

Expt no.	Reactant No.	Reactant Structure	Catalyst	Reaction time, hr	% yield	Products No.	Products A structure	Products No.	Products B structure	Product ratio % A	Product ratio % B
1	1		Na	7.8	33.3	5		6		88	12
2	1		Na	21	33.6	5		6		88	12
3	1		K	7.8	24.1	5		6		86	14
4	1		K	21	32.5	5		6		82	18
5	2		Na	10.3	37	7		8		~100	Traces
6	2		K	10.3	37	7		8		86	14
7	3		Na	7.5	71.1	9		10		87	13
8	3		K	7.5	11	9		10		~100	Traces
9	4		Na	11.5	85.1	11		12		95	5
10	4		Na	22.5	87	11		12		95	5
11	4		K	11.5	26	11		12		~100	Traces
12	4		K	22.5	27.5	11		12		~100	Traces

SCHEME I



Since hydride addition and double bond migration are the two most common reactions of olefins in the presence of alkali metal catalysts,[2,10] it is reasonable to assume that the hydride ion produced from intermediates **1c** and **1d** probably reacts with a second molecule of the starting alkenylpyridine (**1**) to produce a primary carbanion **1e**. This carbanion can then abstract a picolyl proton from yet a third molecule of **1**, yielding intermediate **1a** and a saturated alkylpyridine. The vpc analysis of products did indeed indicate the formation of alkylpyridine and tricyclic products. This results in a net stoichiometry of two molecules of **1** reacting to form one of the tricyclic product.

The extent of cyclization depends largely on the relative rate of intramolecular alkylation *vs.* the rates of the competing reactions, such as isomerization of the double bond, hydride addition, intermolecular alkylation, etc. The total per cent conversion of reactants is not reported in Table I, as it could not be calculated for these reactions because the double bond isomers were inseparable from reactant by vpc. By hydrogenation of the reaction mixture it was found that double bond isomerizations were one of the major side reactions, assuming that the majority of the starting material was consumed. The absence of monocyclized product which could arise by protonation of intermediate **1a** clearly demonstrates that the rate of nucleophilic attack on pyridine is much faster than is transmetalation of the intermediate anion in the case of 2-alkenylpyridines.

The homolog of **1**, 7-(3-pyridyl)-1-heptene (**2**), undergoes a set of reactions that is analogous to those just described (expt 5 and 6, Table I). In this case the tricyclic products formed are 4b,6,7,8,8a,9-hexahydro-5*H*-indeno[2,1-*b*]pyridine (**7**) and 5a,6,7,8,9,9a-hexahydro-5*H*-indeno[1,2-*c*]pyridine (**8**). As in the preceding case, the monocyclized product was not produced and the major dicyclized product was that one arising from nucleophilic attack at the α position of the pyridine ring.

Under the same conditions that give rise to tricyclic products from 3-alkenylpyridines, the corresponding 4-alkenylpyridines undergo only monocyclization. Examination of Table I shows that 6-(4-pyridyl)-1-hexene (**3**) (expt 7 and 8) and 7-(4-pyridyl)-1-heptene (**4**) (expt 9–12) undergo but one intramolecular cyclization to

(10) (a) L. H. Slaugh, *J. Org. Chem.*, **32**, 108 (1967); (b) J. E. Germain, L. Bassery, and R. Maurel, *C. R. Acad. Sci., Ser. C*, **260**, 560 (1965); (c) J. E. Hofmann, P. A. Argabright, and A. Schriesheim, *Tetrahedron Lett.*, 1005 (1964).

produce *cis*- and *trans*-1-methyl-2-(4 pyridyl)cyclopentane (**10** and **9**) and *cis*- and *trans*-1-methyl-2-(4-pyridyl)cyclohexane (**12** and **11**), respectively. The mechanism for this reaction would be the same as that described for the 3-alkenylpyridines, but in this case transmetalation of an intermediate similar to **1b** (Scheme I) is a much more facile reaction than is nucleophilic attack at the electron-rich 3 position of the pyridine ring. The trans to cis ratio found in all cases was much in favor of the more thermodynamically stable trans isomer. The cis and trans compounds were distinguished from one another by nmr, relative retention times on vpc, and by refractive indices, where the cis isomers were found to have higher refractive indices than the trans isomers, in agreement with the von Auwers–Skita rule.[11]

The fact that 3-alkenylpyridines cyclized onto the α or γ positions whereas the 4-alkenylpyridines did not undergo a cyclialkylation reaction agrees with an anionic mechanism. The anions formed would be expected to attack the electron-deficient α and γ positions of the pyridine ring and not the relatively electron-rich β position, as is found. On the other hand, if the intermediate were a radical in nature, it would be just as likely to cyclize in the β as in the α or γ position since radicals are fairly indiscriminate in the position of attack.[12]

In an earlier study on the alkali metal catalyzed cyclizations of ω-phenyl-1-alkenes, it was found that potassium caused cyclization where sodium failed to yield dicyclized products.[9] As can be seen in Table I, sodium and potassium reacted similarly in this study. In the case of 3-alkenylpyridines (expt 1-6), potassium causes slightly more cyclization to occur in the 4 position than does sodium; this is probably due to the greater ionic character of the potassium–carbon bond.[13] The carbanion formed when potassium is used as the catalyst is electrostatically less stabilized by its cation and thus reacts less discriminately. Sodium was found to yield a greater per cent of monocyclized product from 4-alkenylpyridines than potassium (expt 7–12). Under the conditions used in this study, it is reasonable to assume that the 4-alkenylpyridines easily form the picolyl anions with sodium and then cyclize to form the corresponding products (expt 7, 9, 10), whereas the more reactive potassium initiator is less discriminate and abstracts allylic protons more easily, leading to much more double bond isomerization and consequently less cyclized product (expt 8, 11, 12).

Examination of Table I (expt 1 and 4 *vs.* 7 and 9, sodium catalyst) indicates that the 4-alkenylpyridines give about 85% yield of cycliisomerized products **9–12**, whereas the 3-alkenylpyridines give a 35% yield of cyclialkylated products **5–8** which, however, is equivalent to a 70% yield. In the case of cyclialkylation a hydride is liberated which reacts with another molecule of the starting material to produce an alkylpyridine, as shown in Scheme I. A further possibility that might also contribute, to a minor extent, to the still relatively higher yields of cyclized product from 4-alkenylpyridines is the ease of removal of 4-picolyl protons. Since 4-picolyl protons are much more acidic than 3-picolyl protons,[14] more intermediates (such as **1a**, Scheme I) are formed that initiate the cycliisomerization reaction.

Experimental Section

Reagents.—3-Picoline and 4-picoline were purchased from Reilly Tar and Chemical Co. The alkylpyridines were distilled, dried over Linde 5A molecular sieves, and redistilled immediately before use. *sec*-Butylcyclohexane was obtained by catalytic hydrogenation of *sec*-butylbenzene. 1-Bromo-4-pentene (Pfaltz & Bauer) and 1-bromo-5-hexene (Columbia) were used as received.

Synthesis of Alkenylpyridines.—The alkenylpyridines were prepared in liquid ammonia from the corresponding picoline, alkenylbromide, and sodium amide according to the general procedure of Brown and Murphey.[15] Physical constants for these alkenylpyridines are given in Table II.

TABLE II
PHYSICAL CONSTANTS OF REACTION COMPOUNDS

Compd no.	$n^{20}D$	Relative retention time[a]	Bp, °C (mm)[b]
1	1.5036	1.33	75–77 (2)
2	1.5015	1.93	83–85 (2)
3	1.5052	1.36	73 (1.5)
4	1.5005	2.01	99 (3)
5	1.5483	2.16[c]	
6[d]	1.5502	2.75[c]	
7	1.5480	3.07	
8		3.99	
9	1.5175	1.36	
10	1.5258	1.70	
11	1.5188	2.01	
12[e]	1.5271	2.81	

[a] Retention times were obtained using a 4 ft × 0.25 in. column packed with 20% Carbowax 20M + 5% KOH on 60–80 mesh Gas-Pack WAB. Conditions used were 175° and a flow rate of 100 ml/min. The internal standard was naphthalene, retention time = 1.00. [b] Boiling point values are uncorrected. [c] Flow rate used was 85 ml/min. [d] *Anal.* Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.16; N, 8.80. Found: C, 82.61; H, 8.37; N, 8.98. [e] The relative retention times of the following compounds were also determined under the same conditions described in footnote *a*: 3-*n*-hexylpyridine = 1.08; 3-*n*-heptylpyridine = 1.56; 4-*n*-hexylpyridine = 1.09; 4-*n*-heptylpyridine = 1.60.

The following compounds were synthesized by this method.

(1) **6-(3-Pyridyl)-1-hexene** (**1**) was made from 3-picoline and 1-bromo-4-pentene in a 90% yield.

(2) **7-(3-Pyridyl)-1-heptene** (**2**) was isolated from the reaction of 3-picoline with 1-bromo-5-hexene in a 69% yield.

(3) **6-(4-Pyridyl)-1-hexene** (**3**) was synthesized from 4-picoline and 1-bromo-4-pentene. The product was isolated in an 88% yield.[16]

(4) **7-(4-Pyridyl)-1-heptene** (**4**) was isolated in an 89% yield from the reaction of 1-bromo-5-hexene with 4-picoline.

Preparation of Catalyst Solution and General Reaction Procedure.—The apparatus used was that described previously.[9] The catalyst solution was prepared by mixing 0.3 ml of *o*-chlorotolulene, 3 ml of *sec*-butylcyclohexane, and about 0.2 g of alkali metal in a reaction flask. Upon heating the contents for 2–3 hr at 160° under a nitrogen atmosphere, a black finely dispersed suspension of the catalyst was formed. About 2 ml of the appropriate alkenylpyridine was slowly introduced by a syringe through a rubber septum. The reaction mixture was then heated for the desired length of time at 160°. When desired, samples

(11) (a) K. von Auwers, *Justus Liebigs Ann. Chem.*, **420**, 84 (1920); (b) A. Skita, *ibid.*, **431**, 1 (1923).

(12) (a) D. H. Hey, D. A. Shingleton, and G. H. Williams, *J. Chem. Soc.*, 5612 (1963); (b) R. A. Abramovitch and J. G. Saha, *ibid.*, 2175 (1964); (c) J. M. Bonnier, J. Court, and M. Gelus, *Bull. Soc. Chim. Fr.*, 139 (1973).

(13) E. G. Rochow, D. T. Hurd, and K. N. Lewis, "The Chemistry of Organometallic Compounds," Wiley, New York, N. Y., 1957, p 65.

(14) W. N. White and D. Lazdins, *J. Org. Chem.*, **34**, 2756 (1969).

(15) H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

(16) Previously synthesized in this laboratory: W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970).

were removed from the mixture, quenched with methanol, and analyzed by vpc to determine the extent of reaction. The reaction material was then cooled and decomposed with 3 ml of methanol. Analysis was made on this material by vpc or on the hydrogenated products obtained over a 10% palladium/charcoal catalyst.

Reaction Products.—The liquid, cyclized reaction products that were isolated from the general reactions described above were separated from one another by means of preparative vpc. When separation of product from starting material was impossible because of identical relative retention times, *e.g.*, **3** and **9** or **4** and **11** (Table II), the reaction mixture was first hydrogenated and separations were then performed. All products were shown to be of greater than 95% purity by vpc. The products were identified by means of nmr and ir spectral analyses. It is possible to assign the direction of cyclization in the case of the tricyclic products **5–8** by examination of the pyridine ring protons. Compounds **5** and **7** show three different protons at δ 8.20–8.26, 7.26–7.39, and 6.90–6.96 ppm corresponding to the α, γ, and β protons, thus indicating that cyclization occurred in the α position. Similarly, with compounds **6** and **8**, the presence of two α protons a δ 8.20–8.26 ppm and one β proton at δ 6.93–7.00 ppm denotes that cyclization occurred in the γ position. For compounds **5–8** no methyl groups were present, only methylene and methine protons were present as indicated by a broad band at δ 1.00–2.34 ppm that correctly integrated for the proposed number of protons. Compounds **9–12** all had spectra similar to one another. The stereochemistry was determined from nmr by examining the chemical shift fo the methyl group and by coupling constants. Integration again was consistent with the proposed structures. No unsaturation was found by nmr or ir in any of the compounds **5–12**. Refractive indices also indicate cyclic compounds (see Table II).

Analyses.[17]—The nmr spectra of the pure samples in carbon tetrachloride were taken with a Varian T-60 spectrophotometer using tetramethylsilane as an internal standard. The microanalysis was done by M-H-W Laboratories, Garden City, Mich. Vapor phase chromatographic analyses and separations were performed on an F & M Model 720 dual-column instrument equipped with a thermal conductivity detector and using helium as a carrier gas. The separation of products for identification was accomplished with a 6 ft × $^3/_8$ in. column packed with Versamid 900 on Gas-Pack WAB.

Registry No. —**1**, 29883-73-6; **2**, 29883-74-7; **3**, 22241-43-6; **4**, 29883-76-9; **5**, 29883-77-0; **6**, 29883-78-1; **7**, 29883-79-2; **8**, 29905-80-5; **9**, 29864-45-7; **10**, 29864-46-8; **11**, 29864-47-9; **12**, 29868-59-5.

(17) The inclusion of elemental analyses for all the new compounds, suggested by the reviewers, would have been desirable in order to confirm their purity, although the nmr spectra and vpc indicate that all the isolated compounds were of at least 95% purity.

Base-Catalyzed Reactions. XLII.[1] Reactions of *N*-Methyl-2-pyrrolidinone and *N*-Methyl-2-piperidone with Olefins and Diolefins in the Presence of Potassium *tert*-Butoxide as Catalyst

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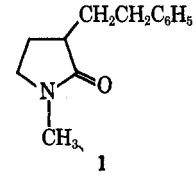
N-Methyl-2-pyrrolidinone (NM-2-Py) and *N*-methyl-2-piperidone (NM-2-Pi), the so-called "aprotic" dipolar solvents, were found to undergo reactions involving protons in the 3 position of their rings, with styrenes and conjugated diolefins. In the reactions studied, NM-2-Py was found to react only half as fast as NM-2-Pi. Also, the reaction of NM-2-Py was found to proceed faster in dimethyl sulfoxide than in hexamethylphosphoramide. Under the same conditions *N*-methylcaprolactam failed to react. A mechanism consistent with the results is proposed.

The reactions of olefins and diolefins with alkylaromatics and alkylpyridines was the subject of intensive research in this laboratory.[2] The experiments were made using sodium and potassium as catalysts. It has been recently observed that with the alkyl heterocyclic compounds the addition to conjugated hydrocarbons can also occur using potassium *tert*-butoxide as catalyst.[3] As an extension of this study the reaction of 3-ethylpyridine with styrene in the "aprotic" solvent *N*-methyl-2-pyrrolidinone (NM-2-Py) and in the presence of potassium *tert*-butoxide was investigated, and it was found that the "solvent" preferentially reacted with the olefins to form mono- and diadducts. The nmr spectrum of the monoadduct **1** conforms with the structure shown.



1

Among widely used dipolar aprotic solvents, only dimethyl sulfoxide (DMSO) has been reported to undergo reactions with olefins,[4] dienes,[5] aldehydes,[6] ketones,[6] and esters[7] in the presence of bases like alkali metal amides, hydrides, and alkoxides through its carbanion. This seems to be the first time that the addition reaction of NM-2-Py to an olefinic double bond is reported. This study was extended to the homologs, namely to *N*-methyl-2-piperidone (NM-2-Pi) and *N*-methylcaprolactam (NMC).

Results and Discussion

The results of the reactions of various olefins with NM-2-Py and NM-2-Pi in the presence of a potassium *tert*-butoxide catalyst are presented in Table I. These reactions are straightforward and occur without opening of the rings of the lactams. The structures of the compounds were assigned on the basis of nmr and ir. The addition of lactams in their 3 position to the olefins

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