Reactions of Epoxides of 5-Norbornene-2,3-dicarboximides. A Concerted, Reductive Cleavage of the Imide Ring by Lithium Aluminum Hydride

ALLAN P. GRAY[1] AND DONALD E. HEITMEIER

Neisler Laboratories, Inc., Decatur, Illinois

Received March 28, 1969

Both N-phenethyl-*exo*-5,6-epoxynorbornane-*endo*-2,3-dicarboximide (**1c**) and its *exo*-dicarboximide isomer (**4**) are stable to vigorous acid treatment. The stability of these norbornene epoxide systems under acid conditions is interpreted in terms of the electron-withdrawing effect of the carbonyl groups inhibiting carbonium ion formation, coupled with steric hindrance of the norbornyl system to intermolecular, backside nucleophilic attack. The epoxide function of these systems is also stable to intermolecular attack under basic conditions. Intramolecular opening of the epoxide ring by appropriately situated nucleophiles can, of course, occur with facility, and peracetic acid epoxidation of *endo*-3-(N-phenethylcarbamyl)-5-norbornene-*endo*-2-carboxylic acid (**12**) proceeds with accompanying attack on the formed (or forming) epoxide function and formation of diol derivatives. Lithium aluminum hydride reduction of N-phenethyl-5-norbornene-*exo*- or *endo*-2,3-dicarboximide gives the expected 4,7-methanohexahydroisoindole (**5** or **3**, respectively). Reduction of **12** also yields **3** in a reductive alkylation process. Lithium aluminum hydride reduction of **4** affords 2-phenethyl-*exo*-5,6-epoxy-*exo*-4,7-methanooctahydroisoindole (**6**) retaining the oxirane ring. On the other hand, treatment of **1c** with lithium aluminum hydride yields N-phenethyl-*endo*-3-hydroxymethyl-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (**9**), formation of which requires reductive cleavage of both the imide and oxirane rings. **9** must arise *via* a concerted, intramolecular process with participation by the epoxide function. Analogs of **9** with other N substituents, and their mono- and diacyl derivatives have been prepared. Treatment of **6** with a small excess of ethereal hydrogen chloride in the cold gives the normal hydrochloride salt, but, when **6** is subjected to a larger excess of ethereal hydrogen chloride in the cold, the chlorohydrin **15** is produced *via* a typical norbornyl carbonium ion rearrangement. This underlines the effect of the electron-withdrawing power of the carbonyl groups in stabilizing the norbornene epoxide system.

Preceding papers dealt with the epoxidation and subsequent reactions of *cis*-Δ^4-tetrahydrophthalic anhydride and derived imides[2] and the rates of epoxidation of corresponding, rigidly fixed, *endo*-methylene (*i.e.*, norbornene) derivatives[3] and provided support for the thesis that tetrahydrophthalic anhydride exists predominantly in an equatorial half-boat conformation.[2-4] In continuing work in this area, we began to examine reactions of the *exo*-5,6-epoxynorbornane-2,3-dicarboximides at hand and were quickly struck by the unusual chemical properties of this ring system. The present report is concerned particularly with the stability of the oxirane ring to acid and with the action of lithium aluminum hydride on these compounds.

The norbornene ring system has been shown to be relatively deactivated to electrophilic attack by the electron-withdrawing effect of attached carbonyl groups.[3,5] Although norbornene epoxides generally undergo acid-catalyzed oxirane ring opening and the typical rearrangements *via* "bridged" (whether "classical" or "nonclassical") carbonium ions with great facility,[6] the literature suggests that epoxynorbornanecarboxylic acid derivatives are more resistant to the effects of acid. Thus, the oxirane ring of *exo*-5,6-epoxynorbornane-*exo*-2,3-dicarboxylic acid is not opened by brief heating in water although it is opened by prolonged heating to give a hydroxylactonic acid of undetermined structure;[7] the oxygen counterpart of this compound (*i.e.*, endoxy in place of *endo*-methylene) retains its oxirane ring through treatment with boiling acetyl chloride, acetic anhydride, and boiling sulfuric acid in methanol;[8] of particular interest is the report that *exo*-5,6-epoxynorbornane-2-carboxylic acid undergoes the typical, acid-catalyzed norbornyl rearrangement, *via* carbonium ion formation on the side away from the carboxyl group, *viz.*, A.[9]

A

In the present work, epoxidation of norbornenedicarboximides with commercial peracetic acid could be effected without neutralization of contained sulfuric acid to prevent cleavage of the oxirane ring, and excellent yields of epoxides were obtained. In fact, treatment of either N-phenethyl-*exo*-5,6-epoxynorbornane-*endo*-2,3-dicarboximide (**1c**) or its *exo*-dicarboximide isomer (**4**) with sulfuric acid in boiling methanol, conditions which had smoothly effected oxirane ring opening of analogous 4,5-epoxy-*cis*-hexahydrophthalimides,[2] resulted in essentially quantitative recovery of starting material. Although the epoxide function of epoxyhexahydrophthalimides could be analytically determined by Siggia's reagent (aqueous calcium chloride–hydrochloric acid),[2,10] no epoxide function (*i.e.*, no ring opening) could be detected when **1c** and **4** were subjected to the same reagent, even with heat. Explanation clearly lies in the blocking of carbonium ion formation by the appended carbonyl groups coupled with the steric hindrance to backside nucleophilic attack offered by the puckered norbornyl system.[3,5,8] It seems most likely that the electron-withdrawing in-

(1) To whom correspondence should be addressed: Department of Pharmacology, College of Medicine, University of Vermont, Burlington, Vt.

(2) A. P. Gray, D. E. Heitmeier, and H. Kraus, *J. Amer. Chem. Soc.*, **84**, 89 (1962).

(3) A. P. Gray and D. E. Heitmeier, *J. Org. Chem.*, **30**, 1226 (1965).

(4) See also G. I. Fray, R. J. Hilton, and J. M. Teire, *J. Chem. Soc., C*, 592 (1966).

(5) And references cited in ref 3. Also see J. A. Berson and R. Swidler, *J. Amer. Chem. Soc.*, **76**, 4057 (1954); J. A. Berson in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 166–168.

(6) H. M. Walborsky and D. F. Loncrini, *J. Amer. Chem. Soc.*, **76**, 5396 (1954); H. Kwart and W. G. Vosburgh, *ibid*, **76**, 5400 (1954).

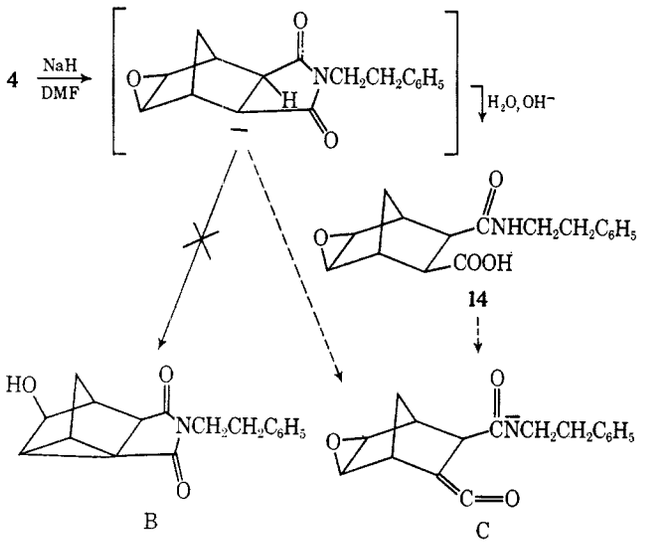
(7) J. A. Berson and S. Suzuki, *ibid.*, **80**, 4341 (1958).

(8) Yu. K. Yur'ev and N. S. Zefirov, *J. Gen. Chem. USSR*, **31**, 772 (1961).

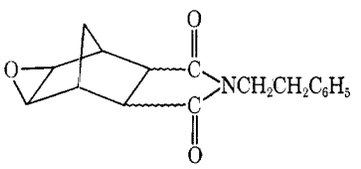
(9) G. Berti, F. Bottari, and B. Macchia, *Gazz. Chim. Ital.*, **90**, 1763 (1960).

(10) S. Siggia, "Quantitative Analysis *via* functional Groups," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1954, p 157.

SCHEME I



fluence of the carbonyl groups is exercised across space by a field effect, as the evidence suggests is the case in the deactivation of the norbornene double bond to per acid attack,[8] and also through a direct inductive effect on the norbornane system. An inductive effect would be expected to have the more important influence in stabilizing the epoxide ring to acidic reagents but present evidence does not cast additional light on the "classical" *vs.* "nonclassical" carbonium ion question.

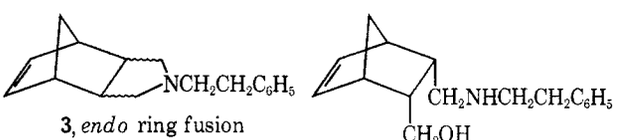


1c, *endo*-imide
4, *exo*-imide

That the epoxide ring was similarly stable under basic conditions, at least to *intermolecular* nucleophilic displacement, was indicated by its retention on treatment of **4** with sodium hydride in dimethylformamide followed by the addition of water. Originally, it had been hoped that the anion derived from **4**, which with the imide ring *exo* should be in the optimum configuration for intramolecular construction of a three-membered ring,[11] would lead to the admittedly highly strained nortricyclene derivative B. Instead, opening of the imide ring and retention of the epoxide function gave *exo*-3-(N-phenethylcarbamyl)-*exo*-5,6-epoxynorbornane-*exo*-2-carboxylic acid (**14**) as the sole isolable product in 58% yield. It has not been proven that isomerization of the carboxyl and/or carbamyl functions had not occurred, but it seems unlikely since from the *endo* position under the alkaline conditions either of these groups should have effected *intramolecular* opening of the oxirane ring. This would appear to argue against a rather attractive ketene intermediate (C) which might have been expected to favor *exo*-proton addition. (A referee has, however, made the valid point that thermodynamic control of proton addition could well have produced **14** *via* C.) It is clear, in any event, that intermolecular nucleophilic displacement on the epoxide function by hydroxide ion did not occur under the conditions (see Scheme I).

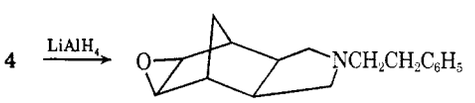
Intramolecular nucleophilic attack on the epoxide function of *exo*-epoxynorbornane derivatives has been amply demonstrated to take place with extreme facility and may follow[7,12] or actually participate in[12] the epoxidation process. Epoxidation of *endo*-3-(N-phenethylcarbamyl)-5-norbornene-*endo*-2-carboxylic acid (**12**), prepared by the reaction of the anhydride with phenethylamine at room temperature, gave, albeit in very low yield, two glycol derivatives (**2** and **13**) which could only have arisen *via* intramolecular backside opening of the oxirane ring (Scheme II). It is not clear whether displacement is on the formed or forming epoxide, but no epoxide product was isolated. The stereochemistry of **2** and **13** is presumed by analogy.

It has long been known[13] that, owing to steric hindrance, reductive cleavage of the oxirane ring of norbornene epoxides by lithium aluminum hydride proceeds extremely slowly, requiring up to 7 days at reflux in tetrahydrofuran solution.[13] It is considered that reduction involves backside attack by hydride facilitated by electrophilic coordination of the oxygen by a trivalent aluminum complex.[14] Lithium aluminum hydride reduction of either N-phenethyl-5-norbornene-*exo*- or -*endo*-2,3-dicarboximide smoothly gave the expected 4,7-methanohexahydroisoindole (**5** or **3**, respectively) in good yield. Interestingly, action of lithium



3, *endo* ring fusion
5, *exo* ring fusion
D

aluminum hydride on the *endo*-amide acid **12** likewise gave **3** in a yield of 50%, indicative either of a base-catalyzed acylation prior to reduction or, more plausibly, of a reductive alkylation process. None of the anticipated amino alcohol D was obtained. Treatment of the *exo*-epoxy-*exo*-imide **4** with lithium aluminum hydride in boiling tetrahydrofuran over a period of 6 hr yielded 61% 2-phenethyl-*exo*-5,6-epoxy-*exo*-4,7-methanooctahydroisoindole (**6**) with no evidence detected of the concomitant formation of a product of reductive cleavage of the oxirane ring. The retention of the epoxy function again underlines the stability of the ring system as long as attack is intermolecular.



6

Analytical data for **2**, **3**, **5**, and **6** appear in Table I.

In view of the foregoing, we were intrigued to find that lithium aluminum hydride reduction of the *exo*-epoxy-*endo*-imide **1c** under similar conditions resulted in smooth opening of the imide ring and, presumably, intramolecular backside attack on the oxirane ring to provide N-phenethyl-*endo*-3-hydroxymethyl-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (**9**) in 63%

(11) See A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3914 (1967); **89**, 3915 (1967).

(12) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 221 (1959).

(13) S. B. Soloway and S. J. Cristol, *J. Org. Chem.*, **25**, 327 (1960); see also Walborsky and Loncrini.[6]

(14) H. Kwart and T. Takeshita, *ibid.*, **28**, 670 (1963).

SCHEME II

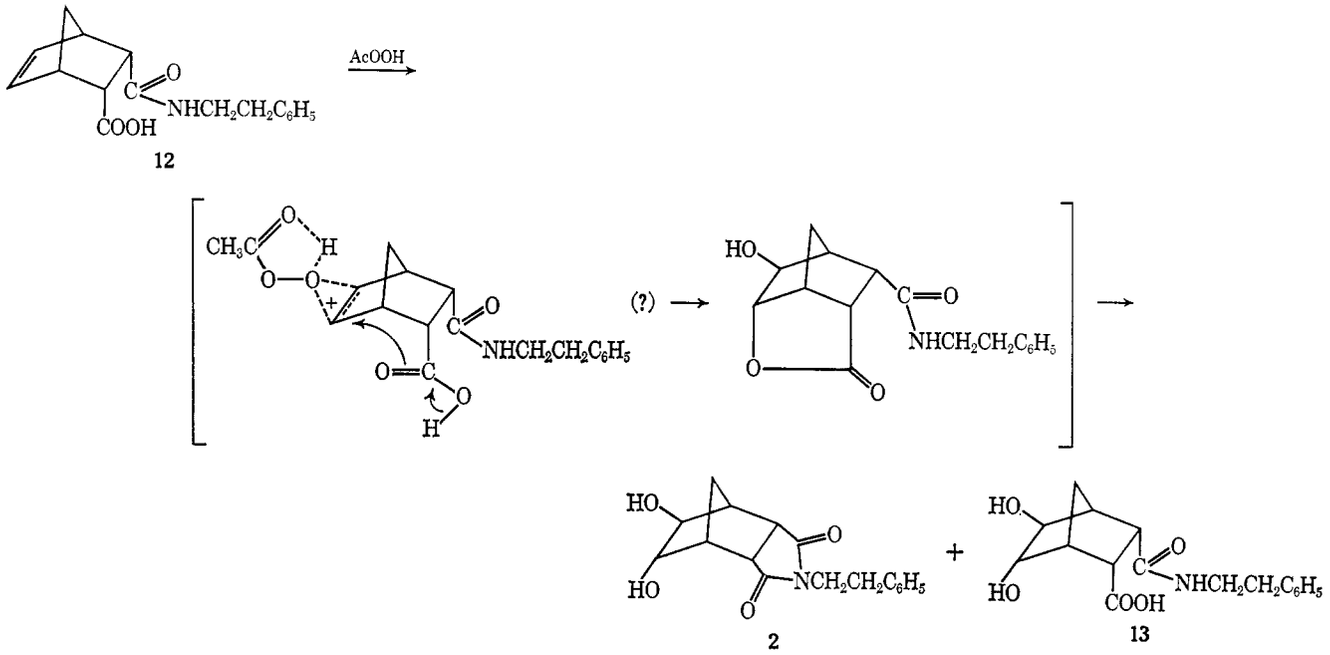
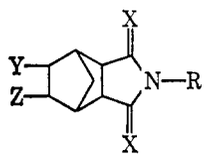


TABLE I

NORBORNENEDICARBOXIMIDE DERIVATIVES



Compd	R	X	Y,Z	Salt	Mp, °C[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Halogen, %[b] Calcd	Halogen, %[b] Found
						A. *endo* Ring Fusion								
1a	Ethyl	O	*exo*-Epoxy		101.5–104	$C_{11}H_{13}NO_3$	63.75	64.00	6.32	6.13	6.76	6.67		
1b	Benzyl	O	*exo*-Epoxy		109–111.5	$C_{16}H_{15}NO_3$	71.36	71.68	5.61	5.69	5.20	5.16		
1d	Phenylpropyl	O	*exo*-Epoxy		95.5–97.5	$C_{18}H_{19}NO_3$	72.72	72.83	6.44	6.36	4.74	4.57		
2	Phenethyl	O	*exo,endo*-Di-OH		186–187	$C_{17}H_{19}NO_4$	67.76	67.70	6.36	6.18	301.3[c]	300.5[c]		
3	Phenethyl	H_2	Δ	HCl	225–228	$C_{17}H_{22}ClN$	74.04	73.94	8.03	7.97			12.85	12.67
						B. *exo* Ring Fusion								
5	Phenethyl	H_2	Δ	HCl	286–287	$C_{17}H_{22}ClN$	74.04	73.90	8.03	8.09			12.85	12.88
6	Phenethyl	H_2	*exo*-Epoxy		52–56	$C_{17}H_{21}NO$					5.48	5.32[d]		
				HCl	217	$C_{17}H_{22}ClNO$	69.95	69.73	7.60	7.53			12.15	12.27

[a] Melting points are corrected. [b] Ionic halogen by potentiometric titration. [c] One-half saponification equivalent. [d] "Basic" nitrogen by titration with acetous–perchloric acid.

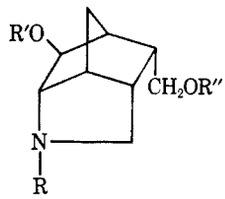
yield. The stereochemistry of **9** was not proved but appears to follow inevitably from the nature of the processes which must be involved. The other *exo*-epoxy-*endo*-imides, **1a**, **1b**, and **1d** (Table I), afforded th corresponding methaniminonorbornane derivatives lis ed in Table II in yields of up to 80%.

Although certain succinimides with specific N substituents capable of contributing to the stabilization of an anionic charge on nitrogen have been reported to give significant yields (up to 35%) of hydrogenolyzed amino alcohols as minor products accompanying the normal pyrrolidine derivatives,[15] it should be noted that in the present series, with N substituents (ethyl, benzyl, phenethyl, and phenylpropyl) which would have caused —and in the case of benzyl did in fact cause—zero hydrogenolysis in the succinimide series,[15] reductive cleavage of the imide ring was at least the major reaction course. Further, it is significant that neither the *endo*- or the *exo*-imide without the epoxy group nor the *exo*-epoxy-*exo*-imide **4** was hydrogenolyzed by lithium aluminum hydride under essentially the same conditions. In fact, in the case of the amide acid **12**, the reverse was true and reductive cyclization to **3** prevailed. These data certainly show that no special instability attaches to a five-membered imide ring fused either *exo* or *endo* to the 2,3 positions of a norbornene nucleus and, moreover, that the reductive cleavage must involve the epoxy function and its special spatial relationship to the *endo*-imide ring. A concerted process is clearly implicated and, because the nitrogen-containing ring is more flexible and the nitrogen can approach the epoxide ring carbons somewhat more closely when the initially carbonyl carbons of the imide ring have been converted from sp^2 into an sp^3 state, we envisage the reaction as proceeding along something like the path shown in Scheme III. The precise mechanism may, of course, differ in detail from this representation of the sequence of events but any explanation to be plausible must incorporate a concerted process with participation by the epoxide function.

(15) K. C. Schrieber and V. P. Fernandez, *J. Org. Chem.*, **26**, 1744 (1961).

TABLE II

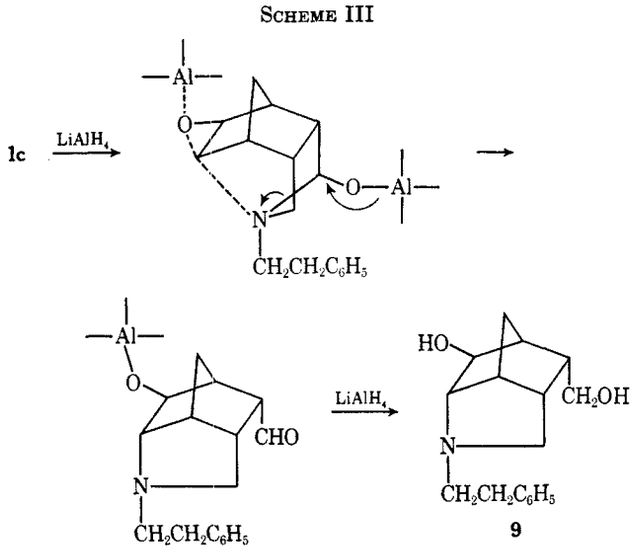
REDUCTION PRODUCTS OF NORBORNENE-*endo*-DICARBOXIMIDES



Compd	R	R′	R″,	Salt	Mp, °C[a]	Formula	—Carbon, %— Calcd	Found	Hydrogen, % Calcd	Found	Nitrogen, %[b] Calcd	Found	Halogen, %[c] Calcd	Found
7	Ethyl	H	H		67–70	$C_{11}H_{19}NO_2$					7.10	6.82		
7a	Ethyl	H	Propionyl	HCl	88–92	$C_{14}H_{24}ClNO_3$	58.03	57.76	8.35	8.66			12.24	12.21
8	Benzyl	H	H		115–118	$C_{16}H_{21}NO_2$					5.40	5.32		
				HCl	201–203	$C_{16}H_{22}ClNO_2$	64.98	64.81	7.50	7.22			11.98	11.86
8a	Benzyl	H	Propionyl	HCl	>75	$C_{19}H_{26}ClNO_3$	64.84	64.26	7.45	7.12	175.9[d]	177.9[d]	10.08	10.04
9	Phenethyl	H	H		106–107	$C_{17}H_{23}NO_2$					5.13	5.16		
				HCl	195–196	$C_{17}H_{24}ClNO_2$	65.88	66.18	7.80	7.91			11.44	11.37
9a	Phenethyl	H	Acetyl	HCl	85–96	$C_{19}H_{26}ClNO_3$	64.84	64.58	7.45	7.32			10.08	10.28
9b	Phenethyl	H	Propionyl	HCl	174–175	$C_{20}H_{28}ClNO_3$	65.65	65.12	7.71	7.65			9.69	9.61
9c	Phenethyl	H	Phenoxycarbonyl		91–93	$C_{24}H_{27}NO_4$					3.56	3.50		
				HCl	103–111	$C_{24}H_{28}ClNO_4$	67.03	67.01	6.56	6.70			8.25	8.21
9d	Phenethyl	H	Carbamoyl		139–141	$C_{18}H_{24}N_2O_3$					4.43	4.35		
				HCl	126–136	$C_{18}H_{25}ClN_2O_3$	61.26	60.81	7.14	7.19			10.05	10.11
9e	Phenethyl	Carbamoyl	Carbamoyl		150–152	$C_{19}H_{25}N_3O_4$					3.90	3.72		
				HCl	213–214	$C_{19}H_{26}ClN_3O_4$	57.64	57.52	6.62	6.47			8.95	8.93
10	Phenyl-propyl	H	H		85–87	$C_{18}H_{23}NO_2$					4.87	4.85		
				HCl	151–154	$C_{18}H_{24}ClNO_2$	66.75	66.81	8.09	8.31			10.95	10.88
10a	Phenyl-propyl	Acetyl	Acetyl	HCl	154–157	$C_{22}H_{30}ClNO_4$	64.77	65.07	7.41	7.57			8.69	8.72
11	Cyclohexyl-methyl	H	H	HCl	154–157	$C_{18}H_{32}ClNO_2 \cdot {}^1/_4H_2O$	62.75	62.31 62.52	9.38	9.26 9.05	1.47[e]	1.06[e]	11.58	11.50

[a] See footnote *a*, Table I. [b] "Basic" nitrogen by acetous–perchloric titration. [c] See footnote *b*, Table I. [d] Saponification equivalent. [e] Water by Karl Fischer titration.

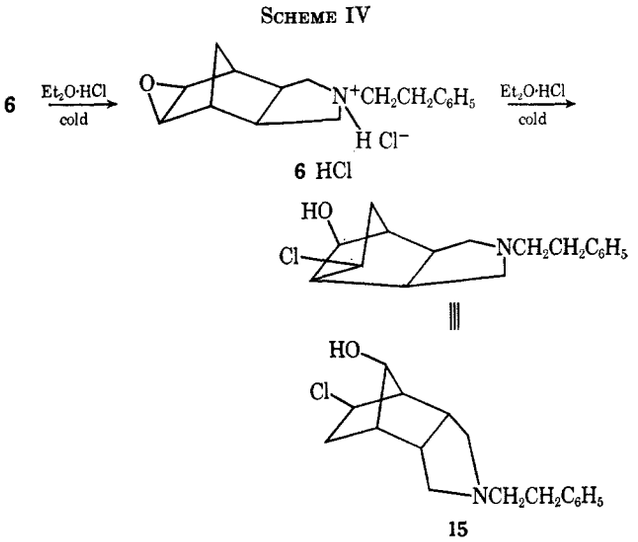
SCHEME III



Treatment of the methaniminonorbornanediols with 1 equiv of acylating agent in the presence of base cleanly provided the monoacyl derivatives indicated in Table II, presumed to be esterified at the primary hydroxyl group. Use of excess esterifying agent afforded diacylated derivatives.

Underlining the influence of the electron-withdrawing power of the carbonyl groups in stabilizing the norbornene epoxide system is the contrasting lability of the analogous epoxy derivative (**6**) in which the carbonyl groups have been reduced. Treatment of an ice-cold ether solution of **6** with a slight excess of ethereal hydrogen chloride gave the hydrochloride salt of **6**, which could be recrystallized from alcohol with retention of the epoxide ring and without skeletal rearrangement. Use of a larger excess of ethereal hydrogen chloride, still in the cold, effected rearrangement and formation of 51% hydrochloride salt of a chlorohydrin, considered to be **15** on the presumption of a typical norbornyl carbonium ion process[16] (Scheme IV)

SCHEME IV



Experimental Section[17]

Materials.—N-substituted 5-norbornene-2,3-dicarboximides and the corresponding epoxy derivatives were prepared essentially

(16) At least **15** should be the principal product. See J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

(17) Analyses were performed by the Galbraith Laboratories, Knoxville, Tenn. See footnotes *a*, *b*, and *d*, Table I. Infrared spectra were determined with a Beckman Model IR-5 spectrophotometer; peak positions are given in reciprocal centimeters. Nmr spectra were determined with a Varian Model A-60; pertinent chemical shifts are expressed in parts per million downfield from tetramethylsilane and coupling constants are in cycles per second.

according to the procedures described in our earlier paper.[3] N-Ethyl-5-norbornene-*endo*-2,3-dicarboximide showed mp 76–79° (lit.[18] mp 77–79°); the N-benzyl compound showed mp 83–85° (lit.[19] mp 82.5–83.5°); the N-phenylpropyl compound was an oil, epoxidized without purification. The preparation of N-phenethyl-*exo*-5,6-epoxynorbornane-*endo*-2,3-dicarboximide (**1c**) and the *-exo*-2,3-dicarboximide isomer (**4**) has been reported.[3]

Treatment of N-Phenethyl-*exo*-5,6-epoxynorbornane-2,3-dicarboximides (1c and 4) with Acid.—A solution of 38.0 g of **1c** in 300 ml of methanol containing 8 drops of concentrated sulfuric acid was heated for 6 hr at reflux, essentially the conditions used for the methanolysis of the analogous 4,5β-epoxy-*cis*-hexahydrophthalimides.[2] Colorless needles [35.3 g (93%)] of recovered **1c** crystallized from the solution which was allowed to stand at room temperature: mp 130–133°, pure **1c** mp 134–136°,[3] mixture melting point undepressed. The ir spectrum[3] demonstrated retention of the epoxide ring: nmr ($CDCl_3$) δ 7.28 (s, 5, phenyl protons), 3.8 (q, 2, NCH_2), 3.07 (broadened s, 2, epoxide ring protons[20]), 2.82 (broadened s, 2, imide ring protons), 1.6 (d, 1, J = 11 Hz, *endo*-methylene proton *syn* to epoxide ring[20]), 1.0 (d, 1, J = 11 Hz, *anti,endo*-methylene proton[20]), 3.0 (m, 4, remaining protons). No epoxide oxygen could be detected when **1c** was treated with Siggia's reagent (aqueous calcium chloride–hydrochloric acid).[10]

The *exo* isomer (**4**) likewise did not react with Siggia's reagent: nmr ($CDCl_3$) δ 7.28 (s, 5, phenyl protons), 3.8 (q, 2, NCH_2), 3.25 (broadened s, 2, epoxide ring protons[20]), 2.67 (d, 2, J = 1.5 Hz, imide ring protons), 1.3 (d, 1, J = 12 Hz, *endo*-methylene proton *syn* to epoxide ring), 0.4 (d, 1, J = 12 Hz, *anti,endo*-methylene proton[20]), 2.9 (m, 4).

***endo*-3-(N-Phenethylcarbamyl)-5-norbornene-*endo*-2-carboxylic Acid (12).**—To a solution of 159 g (0.97 mol) of 5-norbornene-*endo*-2,3-dicarboxylic anhydride in 2300 ml of benzene, cooled to 15°, was added, dropwise over a period of 35 min with stirring and maintenance of the temperature at 15–20°, a solution of 119 g (0.98 mol) of phenethylamine in 150 ml of benzene. The precipitated solid was recrystallized from ethanol and then dissolved in ice-cold 10% aqueous sodium hydroxide; the alkaline solution was washed with benzene and acidified with aqueous hydrochloric acid to precipitate 167 g (60%) of **12**, mp 152–154°. Recrystallization from ethanol yielded colorless needles, mp 155–156°.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.57; H, 6.71; neut equiv, 285.3. Found: C, 71.60; 6.69; neut equiv, 288.2.

Epoxidation of 12.—To a slurry of 80.0 g (0.28 mol) of **12** in 500 ml of chloroform was added, dropwise over a 15-min period with stirring and intermittent ice cooling to maintain the temperature between 35 and 40°, 54 ml of peracetic acid solution (FMC, *ca.* 44% peracetic acid by analysis, 0.36 mol) containing 3 g of sodium acetate trihydrate. After the addition was complete, the resultant solution was stirred at room temperature for 20 hr, washed with water, and then extracted with 5% aqueous sodium hydroxide. The remaining chloroform layer was again washed with water, dried, and concentrated under reduced pressure and the residue was crystallized from acetonitrile to yield 6.2 g (7.3%) of **N-phenethyl-*exo*-5-*endo*-6-dihydroxynorbornane-*endo*-2,3-dicarboximide (2)** as colorless needles: mp 186–187°; ir (KBr) 3440 (OH), 1770 (medium), and 1685 (strong, succinimide C=O[2,3]).

The aqueous alkaline layer was washed with ether, cooled, and acidified with aqueous hydrochloric acid to precipitate a solid which crystallized from methanol to give 4.0 g (4.5%) of ***endo*-3-(N-phenethylcarbamyl)-*exo*-5-*endo*-6-dihydroxynorbornane-*endo*-2-carboxylic acid (13)** as colorless crystals: mp 126–128°; ir (KBr) 3310 and 3125 (OH and amide NH), 2610 (bonded acid OH), 1700 (acid C=O), 1635 (amide C=O).

Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; neut equiv, 319.3. Found: C, 63.95; H, 6.67; neut equiv, 320.4.

No other product was isolated.

***exo*-3-(N-Phenethylcarbamyl)-*exo*-5,6-epoxynorbornane-*exo*-2-carboxylic Acid (14).**—A solution of 29.0 g (0.1 mol) of **4** in 150 ml of dry dimethylformamide was added, dropwise with stirring, to a slurry of 10.0 g of a 50% oil dispersion of sodium hydride (0.2 mol) in 100 ml of dry dimethylformamide. The reaction mixture was stirred for 6 hr at room temperature as a white precipitate gradually formed. Stirring was continued and the reaction mixture was cautiously treated, dropwise, with water. The aqueous solution was washed with chloroform, ice cooled, and acidified with 10% hydrochloric acid to precipitate a white solid which was recrystallized from isopropyl alcohol to yield 17.8 g (58%) of **14** in the form of fine, colorless needles: mp 170–171°; ir (KBr) 3345 (NH), 2650 (shoulder, bonded acid OH), 1725 (acid C=O), 1615 (amide C=O), 850 (norbornene epoxide[3]).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; neut equiv, 301.3. Found: C, 68.14; H, 6.42; neut equiv, 300.4.

Lithium Aluminum Hydride Reduction of *exo*-Imides. 2-Phenethyl-*exo*-5,6-epoxy-*exo*-4,7-methanooctahydroisoindole (6).—To a slurry of 15.2 g (0.4 mol) of lithium aluminum hydride in 300 ml of dry tetrahydrofuran was added, dropwise with stirring, a solution of 50.0 g (0.17 mol) of **4** in 250 ml of tetrahydrofuran. After the addition was complete, the reaction mixture was heated at reflux for 6 hr, allowed to cool, and treated dropwise with ethyl acetate to decompose excess lithium aluminum hydride. The reaction mixture was cooled in an ice bath and 200 ml of tetrahydrofuran followed by 50 ml of water was added. The aluminum hydroxide precipitate was filtered off and the filtrate was dried and concentrated to dryness under reduced pressure. Distillation of the residual oil afforded 33.6 g (75%) of crude **6** as an oil boiling over the range of 120–150° (0.2 mm), which solidified on standing. Recrystallization from pentane gave 27.3 g (61%) of **6**: mp 52–56°; ir ($CHCl_3$) OH band absent, C=O band absent, 1605 (phenyl), 847 (norbornene epoxide).

Treatment of an ice-cold, anhydrous ether solution of 10.0 g (0.039 mol) of **6** with ethereal hydrogen chloride (0.05 mol) and recrystallization of the precipitate from isopropyl alcohol gave 8.7 g (76%) of the **hydrochloride salt** as colorless needles: mp 217°; ir ($CHCl_3$) 1605 (phenyl), 848 (norbornene epoxide); nmr (CD_3OD) δ 7.38 (s, 5, phenyl protons), 3.8 (m, 2, NCH_2), 3.22 (broadened s, 2, epoxide ring protons), 1.29 (broadened s, 2, *endo*-methylene protons).

Effect of Acid on 6. 2-Phenethyl-*exo*-5-chloro-*syn*-8-hydroxy-*endo*-4,7-methanooctahydroisoindole (15).—An ice-cold, anhydrous ether solution of 12.2 g of **6** was treated with excess ethereal hydrogen chloride and the precipitate was recrystallized from isopropyl alcohol, then from ethanol–ether, and finally from ethanol to yield 8.0 g (51%) of the **hydrochloride salt** of **15**: mp 256–258°; ir (KBr) 3390 (OH), 2710 and 2620 (broad bands, amine hydrochloride), 1605 (phenyl), epoxide band absent; nmr (CD_3OD) δ 7.42 (s, 5, phenyl protons), highest field band at 1.83 (broadened s, 2, CH_2 at 6 position), bands for epoxide ring protons and unsubstituted *endo*-methylene absent.

Anal. Calcd for $C_{17}H_{23}Cl_2NO$: C, 62.19; H, 7.06; Cl, 21.60; ionic Cl, 10.80. Found: C, 62.40; H, 7.00; Cl (Schöniger), 21.59; ionic Cl, 10.82.

An aqueous solution of the hydrochloride salt was treated with sodium bicarbonate and the resultant precipitate was taken into benzene. Drying and removal of the benzene left an oil which was crystallized from aqueous isopropyl alcohol to give **15** in the form of colorless plates: mp 122–124°; ir ($CHCl_3$) 3635 (OH), 1610 (phenyl), epoxide band absent.

Anal. Calcd for $C_{17}H_{22}ClNO$: N, 4.80. Found: basic N, 4.78.

Lithium Aluminum Hydride Reduction of *endo*-Imides. A. N-Phenethyl-*endo*-3-hydroxymethyl-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (9).—A solution of 18.0 g (0.064 mol) of **1c** in 200 ml of dry dimethoxyethane was added, dropwise with stirring, to a slurry of 11.5 g (0.3 mol) of lithium aluminum hydride in 300 ml of dimethoxyethane. Stirring was continued and the reaction mixture was heated at reflux for 6 hr, cooled, and treated with ethyl acetate followed by the dropwise addition of 60 ml of water. The aluminum hydroxide precipitate was removed by filtration and the filtrate was concentrated under reduced pressure to a thick, yellow oil which crystallized from acetone to yield 10.9 g (63%) of **9**: mp 106–107°; ir ($CHCl_3$) 3400 (broad band, OH), 1605 (phenyl), epoxide band absent.

The **hydrochloride salt** of **9**, recrystallized from isopropyl alcohol, showed mp 195–196°.

B. N-(3-Phenylpropyl)-*endo*-3-hydroxymethyl-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (10).—To a slurry of 19.0 g (0.5 mol) of lithium aluminum hydride in 300 ml of tetrahydro-

(18) H. W. Arnold and N. E. Searle, U. S. Patent 2,462,835 (1949) [*Chem. Abstr.*, **43**, 4421 (1949)].

(19) M. S. Morgan, R. S. Tipson, A. Lowry, and W. E. Baldwin, *J. Amer. Chem. Soc.*, **66**, 404 (1944).

(20) For a detailed analysis of the nmr spectra of norbornene epoxides, see K. Tori, K. Aono, K. Kitahonoki, R. Muneyuki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Lett.*, 2921 (1966).

furan was added, dropwise with stirring, a solution of 49.8 g (0.16 mol) of **1d** in 250 ml of tetrahydrofuran. The reaction mixture was heated at reflux for 4 hr, cooled, and treated with ethyl acetate followed by the dropwise addition of 60 ml of water. Approximately 200 ml of ether was added to facilitate stirring. Removal of the aluminum hydroxide precipitate and concentration of the filtrate left an oil which crystallized from benzene–hexane to give 37.5 g (78%) of **10**, mp 85–87°.

The **hydrochloride salt** of **10** showed mp 151–154° after recrystallization from ethanol–ethyl acetate.

2-Phenethyl-*endo*-4,7-methano-1,3,3a,4,7,7a-hexahydroisoindole (3).—To a stirred slurry of 19.0 g (0.5 mol) of lithium aluminum hydride in 400 ml of tetrahydrofuran was added, in small portions, 58.0 g (0.2 mol) of **12**. After being stirred for 1 hr at room temperature, the reaction mixture was heated at reflux for 2 hr. More tetrahydrofuran was added to the cooled reaction mixture followed by the dropwise addition of 35 ml of ethyl acetate and 75 ml of water. The reaction mixture was filtered and the filtrate was concentrated to an oil that could not be crystallized. An ether solution of the oil was treated with ethereal hydrogen chloride and the precipitated solid was recrystallized from a mixture of isopropyl alcohol, ethyl acetate, and ether to yield 27.8 g (50%) of the hydrochloride salt of **3**: mp 219–221°, mp 225–228° after further recrystallization; neutralization of the salt gave the base as an oil; ir ($CHCl_3$) OH, NH band absent, 1600 (phenyl); nmr ($CDCl_3$) δ 7.32 (s, 5, phenyl protons), 6.38 (unresolved m, 2, double-bond protons), highest field band at 1.76 (m, 2, *endo*-methylene protons).

N-Cyclohexylmethyl-*endo*-3-hydroxymethyl-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (11).—A solution of 16.1 g (0.062 mol) of **8** and 5.5 ml of concentrated (37%) hydrochloric acid in 175 ml of ethanol was shaken with 1.5 g platinum oxide catalyst at room temperature in an Adams–Parr apparatus under a hydrogen pressure of 50 psi. Approximately 50% over 1 equiv of hydrogen was absorbed in 2 hr. The filtered solution was concentrated to dryness under reduced pressure and the residual, tacky solid was dissolved in water. The aqueous solution was ether washed and made alkaline, and the precipitated oil was taken into ether. Drying and evaporation of the ether solution left an oil that solidified on standing. Recrystallization from benzene–hexane yielded 7.3 g (45%) of recovered **8**, mp 114–117°, mixture melting point undepressed. Concentration of crystallization mother liquors to dryness left an oil which could not be crystallized. An ether solution of the oil was treated with ethereal hydrogen chloride and the precipitated gum was crystallized from a mixture of ethanol, ethyl acetate, and ether to give 3.3 g (17%) of the hydrochloride salt of **11** as colorless, hygroscopic crystals which retained 0.25 mol of water after drying at 100° *in vacuo:* mp 154–157°; ir ($CHCl_3$) 3290 (broad, strong band, OH, NH), phenyl absorption absent. No product of hydrogenolysis of the N-benzyl group was obtained.

N-Phenethyl-*endo*-3-(propionoxymethyl)-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (9b).—To an ice-cold solution of 15.0 g (0.055 mol) of **9** and 14 ml (0.1 mol) of triethylamine in 150 ml of dry benzene was added, dropwise with stirring, a solution of 5.7 g (0.061 mol) of propionyl chloride in 15 ml of benzene. The ice bath was removed and the reaction mixture was stirred for 6 hr at room temperature. The precipitate of 8.4 g (quantitative) of triethylamine hydrochloride, mp 253–256°, was removed and the filtrate was concentrated to dryness under reduced pressure to yield an oil that started to decompose on attempted vacuum distillation. Treatment of an ether solution of the oil with ethereal hydrogen chloride and recrystallization of the resultant precipitate from isopropyl alcohol–ethyl acetate afforded 11.4 g (57%) of the hydrochloride salt of **9b**: mp 174–175°; ir (KBr) 3330 (OH), 2500 (broad band, N^+—H- - -Cl), 1730 (ester C=O).

N-(3-Phenylpropyl)-*endo*-3-acetoxymethyl-*exo*-5-acetoxy-*endo*-2,6-methaniminonorbornane (10a).—A solution of 10.0 g (0.03 mol) of **10** and 30 ml of acetic anhydride in 50 ml of dried pyridine was allowed to stand for 4 days at room temperature. The solution was concentrated under reduced pressure and the residual amber oil was dissolved in ether. The ether solution was water washed and extracted with dilute hydrochloric acid, the aqueous acid solution was ice cooled and made basic with potassium carbonate, and the precipitated oil was taken into ether. Drying and removal of the ether left an oil which could not be crystallized. It was redissolved in ether and treated with ethereal hydrogen chloride and the precipitated gum was crystallized from ethyl acetate–ether and finally from ethyl acetate to give 4.8 g (34%) of the hydrochloride salt of **10a** as colorless crystals: mp 153–156°, mp 154–157° after further recrystallization; ir ($CHCl_3$) 2500 (N^+—H- - -Cl), 1740 (ester C=O), 1600 (phenyl).

N-Phenethyl-*endo*-3-(phenoxycarbonyloxymethyl)-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (9c).—A solution of 12.6 g (0.08 mol) of phenyl chloroformate in 25 ml of dry benzene was added, dropwise with stirring, to an ice-cooled solution of 20.0 g (0.073 mol) of **9** and 13 ml of triethylamine in 200 ml of benzene. The reaction mixture was stirred for 2 hr at ice-bath temperature and then for 4 hr at room temperature. The precipitated triethylamine hydrochloride (11.0 g, quantitative), mp 251–252°, was removed and the filtrate was concentrated under reduced pressure to give an oil that crystallized on standing. Recrystallization from hexane afforded 18.0 g (63%) of **9c**, mp 91–93°.

The **hydrochloride salt** of **9c** resisted crystallization attempts and was fractionally reprecipitated from acetone solution with ether to give a hygroscopic solid melting over the range of 103–111°.

N-Phenethyl-*endo*-3-(carbamoyloxymethyl)-*exo*-5-hydroxy-*endo*-2,6-methaniminonorbornane (9d).—A solution of 16.4 g (0.04 mol) of **9c** in 275 ml of dry ether was added, dropwise with stirring, to 250 ml of anhydrous liquid ammonia. Stirring was continued for a period of 6 hr during which the ammonia was allowed to evaporate. An additional 200 ml of liquid ammonia was added to the reaction mixture which was allowed to stand for about 20 hr longer. Benzene was added to the remaining ether solution and the organic layer was washed with cold aqueous sodium hydroxide and then with water, dried, and concentrated to give an oil that solidified on standing. Recrystallization from isopropyl alcohol–pentane and from acetone–pentane yielded 4.75 g (36%) of **9d** as colorless crystals, mp 139–141°.

The **hydrochloride salt** of **9d** formed as a hygroscopic solid with a melting range of 126–136° after reprecipitation from isopropyl alcohol solution with ether.

N-Phenethyl-*endo*-3-carbamoyloxymethyl-*exo*-5-carbamoyloxy-*endo*-2,6-methaniminonorbornane (9e).—To an ice-cooled solution of 25.0 g (0.091 mol) of **9** and 32 ml of triethylamine in 250 ml of dry benzene was added, dropwise with stirring, a solution of 36.5 g (0.23 mol) of phenyl chloroformate in 50 ml of benzene. Stirring was continued for 1.5 hr at ice-bath temperature and then for 4 hr at room temperature. The precipitated triethylamine hydrochloride, 23.5 g (94%), mp 246–253°, was removed and the filtrate was washed with cold aqueous sodium bicarbonate solution and water, dried, and concentrated under reduced pressure to yield 50 g (calculated yield 46.6 g) of crude dicarbophenoxy ester as a thick amber gum that could not be crystallized.

The crude gum, dissolved in 100 ml of benzene, was added, dropwise with stirring, to 400–500 ml of liquid ammonia. After being stirred for an additional 2.5 hr, the reaction mixture was allowed to stand for 20 hr while the ammonia evaporated. The residual solution was diluted with ether, washed with cold aqueous sodium hydroxide and water, and extracted with dilute hydrochloric acid. The filtered, aqueous acid solution was cooled and made alkaline and the precipitate was taken into ether. Drying and removal of the ether left a white solid which was recrystallized from acetone–pentane to give 7.6 g (23% over-all yield) of **9e**, mp 150–152°, mixture melting point with **9d** depressed.

The **hydrochloride salt** of **9e**, recrystallized from methanol–ethanol and from methanol–ether, showed mp (gas evolution) 213–214°.

Registry No.—Lithium aluminum hydride, 16853-85-3; **1a**, 21449-83-2; **1b**, 21449-84-3; **1c**, 21449-85-4; **1d**, 21449-86-5; **2**, 21449-87-6; **3**, 21449-88-7; **3** (HCl), 21449-68-3; **4**, 21449-89-8; **5** (HCl), 21449-90-1; **6**, 21449-91-2; **6** (HCl), 21449-92-3; **7**, 21449-93-4; **7a** (HCl), 21449-94-5; **8**, 21449-95-6; **8** (HCl), 21449-96-7; **8a** (HCl), 21449-97-8; **9**, 21449-98-9; **9** (HCl), 21449-99-0; **9a** (HCl), 21449-61-6; **9b** (HCl), 21449-62-7; **9c**, 21449-63-8; **9c** (HCl), 21449-64-9; **9d**, 21449-65-0; **9d** (HCl), 21449-66-1; **9e**, 21449-67-2; **9e** (HCl), 21431-03-8; **10**, 21372-07-6; **10** (HCl), 21372-08-7; **10a** (HCl), 21372-09-8; **11** (HCl), 21372-10-1; **12**,

21372-11-2; **13**, 21372-12-3; **14**, 21372-13-4; **15**, 21372-14-5; **15** (HCl), 21372-15-6.

Acknowledgments.—We thank Mr. D. F. Cortright and associates for analytical data and for ir spectral determinations, Dr. E. B. Whipple and associates for nmr spectra, and Dr. A. B. Evnin for a helpful discussion of the nmr data.

N-Alkyl Cleavage of Amides. I. Amide Racemization in Polyphosphoric Acid[1]

ARTHUR G. MOHAN AND ROBERT T. CONLEY[2]

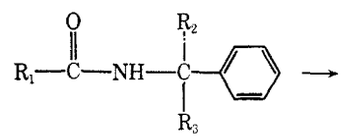
Department of Chemistry, Seton Hall University, South Orange, New Jersey 07079, and Department of Chemistry, Wright State University, Dayton, Ohio 45431[2]

Received April 17, 1968

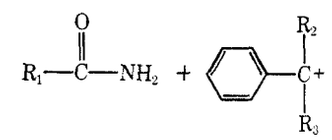
The behavior of a number of secondary amides on treatment with polyphosphoric acid indicates that the stability of the potential cationic fragment (the N-alkyl group) is an important factor for facile N-alkyl fission. When amides with optically active N-alkyl groups were subjected to the cleavage process, significant and structure-dependent amounts of racemization were observed in the recovered amides, indicating that recombination had taken place. Possible mechanisms for the N-alkyl heterolysis of amides have been considered in the light of these results.

Although the acid-catalyzed oxygen–alkyl fission in the reactions of certain esters has been well documented in the literature,[3] the analogous N-alkyl heterolysis of amides has not been investigated extensively. In a study of the effect of ring substituents on the ease of N-alkyl cleavage of N-*t*-butylbenzamides, Lacey[4] proposed a mechanistic scheme similar to the $A_{al}1$ hydrolysis of esters. Knopka and Conley[5] have reported that amides with a primary or secondary alkyl group substituted on the nitrogen are resistant to N-alkyl cleavage in polyphosphoric acid (PPA). Hill, Conley, and Chortyk[6] have reported that a 20% yield of N-benzoyl-α,α-dimethylbenzylamine (**1**) can be realized from the reaction of α-methylstyrene and benzamide in PPA at 120°. It was shown that **1** undergoes facile cleavage to benzamide under comparable conditions, suggesting that the N-alkyl fission is reversible in some systems. Concurrent studies in these laboratories on the fate of optically active groups in the Beckmann and related carbon–nitrogen rearrangements led us to examine the behavior of the optically active amides normally expected from these reactions in PPA, with particular emphasis on the question of reversibility.

When N-(α-methyl)benzylbenzamide (**2a**) is treated with PPA, heterolysis occurs at the carbon–nitrogen bond, giving rise to benzamide and presumably the 1-phenylethyl cation. Neither styrene nor α-methylbenzyl alcohol was observed by vapor phase chromatography (vpc) of the product mixture, but two major components other than benzamide were evident. These materials were not fully characterized, but the ir spectrum of the yellow oil remaining after separation of the benzamide was quite similar to the spectrum of polystyrene, suggesting that these products were dimers and higher polymers of styrene. Similar products have been obtained from the acid-catalyzed telomerization of styrene[7a] and from the PPA-catalyzed dimerization of 2-isopropenylnaphthalene.[7b]



2a, $R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$
b, $R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = C_4H_9$
c, $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = C_4H_9$
d, $R_1 = H$, $R_2 = CH_3$, $R_3 = C_4H_9$
e, $R_1 = CH_3$, $R_2 = H$, $R_3 = CH_3$



The N-alkyl cleavage of **2a** is apparently promoted by stabilization of the resultant carbonium ion through conjugative charge dispersal into the phenyl ring of the 1-phenylethyl cation. Substitution of a second alkyl group on the benzyl carbon enhanced the ease of cleavage. Thus, N-benzoyl-α-methyl-α-butylbenzylamine (**2b**) undergoes 97% N-alkyl cleavage when treated with PPA for only 1 hr at room temperature. In contrast, only 3.5% cleavage is obtained from the reaction of **2a** under comparable conditions.

Three monomeric olefins as well as some polymers were observed in the product mixture from the N-alkyl cleavage of N-acetyl-α-methyl-α-butylbenzylamine (**2c**), and two of these olefins were produced from similar reactions of **2b** and the formamide **2d**. The olefins were isolated by preparative vpc and were identical with those obtained from the thermal dehydration of α-methyl-α-butylbenzyl alcohol. The structures were established by ir and nmr spectroscopy as *cis*- and *trans*-2-phenyl-2-hexene and 2-phenyl-1-hexene. These assignments are in agreement with those of the homol-

(1) (a) Presented in part at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965; (b) taken from the Ph.D. Thesis of A. G. Mohan, Seton Hall University, 1966.

(2) To whom inquiries should be directed.

(3) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell Publishers, London, 1953, p 779; (b) A. G. Davis and J. Kenyon, *Quart. Rev.* (London), **9**, 203 (1955); (c) C. A. Bunton, E. D. Hughes, C. K. Ingold, and D. F. Meigh, *Nature*, **166**, 679 (1950).

(4) R. N. Lacey, *J. Chem. Soc.*, 1633 (1960).

(5) W. N. Knopka and R. T. Conley, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 57C.

(6) R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Amer. Chem. Soc.*, **87**, 5646 (1965).

(7) (a) M. J. Rosen, *J. Org. Chem.*, **18**, 1701 (1953); (b) L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965).