Spiro Compound Formation by the Reaction of Cycloalkene with Friedel–Crafts Catalysts. I. Reaction of Cyclohexene with Aluminum Chloride. The Rearrangement of Cyclohexylcyclohexene

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The reaction of cyclohexene with aluminum chloride in refluxing *n*-hexane has been studied. The products were separated by fractional distillation and preparative gas–liquid partition chromatography. The dimeric fraction was found to contain 2-methylspiro[5.5]undecane and other products. The ratio of the spiro compound to other products was found to vary with experimental conditions. The mechanism of this reaction is discussed.

It is well known that cycloalkenes polymerize in the presence of acidic catalysts. For example, Truffault[1] obtained cyclohexylcyclohexene (I) in a high yield (80–90%) by the action of phosphorus pentoxide on cyclohexene.

Concentrated sulfuric acid was used by Nametkin[2] to convert cyclohexene at 5° to an oil (40%) which consisted of a saturated dimer, a trimer, and an unsaturated tetramer. From the residue of this oil, tetracyclohexylcyclohexene and tetracyclohexylbenzene were isolated and identified. Sperling[3] also studied the polymerization of cyclohexene by using concentrated sulfuric acid and obtained a dimeric fraction containing 1-cyclohexyl-2-methylcyclopentane and 1-cyclohexyl-3-methylcyclopentane. The polymerization of cyclohexene by hydrogen fluoride was investigated by McElvain and Langston,[4] who obtained dicyclohexyl (C), cyclohexylcyclohexene (I), and some trimeric products.

Watterman, Leendertse, and Ter Poorten[5] studied the polymerization of cyclohexene with aluminum chloride; they found that this catalyst had no effect at −78°, but at 70° a considerable amount of unidentified polymers was produced.

The objective of the present work was to determine the structures of the polymeric products obtained from the reaction of cyclohexene with aluminum chloride in *n*-hexane and to study mechanistic aspects of the reaction.

Results and Discussion

Reactions of cyclohexene with equivalent amounts of aluminum chloride in refluxing *n*-hexane (68°) were studied under two reaction conditions as follows.

Reaction Condition i.—Cyclohexene was added at 68° to a mixture of aluminum chloride and *n*-hexane during 10 min and the mixture was further heated under reflux.

Reaction Condition ii.—Cyclohexene, aluminum chloride, and *n*-hexane were mixed simultaneously at room temperature and the reaction was allowed to proceed under reflux.

The products were separated into a dimer fraction and a residue. The dimer fraction was shown to consist of several components by gas–liquid partition chromatography. The main products which were isolated by preparative gas chromatography are listed in Table I. The residues were not examined in detail, but among them were found a trimer which was a saturated compound and a higher polymer which was an unsaturated compound.

TABLE I

THE REACTION OF CYCLOHEXENE WITH ALUMINUM CHLORIDE. THE VARIATION OF THE RATIO OF THE PRODUCTS WITH THE CHANGE OF THE EXPERIMENTAL CONDITIONS

Reaction cond	Product reacn time	Dimer yield, wt %	Residue yield, wt %	Ratio of the products[a] of the dimeric fraction A	B	C
i	10 min	42.6	59.8	16.5	83.5	0
	30 min	36.8	57.3	17.5	82.5	0
	1 hr	36.8	65.9	37.5	62.5	0
	2 hr	40.2	58.5	38.3	61.7	0
	4 hr	45.8	54.9	59.0	41.0	0
ii	10 min	19.5	34.1	20.0	60.0	20.0
	2 hr	42.6	54.9	37.5	45.8	16.7

[a] Calculated from the glpc peak areas.

Elemental analysis, mass spectra, and cryoscopic molecular weight determination (*Anal.* Calcd for $C_{12}H_{22}$: 166. Found: 167.) of the dimeric fraction suggest that the molecular formula may be written as $C_{12}H_{22}$. Moreover, a bromine test gave negative results and the nmr spectrum showed that this dimeric fraction contained no vinylic proton. From these results the dimeric fraction was concluded to be a mixture of saturated hydrocarbons having the empirical formula $C_{12}H_{22}$.

The gas–liquid partition chromatography (glpc) of the dimeric fraction showed that the main products consisted of two components (A) (which displayed a major peak with a shoulder and were not further identified), 2-methylspiro[5.5]undecane (B), and dicyclohexyl (C).

The spiro compound B and dicyclohexyl (C) were isolated from the dimeric fraction by preparative gas chromatography. Elemental analysis indicated that these samples have a molecular formula $C_{12}H_{22}$. The glpc retention times, mass spectra, and indices of refraction coincided with the respective properties of authentic samples.

The principal ions of diagnostic interest in the mass spectrum of 2-methylspiro[5.5]undecane occur at mass 166, 151, 95, 82, and 81. The characteristic peak occurred at *m/e* 151 arising from the loss of the methyl group from the molecular ion (*m/e* 166).

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(1) R. Truffault, *Compt. Rend.*, **200**, 406 (1935).

(2) S. Nametkin and L. Abskumowskumowskaja, *Chem. Ber.*, **66**, 358 (1933).

(3) R. Sperling, *J. Chem. Soc.*, 1928 (1949).

(4) S. McElvain and J. W. Langston, *J. Am. Chem. Soc.*, **66**, 1759 (1944).

(5) H. I. Watterman, J. J. Leendertse, and A. C. Ter Poorten, *Rec. Trav. Chim.*, **54**, 245 (1935).

The mass spectrum of dicyclohexyl is noteworthy because of the presence of a *m/e* 83 ion, which must arise from the loss of the cyclohexyl group from the molecular ion (*m/e* 166).

Fraction A was not dehydrogenated by palladium-charcoal;[6] hence the presence of derivatives of decalin is ruled out.[7] Moreover the glpc retention time of this species differed from those of 1-methylspiro[5.5]undecane, spiro[5.6]dodecane,[8] 1-cyclohexyl-2-methylcyclopentane, and 1-cyclohexyl-3-methylcyclopentane prepared by other methods.

The results summarized in Table I showed that cyclohexene polymerized quantitatively during 10 min in the case of reaction condition i, and in the case of reaction condition ii the yield of polymer reached 54% during the same reaction time. These results are of some interest that in the reaction period of 10 min the dimer fraction was composed of about 80% spiro compound B and 20% compound A, while after more prolonged reaction times, the spiro compound B was found to have isomerized to fraction A. This observation was also supported by the fact that the ratio of fraction A to the spiro compound B obtained in the 4-hr reaction was almost the same as that obtained from the isomerization reaction of the spiro compound B alone under the same conditions.

Dicyclohexyl was obtained only in the case of reaction condition ii. As is shown in Table II, dicyclohexyl is only 16.5% isomerized in the presence of aluminum chloride after 4 hr at 68°; hence there is a small possibility of the isomerization of the dicyclohexyl produced in the cyclohexene reaction.

TABLE II

THE REACTIONS OF VARIOUS HYDROCARBONS WITH ALUMINUM CHLORIDE

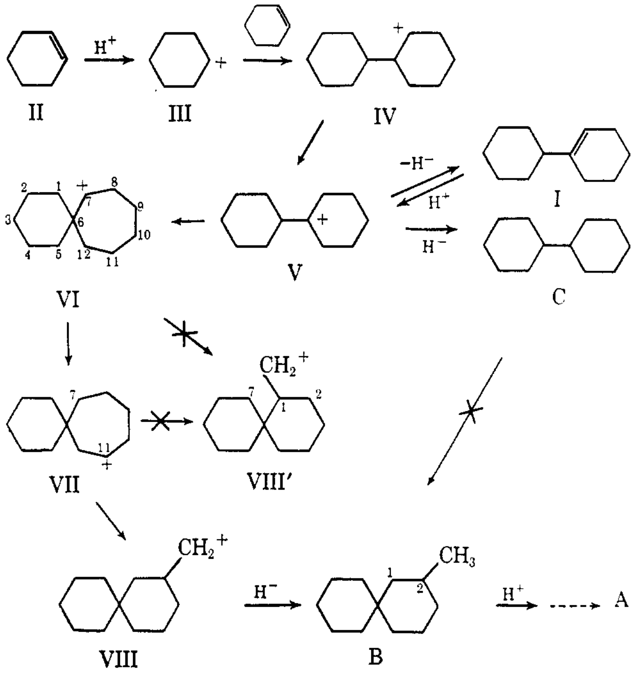
Reagent[a]	Reacn time, hr	Dimer yield, wt %	Residue yield, wt %	Ratio of the products[b] of the dimeric fraction A	B	C
B	4	91	Trace	53.8	46.2	0
C	4	90	Trace	8.5	8.0	83.5
I	1.5	95	5	57.2	38.2	10.6

[a] B, 2-methylspiro[5.5]undecane; C, dicyclohexyl; I, cyclohexylcyclohexene. [b] Calculated from the glpc peak areas.

We propose the reaction mechanism given in Scheme I.

It is not certain whether the catalyst is aluminum chloride itself or aluminum chloride with a cocatalyst, but the active agent[9] is likely to be a proton formed by the interaction of the metal halide with a cocatalyst such as water in this case. At the first step, a proton attacks cyclohexene (II) to produce the cyclohexyl cation (III). This cation (III) reacts further with cyclohexene to give a secondary carbonium ion (IV) which isomerizes to a tertiary carbonium ion (V) by a hydride shift. This sequence is plausible because, as was shown in Table II, cyclohexyl cyclohexene (I) gave the same products as those obtained by the reaction of cyclohexene. This carbonium ion (V) may change by ring expansion to VI.[10-12] Then isomerization to VIII follows, after which VIII abstracts hydride ion from the system to give 2-methylspiro[5.5]undecane. The 2-methylspiro[5.5]undecane obtained as the predominant product may undergo further reaction as is shown in Table II and by the decrease in relative yield with increasing time seen in Table I.

SCHEME I



As the products have the molecular formula, $C_{12}H_{22}$, it is apparent that two hydrogen must have been abstracted from the reaction medium. It is known that alkyl carbonium ions can more readily accept hydrogen from the α carbon of a double bond to form an allylic-stabilized carbonium ion than from a paraffin; so the fact that dicyclohexyl can be produced only in reaction condition ii, in which cyclohexene is present in excess, may be reasonably explained. The intermediates IV

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[6] R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 685.

[7] R. P. Linstead, A. F. Millidge, S. L. S. Thomas, and A. L. Walpole, *J. Chem. Soc.*, 1146 (1937).

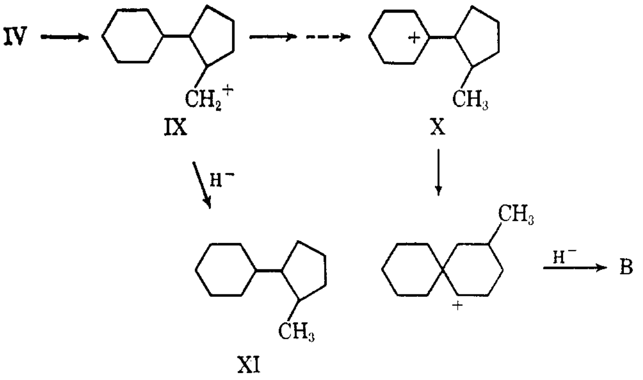
[8] This compound was prepared by Naro's method: J. A. Dixon and P. L. Naro, *J. Org. Chem.*, **26**, 2094 (1961).

[9] G. A. Olah in "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 89.

[10] This proposed reaction path is similar to that considered in the formation of the spiro ketone from 1,1,-dihydroxydicyclohexyl: M. Qudrat-I-Kuda and A. K. Ray, *J. Indian Chem. Soc.*, **16**, 525 (1939).

[11] A support for the mechanism to proceed *via* the intermediate VI is the fact that 7-chlorospiro[5.6]dodecane also gives the same products as those obtained from cyclohexene in the present condition. The details of the results will be reported in the near future.

[12] Another possible mechanism for the formation of 2-methylspiro[5.5]undecane is as follows. From this mechanism, the formation of 1-cyclohexyl-2-methyl cyclopentane along with the spiro compound B will be considerable. However the expected compound as 1-cyclohexyl-2-methylcyclopentane (XI) was not detected among the reaction products. Thus this mechanism is improbable.



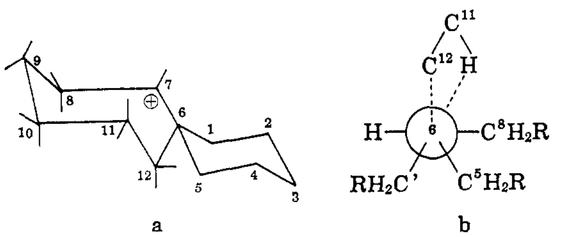


Figure 1.—The probable conformation (a) for the intermediate VI and the probable transition state (b) from VI leading to the intermediate VII.

or V (in Scheme I) may abstract hydride ion from the excess cyclohexene before isomerizing to VI.

The isomerization of paraffins such as *n*-hexane by aluminum chloride has been described previously.[13] Thus it is reasonable to assume that *n*-hexane acts only as the source of hydrogen.[14] Moreover, Watterman, *et al.*,[5] have reported that the higher polymers obtained from cyclohexene were highly unsaturated. Therefore in the reactions described above, it is possible that cyclohexene, the polymer of cyclohexene, and *n*-hexane act as the sources of hydrogen.

These proposals suggest that the conformation at the transition state may be important. Figure 1a shows the most probable conformation for the intermediate VI in which both rings have distorted chair forms. Owing to their steric hindrance, other conformation may not play an important role in the process of giving 2-methylspiro[5.5]undecane.

As is shown in Figure 1a the transannular hydrogen at C-11 occupies the preferential position for transfer of hydrogen to the C-7 which is positively charged. Hence the transition state 2b may be possible and the intermediate VII will further isomerize to VIII, ultimately resulting in the formation of 2-methylspiro[5.5]undecane. Along with the reaction described above it may be possible that the intermediate VII could isomerize to VIII′ which would give 1-methylspiro-[5.5]undecane as a final product. However such a product was not observed. This may be understood by considering the configuration of VIII′ where the methylene group at the C-1 position would interact strongly with the hydrogen at C-7 making the formation of the 1-methyl isomer unlikely.

The result that dicyclohexyl was not formed predominantly in this reaction may be explained by the absence of an effective hydrogen source such as cyclohexene and also by the following viewpoint. A counterion in the intermediate V which may be described as $AlCl_3OH^-$ will exist in the neighborhood of the cation and will resist the attack of hydride ion. From this consideration V may either convert to cyclohexylcyclohexene (I) by giving up a proton or it may convert to VIII in which the attack of hydride ion is easier. However, as was mentioned previously, cyclohexylcyclohexene was not stable in this reaction system giving similar products as were obtained from cyclohexene. The above considerations may also be applied to explain why spiro[5.6]dodecane is not produced in these reaction systems.

Experimental Section

Materials.—Cyclohexene[15] was prepared by the dehydration of cyclohexanol with phosphoric acid and was distilled over sodium, bp 81–82° (760 mm). *n*-Hexane was purified by the ordinary method and was dried over sodium. Aluminum chloride of technical grade was used.

The Reaction of Cyclohexene with Aluminum Chloride. Reaction Condition i.—To a mixture of 13.5 g (0.1 mole) of aluminum chloride and 200 ml of *n*-hexane at 68°, 8.2 g (0.1 mole) of cyclohexene was added with stirring during 10 min. The reaction was continued under reflux for a definite time measured from the beginning of the addition of the cyclohexene. Then the solution was washed with water and the organic layer was separated and dried over anhydrous Na_2SO_4. After removing the solvent, the products were separated by distillation under reduced pressure into a dimer fraction [bp 80–82° (7 mm)] and a residue.

Reaction Condition ii.—Into a four-necked reaction flask equipped with a thermometer, reflux condenser, and a dropping funnel was added 200 ml of *n*-hexane, 13.5 g (0.1 mole) of aluminum chloride, and 8.2 g (0.1 mole) of cyclohexene. Then the mixture was heated to reflux temperature. The reaction time was measured from the beginning of reflux. The product thus formed was treated as described above in the case of reaction condition i.

The Preparation of 2-Methylspiro[5.5]undecane (B).—Spiro[5.5]undecane-2-one[16] was prepared in two steps from spiro-[5.5]undecane-2.4-dione. 2-Methylspiro[5.5]undecene was prepared by the action of methylmagnesium iodide on the spiro ketone, bp 58–60° (10 mm). A bromine test gave a positive result. 2-Methylspiro[5.5]undecane was prepared from 2-methylspiro[5.5]undecene using Raney nickel and hydrogen (117 atm) at 80°, bp 79–80° (9 mm), $n^{20}{}_{D}$ 1.4655. A bromine test gave a negative result.

Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.43; H, 13.58.

The Preparation of 1-Methylspiro[5.5]undecane.—Spiro[5.5]-undecane-1-one was prepared by the modification of Naro's method.[8] 1-Methylspiro[5.5]undecane was prepared from the spiro ketone in the same routes as was used in the preparation of 2-methyl derivative.

Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.34; H, 13.64.

The Preparation of Dicyclohexyl (C).—Dicyclohexyl was prepared by the reduction of diphenyl over Raney nickel at 100° (120 atm), bp 238° (760 mm).

The Reaction of Dicyclohexyl with Aluminum Chloride.—A mixture of 1.7 g of aluminum chloride and 150 ml of *n*-hexane was heated at 68°. Then 2.0 g of dicyclohexyl was added during 10 min and the reaction was continued at the same temperature for 4 hr. The product was treated as described above and 1.8 g (90%) of dimeric fraction was obtained, bp 85–88° (10 mm).

The Reaction of Cyclohexylcyclohexene (I) with Aluminum Chloride.—Cyclohexylcyclohexene (2.0 g) was treated with 1.7 g of aluminum chloride in *n*-hexane for 1.5 hr under reflux, and 1.9 g (95%) of dimeric fraction and 0.1 g (5%) of residue were obtained. The dimeric fraction showed a boiling point at 95–105° (40 mm).

The Reaction of Cyclohexene in No Solvent.—Aluminum chloride (15.0 g) was added to 25.0 g of refluxing cyclohexene and the mixture was maintained at 80° for 1 hr. The cyclohexene reacted almost quantitatively and 3.1 g (12.4%) of dimeric fraction was obtained.

The Isolation of 2-Methylspiro[5.5]undecane by Preparative Gas Chromatography.—2-Methylspiro[5.5]undecane was isolated from the dimeric fraction by a Yanagimoto Model GCS-100 preparative gas chromatograph using a column coated with silicon hivac grease. Hydrogen at 0.4 atm was used as a carrier gas and the column temperature was 156°. The separated sample was shown to be pure by analytical gas–liquid partition chromatography, $n^{20}{}_{D}$ 1.4600.

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[13] G. M. Kramer, R. M. Skomoroaki, and J. A. Hinlicky, *J. Org. Chem.*, **28**, 1029 (1963).

[14] The question of whether *n*-hexane shapes the skeleton of the main products was examined by the treating cyclohexene without *n*-hexane as the solvent. The main products thus formed were the same as those obtained in *n*-hexane solution. Therefore it was concluded that *n*-hexane does not influence the nature of the main products.

[15] B. B. Corson and V. N. Ipatieff, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p 151.

[16] W. S. G. P. Norris, *J. Chem. Soc.*, 245 (1926).

Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.40; H, 13.26.

The Isolation of Dicyclohexyl by Preparative Gas Chromatography.—The conditions used for the separation of dicyclohexyl was the same as that used for 2-methylspiro[5.5]undecane, $n^{20.0}\text{D}$ 1.4780 (lit.[17] $n^{21.1}\text{D}$ 1.4798).

Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.34. Found: C, 86.67; H, 13.04.

Vapor Phase Chromatography.—Routine separation and quantitative determinations were carried out on a Yanagimoto Model GCS-100 gas chromatograph. A 2 m × 0.25 in. stainless steel column packed with silicone hivac grease was used. The column temperature was kept at 156° for all dimeric fractions. Hydrogen (70 ml/min) was used as the carrier gas. The retention times in minutes were as follows: 6.5 (A), 9 (B), and 12.5 (C).

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[17] W. Hückel, O. Neunhoeffer, A. Gercke, and E. Frank, *Ann.*, **477**, 99 (1930).

Alkylations of Heterocyclic Ambident Anions. I. 2-Hydroxypyrimidines[1a]

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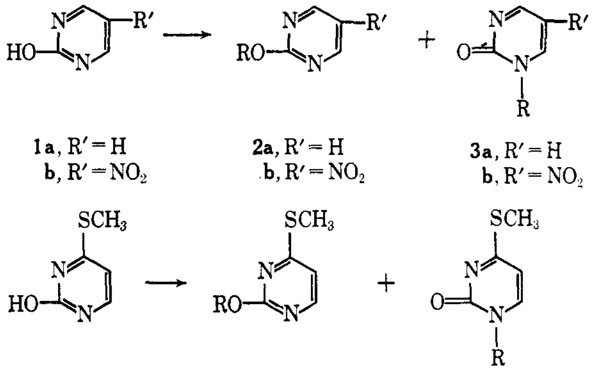
The reaction of salts of 2-hydroxypyrimidine, 2-hydroxy-5-nitropyrimidine, and 2-hydroxy-4-methylthiopyrimidine with alkyl halides and tosylates was investigated. The site of alkylation is primarily a function of the alkylating agent and is insensitive to a variety of experimental and structural variations. Steric factors are proposed to account for the influence of alkylating agent, while insensitivity to other variables is related to the structure of the anions. The preparation, identification, and physical properties of several new alkyl derivatives of the pyrimidines are reported.

We have initiated a study to evaluate the sensitivity of simple monohydroxypyrimidines[2] and related heterocyclic compounds toward factors which are known to influence alkylation sites in other systems such as phenols, enols, and nitroalkanes. We report here the results of an examination of the alkylation of 2-hydroxypyrimidine (**1a**), 2-hydroxy-5-nitropyrimidine (**1b**), and 2-hydroxy-4-methylthiopyrimidine (**4**) with simple alkyl halides, benzyl halides, and tosylates.

Recent alkylation studies,[3] particularly by Kornblum,[4] have been useful in indicating those factors which could be of importance in governing the site of alkylation of heterocyclic ambident anions. Although there have been many investigations and examples of this method of alkylation with hydroxypyrimidines[5a] and related heterocyclic compounds,[5b–g] studies in this area have been limited by technical difficulties associated with the separation and analysis of resulting product mixtures.

Alkali metal and silver salts of **1a**, **1b**, and **4** were treated with alkyl and benzyl halides or tosylates under conditions in which variables such as alkylating agent, solvent, and metal salt were changed systematically. The product distributions resulting from these transformations were conveniently determined by quantitative vapor phase chromatography based on calibrations established with authentic samples of each alkylation product. Although two isomeric nitrogen alkylated products could have formed from the unsymmetrical pyrimidine **4**, 3-alkyl-4-methylthio-2-pyrimidones were not detected. Similarly, no product resulting from carbon alkylation was found. (See Scheme I.)

SCHEME I



1a, R′ = H
b, R′ = NO_2
2a, R′ = H
b, R′ = NO_2
3a, R′ = H
b, R′ = NO_2
4
5
6

Results and Discussion

Pertinent product distribution data are presented either in Tables I–IV or discussed in general terms in the following text and are representative of a larger amount of data actually obtained.

The ratio of nitrogen to oxygen alkylation observed with salts of the 2-hydroxypyrimidines depends primarily on the alkylating agent. Results of representative studies in dimethylformamide at room temperature with sodium salts are summarized in Table I. Oxygen alkylation progressively increases from negligible amounts to as much as 56% when the halides are varied from methyl or benzyl to isopropyl. Treatment of **4** with isopropyl halides gives more oxygen alkylation than does **1a** or **1b**. Since alkylation occurs at only one nitrogen in **4** compared to two in **1a** and **1b**, the increased oxygen alkylation with **4** is attributed to a statistical factor. While models show considerable steric opposition to the formation of 3-

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[1] (a) This investigation was supported by Public Health Service Research Grant No. GM-12112 from the National Institute of General Medical Sciences; (b) Allied Chemical Corp. Fellow, 1964–1965.

[2] Although generally existing in the lactam structure, the term hydroxypyrimidine will be used to indicate the presence of an ionizable hydrogen and serve to distinguish these compounds from N-alkylated pyrimidones.

[3] A. Brändström, *Arkiv Kemi*, **6**, 155 (1953).

[4] (a) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955); (b) N. Kornblum, P. J. Berrigan, and W. J. LeNoble, *ibid.*, **85**, 1141 (1963); (c) N. Kornblum, R. Seltzer, and P. Haberfield, *ibid.*, **85**, 1148 (1963), and references therein.

[5] Brief accounts of early work in this area and leading references are contained in the following monographs: (a) D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp 359–371; (b) H. Meislich, "Pyridine and Its Derivatives," Part III, E. Klingsberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, pp 631–640; (c) R. C. Elderfield, "Heterocyclic Compounds," Vol IV, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, pp 151–153; (d) W. J. Gensler, 5c, p 435; (e) T. L. Jacobs, "Heterocyclic Compounds," Vol VI, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, pp 121, 122, 132; (f) J. C. E. Simpson, "Condensed Pyridazine and Pyrazine Rings," Interscience Publishers, Inc., New York, N. Y., 1953, p 241; (g) T. A. Williamson, ref 5e, pp 354–356.