Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73; O, 18.47. Found: C, 72.71; H, 8.82; O, 18.43.

12-Methoxy-13-acetylpodocarpa-8,11,13-trien-19-oic Acid (1c).[18]—A solution of methyl 12-methoxy-13-acetylpodocarpa-8,11,13-trien-19-oate (**1b**) (0.500 g, 1.51 mmol) in concentrated sulfuric acid (6 ml) was kept at room temperature for 5 min and then poured over ice. A solution of the precipitate in aqueous sodium hydroxide was filtered. Acidification of the filtrate with hydrochloric acid gave a solid which crystallized from aqueous ethanol to give **1c** (0.280 g, 59%) as needles: mp 205–207°; a second crop (0.037 g) brought the yield to 65%; ν_{max} 3490, 1720, 1690, 1670, and 1600 cm^{-1}; nmr δ 1.05–3.05 (20 H, m with s at 1.14, 1.36, and 2.60), 3.87 (3 H, s, OCH_3), 6.82 (1 H, s, C_{arom} H), and 7.48 (1 H, s, C_{arom} H).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.41; H, 8.07.

12-Methoxy-13-(1-hydroxyethyl)podocarpa-8,11,13-trien-19-oic Acid (1d).—A solution of sodium borohydride (90 mg, 2.4 mmol) in water (5 ml) was added to a solution of **1c** (0.237 g, 0.72 mmol) in 0.2 *N* sodium hydroxide (4.5 ml). The mixture was kept in ice water for 30 min and then was stirred at room temperature for 5 min. The solution was acidified with dilute hydrochloric acid and the resulting tan precipitate was crystallized from aqueous ethanol to yield **1d** (0.184 g, 78%) as fine needles: mp 160–168°; $\nu_{max}^{CHCl_3}$ 3600–2350 (broad absorption), 1695, and 1615 cm^{-1}; nmr δ 0.95–3.0 (20 H, m with s at 1.05 and 1.32 and a d at 1.49), 3.65 (3 H, s, OCH_3), 6.77 (1 H, s, C_{arom} H) and 7.00 (1 H, s, C_{arom} H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25. Found: C, 72.27; H, 8.50; O, 19.06.

Registry No.—**1a**, 5947-49-9; **1c**, 30801-46-8; **1d**, 36504-20-8; **1e**, 36504-21-9; **3**, 36504-22-0; **4a**, 36504-23-1; **4c**, 36504-24-2; **4d**, 36504-25-3; **4f**, 36504-26-4; **5a**, 36504-27-5; **5b**, 36504-28-6.

Acknowledgments.—P. R. W. was an NDEA Title IV Fellow, 1966–1969. Financial support was also supplied by NSF Grant GU-2054 and the Research Council of the University of Nebraska. We are grateful for this support and also to the Searle Company for a gift of rimu resin, to Drs. R. H. Bible and D. Goldsmith for details of unpublished work, and Dr. M. M. Wheeler for assistance.

(18) The acid **1c** was first prepared by Picha[19] who reported mp 198–202.5°. Our preparation is based on unpublished work by Bible.[20]

(19) G. M. Picha, U. S. Patent 2,774,784 (Dec 18, 1956); *Chem. Abstr.*, **51**, 9695*e* (1957).

(20) R. H. Bible, Abstracts, 138th National Meeting of the American Chemical Society, New York, N. Y., Sept 1960, p 49p.

Dehydrogenase Enzyme Models. Approximation of an Alcohol and a Pyridinium Ring

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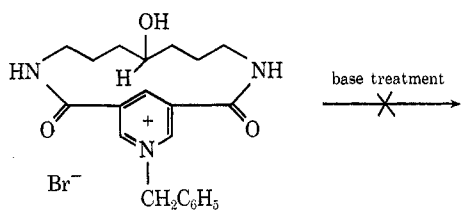
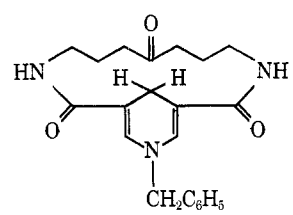
The pyridine nucleotides (NAD^+, $NADP^+$) with their reduced forms (NADH, NADPH) are coenzymes in many biological oxidation–reduction reactions,[2] *e.g.*, the interconversions of ethanol $\rightleftharpoons$ acetaldehyde and lactate $\rightleftharpoons$ pyruvate, which are catalyzed by the dehydrogenase enzymes liver alcohol dehydrogenase and muscle lactate dehydrogenase, respectively. Although it has been possible to achieve the nonenzymatic reduction of reactive carbonyl compounds *via* direct hydride transfer from several 1,4-dihydropyridine reductants, the reverse reaction, the oxidation of an alcohol by a pyridinium salt (NAD^+ model), has not been reported.[2] Attempts in this direction involving flexible intramolecular model systems[3] were unsuccessful and involved in part addition of the side chain to the 2 position of the pyridinium ring. We wish to report studies of a rigid model system, **1**, in which intramolecular hydride transfer to positions other than the 4 position is precluded, and to report that the mere existence of intramolecular approximation is *not* sufficient to guarantee intramolecular hydride transfer, as depicted in eq 1. Compound **1** appeared to be a likely



1



1a

$$+ H^+ + Br^- \quad (1)$$

candidate for the observation of intramolecular hydride transfer since, even though transannular hydride migrations in 14-membered rings has to our knowledge not been reported, space-filling models (CPK) show that the hydroxyl methine hydrogen and the pyridinium 4 position are held tightly together and that conformations of the 14-membered ring do exist in which hydride addition could occur perpendicular to the plane of the pyridinium ring. Moreover attempts to make analogs of **1** with only five bridging methylenes were unsuccessful, presumably owing to the even tighter fit in this case.[4]

The synthesis of **1** by high-dilution cyclization followed the route used by Stetter[5] for the preparation of macrocyclic bisamides of isopthalic acid, and is outlined in Scheme I. For the cyclization step, the hydroxyl group was blocked as the *tert*-butyl ether. The crucial step in this synthesis, high-dilution cyclization of **4** with dinicotinoyl dichloride, was affected in 6.6% yield as described in the Experimental Section. The 4-deoxy analog, **7**, was prepared by similar cyclization in 6.9% yield.

(1) (a) NIH Postdoctoral Fellow, 1969–1971, Columbia University; (b) Address inquiries to author at this address.

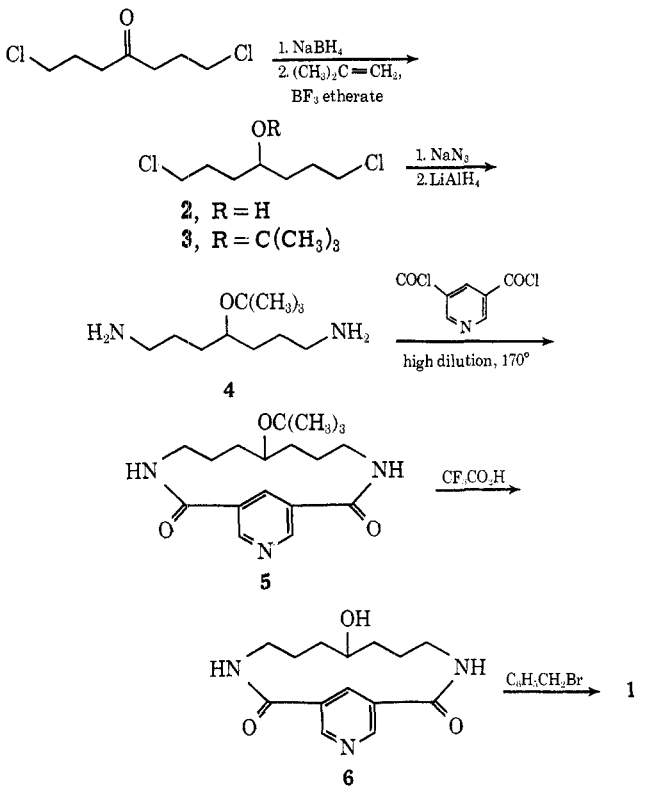
(2) (a) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, Chapter 9; (b) S. Chaykin in "Annual Review of Biochemistry," Vol. 36, Part 1, P. D. Boyer, Ed., Annual Reviews, Inc., Palto Alto, Calif., 1967, pp 149–170.

(3) E. J. Gabbay, Ph.D. Thesis, Columbia University, New York, N. Y., 1965.

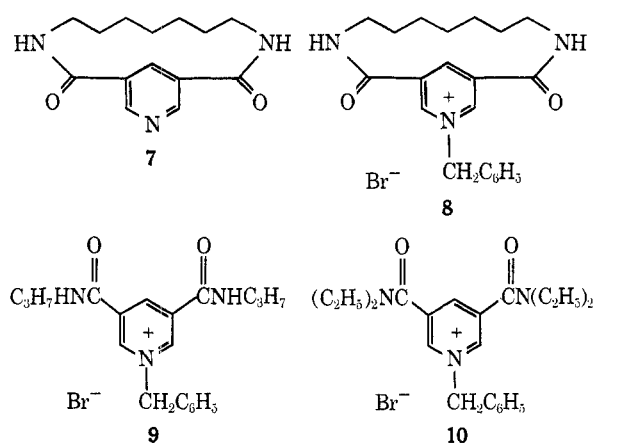
(4) High-dilution cyclization of dinicotinoyl dichloride and 1,5-diaminopentane afforded no macrocyclic bisamide, and only a dimeric tetraamide (*m/e* 466) could be isolated.

(5) H. Stetter, L. Marx-Moll, and H. Rutzen, *Chem. Ber.*, **91**, 1775 (1958).

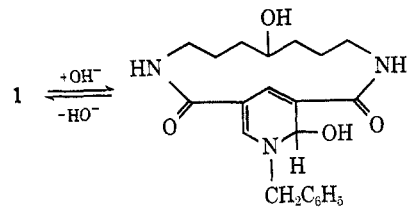
SCHEME I



Initial attempts to effect intramolecular hydride transfer involved treatment of **1** with aqueous base. When an aqueous solution of **1** was basified to pH 12, two new peaks in the uv spectrum at 272 nm (ϵ 10 × 10^3) and 345 (7.7 × 10^3) were obtained. That these new peaks were not related to the formation of the ketodihydropyridine **1a** was apparent from the observed similar behavior at pH 12 of the deoxy analogs **8** [λ_{max} 274 nm (ϵ 14 × 10^3) and 348 (8.6 × 10^3)] and



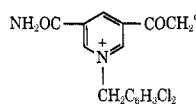
9 [λ_{max} 273 nm (ϵ 12 × 10^3) and 346 (8.0 × 10^3)]. In all cases the spectral changes observed at high pH were completely reversible, the spectra of the original salt being obtained upon acidification. That one is not observing simple titration of the NH hydrogens is evident from the similar behavior of **10** [λ_{max} 281 nm (ϵ 12 × 10^3) and 336 (10 × 10^3), 1.0 *M* NaOH)].[6] The simplest explanation for the uv changes at high pH is the reversible addition of hydroxide to the pyridinium ring, as illustrated for **1** in eq 2. Consistent with this inter-



pretation are nmr experiments which show that the addition of 1 drop of 1 *N* NaOH to **9** (0.4 ml of a 0.06 *M* solution in 1:1 H_2O–methanol) results in the immediate disappearance of the resonances of the pyridine aromatic hydrogens, which can be then regenerated by the addition of 1 drop of acetic acid. Hydroxide addition is certainly occurring at the 2 position, since in all cases two distinct absorption maxima which are characteristic of a cross-conjugated 3-carboxamido-1,2-dihydropyridine (or a 3,5-dicarboxamide-1,2-dihydropyridine)[7,8] are observed. Table I summarizes the uv

TABLE I

UV MAXIMA OF 3,5-DICARBOXAMIDODIHYDROPYRIDINES[a]

Bromide salt λ_{max}, nm (ϵ)	λ_{max}, nm (ϵ) 1,4-Dihydropyridine ($Na_2S_2O_4$ product)	λ_{max}, nm (ϵ) 1,2-Dihydropyridine ($NaBH_4$ product)
	378 (7.9 × 10^3)[b] Shoulder 255 (10 × 10^3)	391 (7.4 × 10^3)[b] 286 (15.4 × 10^3)
Shoulder 275 (4.1 × 10^3)[b]		
9	379 (8.0 × 10^3)[c,f]	386 (7.5 × 10^3)[c,g]
Shoulder 283 (9.9 × 10^3)	Shoulder 255 (10 × 10^3)	287 (14 × 10^3)
1	No reduction[d]	387 (8 × 10^3)[h]
Shoulder 243 (7.0 × 10^3)	product isolated	285 (12 × 10^3)

[a] Solvent methanol unless otherwise noted. [b] K. Wallenfels and H. Schuly, *Justus Liebigs Ann. Chem.*, **621**, 106 (1957). [c] Crude, chloroform-soluble reduction product, in chloroform; extinction coefficient calculated assuming quantitative reduction. [d] No chloroform-soluble product from the dithionite reduction (excess aqueous $Na_2S_2O_4$, 25°, 18 hr) could be isolated. [e] Registry no., 36608-50-1. [f] Registry no., 36611-99-1. [g] Registry no., 36612-00-7. [h] Registry no., 36612-01-8.

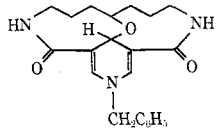
spectra of some authentic 1,2- and 1,4-dihydro-3,5-dicarboxamidopyridines prepared in this and other work by selective reduction of the corresponding pyridinium salts with either sodium borohydride or sodium dithionite.

In order to avoid hydroxide addition to the pyridinium ring, treatment of **1** with basic catalysts under rigorously anhydrous conditions in the nonnucleophilic solvent hexamethylphosphoramide (HMPA) was investigated. A variety of bulky, relatively nonnucleophilic bases have been tried in an unsuccessful attempt

(6) For a report of the spectral changes resulting from ionization of the NH hydrogens of benzyl nicotinamide, see R. B. Martin and J. G. Hull, *J. Biol. Chem.*, **239**, 1237 (1964).

(7) For a discussion of the preparation and uv absorption spectra of 1,4- and 1,2-dihydropyridines, see ref 2a, pp 310–343.

(8) The uv spectrum undoubtedly also rules out the tricyclic ether i as the product formed from base treatment of **1**, since this should also show a single absorption maximum.



i

to convert **1** into **1a**.[9] For example, when **1** was treated with a threefold excess of the weak base aluminum isopropoxide, the nmr spectrum indicated that alkoxyl interchange had occurred to form the aluminum alkoxide of **1** as judged from the appearance of 1 equiv of isopropyl alcohol [doublet (J = 4 Hz) 161 Hz downfield from HMPA]. The aluminum alkoxide of **1**, however, does not undergo intramolecular hydride transfer, as the nmr spectrum of the pyridinium hydrogens are unchanged after 12 hr at 30°. Typical of the results with strong bases is the treatment of **1** with 1 equiv of freshly sublimed lithium bis(trimethylsilyl)-amide, which results in the destruction of **1** without the production of **1a** as determined by both the absence in the product of a carbonyl absorption in the ir spectrum and maximum at 380 nm in the uv spectrum.[10]

Although intramolecular approximation is often an effective method of modeling enzymatic processes,[2a,11] simple approximation of a secondary alcohol and the 4 position of an electron-deficient[12] pyridinium salt does not in the case of **1** lead to intramolecular hydride transfer. Possibly the preferred conformation of the medium ring in **1** is such that the hydroxyl methine hydrogen and the 4 position of the pyridinium ring, although spatially close, are not held in the proper orientation for hydride transfer, a situation which undoubtedly is not the case in the corresponding enzyme bound coenzyme–substrate complex.

Experimental Section[13]

1,7-Dichloro-4-heptanol (**2**).—A solution of 1,7-dichloro-4-heptanone[14] (18.3 g, 0.10 mol) and 100 ml of absolute ethanol was added dropwise over 15 min to a stirred mixture of $NaHCO_3$ (16.8 g, 0.20 mol), sodium borohydride (3.78 g, 0.10 mol), and 300 ml of absolute ethanol at 0° under a nitrogen atmosphere. After stirring for an additional 6 hr at 0°, the mixture was neutralized with 50% HCl, 200 ml of ether and 200 ml of saturated aqueous NaCl solution were added, and then enough water was added to just dissolve the inorganic salts. The ether layer was separated and washed with 200 ml of saturated $NaHCO_3$ solution, and the product was isolated[13a] and distilled to afford 11.2 g (61%) of **2**: bp 110–115° (0.4 Torr); ν_{max}^{plates} 3100–3700 cm^{-1} (OH); $\tau_{CDCl_3}^{TMS}$ 6.2–6.6 (m, 5 H, CH_2Cl and CHOH), 7.60 (s, exchangeable with D_2O, 1 H, OH). This substance deteriorated rapidly (with evolution of HCl) even when stored at 0° and it was therefore used immediately after distillation.

4-*tert*-Butoxy-1,7-dichloroheptane (**3**).—A solution of **2** (10.0 g, 54.0 mmol) and 75 ml of methylene chloride in a 250-ml pressure bottle was cooled in a Dry Ice–acetone bath. Freshly distilled boron trifluoride etherate (2.50 ml, 19.0 mmol), 100% phosphoric acid (1.04 ml, 19.0 mmol), and condensed isobutylene (50 ml, 0.60 mol) were added, the pressure bottle was closed, and the solution was warmed to 25° in a water bath. After the solution was stirred for 1 hr at 25°, the pressure bottle was cooled in a Dry Ice–acetone bath and opened, and the contents were poured into 500 ml of saturated $NaHCO_3$ solution. This procedure was repeated on two more batches using an additional 18.1 g of **2**. Isolation[13a] of the product with methylene chloride afforded 34.6 g of a colorless oil, which was diluted with 20 ml of hexane–ether (3:2) and chromatographed on 1 lb of silica gel. Elution with hexane–ether (3:2) afforded 14.19 g (39%) of pure (tlc) **3**.

The analytical sample was prepared by evaporative distillation [110° (0.1 Torr)]: ν_{max}^{plates} 1195 cm^{-1} (CO-*t*-Bu); $\tau_{CDCl_3}^{TMS}$ 6.2–6.6 (m, 5 H, CH_2Cl and CHOR), 8.83 [s, 9 H, $C(CH_3)_3$].

Anal. Calcd for $C_{11}H_{22}OCl_2$: C, 54.77; H, 9.19; Cl, 29.40. Found: C, 54.67; H, 9.23; Cl, 29.12.

4-*tert*-Butoxy-1,7-diaminoheptane (**4**).—A solution of **3** (14.19 g, 58.9 mmol), sodium azide (38.2 g, 589 mmol), 600 ml of dimethylformamide (reagent grade), and 40 ml of water was stirred for 2 hr under a nitrogen atmosphere at 85–90°. After cooling to room temperature, the solution was diluted with 300 ml of water and after isolation[13a] with ether 13.98 g of crude diazide (ν 2090 cm^{-1}) was obtained as a yellow oil. This material was dissolved in 120 ml of anhydrous ether and added dropwise during 0.5 hr to a stirred mixture of lithium aluminum hydride (9.00 g, 237 mmol) and 600 ml of anhydrous ether. Nitrogen was vigorously evolved and the addition rate had to be carefully controlled. After the addition was complete the mixture was stirred at 25° for an additional 6 hr. Tetrahydrofuran (500 ml) was then added followed by the careful addition of 50 ml of 1:1 tetrahydrofuran–H_2O and 220 ml of 10% NaOH. Isolation[13a] of the ether-soluble product and distillation afforded 8.54 g (72%) of **4**: bp 92–98° (1 Torr); ν_{max}^{plates} 3240 and 3200 (NH_2), 1195 cm^{-1} (CO-*t*-Bu); $\tau_{CDCl_3}^{TMS}$ 6.52 (quintet, J = 2.7 Hz, 1 H, CHOR), 7.1–7.5 (m, 4 H, CH_2NH_2), 8.78 (s, exchangeable with D_2O, 4 H, NH_2), 8.81 [s, 9 H, $C(CH_3)_3$]; bisbenzamide mp 138–139.5°.

Anal. Calcd for $C_{25}H_{34}N_2O_3$ (bisbenzamide): C, 73.14; H, 8.35; N, 6.82. Found: C, 73.28; H, 8.31; N, 6.74.

7-*tert*-Butoxy-2,12-dioxo-3,11,15-triazabicyclo[11.3.1]hepta-deca-1(17),13,15-triene (**5**).—The general procedure of Stetter[5] was followed. A 5-l. flask was fitted with two "constant addition rate" funnels,[15] a nitrogen inlet, and a mechanical stirrer. The entire apparatus was flame dried under a stream of dry, carbon dioxide free nitrogen (passed through a trap of Dreirite and Ascarite). One of the addition funnels was removed and under an atmosphere of dry nitrogen 3 l. of *o*-dichlorobenzene was distilled from molecular sieves [Linde 4A, activated at 220° (1 Torr)] into the reaction flask. In a similar manner 500 ml *o*-dichlorobenzene was distilled into each addition funnel.

To one funnel dry **4** (6.06 g, 30 mmol, freshly vacuum distilled from CaH_2) was added and to the other funnel freshly sublimed 3,5-dicarbochloropyridine[16] (3.06 g, 15 mmol). The two solutions were added dropwise at the same rate over a period of 18 hr to the stirred reaction solution, which was maintained at 165–175° by means of a heating mantel and a Thermowatch (I^2R). After the addition was complete the funnels were removed, the flask was fitted with a distillation head, and the *o*-dichlorobenzene was removed by vacuum distillation (40 Torr). The residual brown glass was powdered, placed in a Soxhlet, and continuously extracted with chloroform for 22 hr. The crystalline chloroform-soluble material (2.353 g) was dissolved in 10 ml of chloroform–methanol (9:1) and chromatographed on 120 g of Florisil. Elution with 4% methanol in chloroform afforded 329 mg (6.6%) of pure (tlc) **5**, R_f 0.50 (silica, 50% chloroform, 40% acetone, 10% diethylamine).

The analytical sample was prepared by sublimation [175° (5×10^{-4} Torr)]: mp 310–312° dec; ν_{max}^{KBr} 3280 (NH), 1658 (C=O), and 1195 cm^{-1} (CO-*t*-Bu); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.8–1.4 (m, 3 H, pyridine H), 1.7–1.9 (m, exchangeable with D_2O/OD^-, 2 H, NH), 6.3–7.3 (m, 5 H, CH_2N and CHOR), 8.98 [s, 9 H, $C(CH_3)_3$];

(9) The bases which have been tried are sodium hydride, lithium bis-(trimethylsilyl)amide, potassium *tert*-butoxide, *tert*-butyllithium, and aluminum isopropoxide.

(10) Although we were not able to prepare an authentic sample of a macrocyclic 1,4-dihydropyridine (see footnotes to Table I), it is not unreasonable to expect that **1a**, if formed, would show absorption maxima similar to that of the 1,4-dihydropyridine derived from **9**. The similarity in the uv maxima of the 1,2-dihydro products formed from **9** and **1** indicates that the distortion resulting from the fused macrocyclic ring probably does not seriously perturb the uv spectrum.

(11) T. C. Bruice in "The Enzymes," Vol. II, 3rd ed, P. D. Boyer, Ed., Academic Press, New York, N. Y., 1970, Chapter 4.

(12) The failure of **1** to undergo intramolecular hydride transfer is surely not a result of the low oxidizing power of the pyridinium compound chosen, since **1** is much more reactive toward the addition of hydroxide than benzyl nicotinium bromide itself.[2]

(13) (a) The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with saturated aqueous sodium chloride solution, drying the extracts over anhydrous magnesium sulfate, and removal of solvent from the filtered extracts under reduced pressure on a rotary evaporator. Amines were dried over anhydrous potassium carbonate. (b) Microanalyses were performed by Schwartzkopf Laboratories, New York, N. Y., or Chemalytics, Inc., Tempe, Ariz. (c) All ultraviolet spectra were run in 1-cm quartz cells on a Cary Model 15 recording spectrophotometer at 25.0 ± 0.1°.

(14) O. E. Curtis, Jr., J. M. Sandri, R. E. Crocker, and H. Hart, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 278.

(15) The addition funnels described by Setter[5] were modified to use Teflon adjustable stopcocks and to hold a volume of 600 ml.

(16) Mp 69–70° [reported 66°: H. Meyer and H. Tropsch, *Monatsh. Chem.*, **35**, 782 (1914)].

mass spectrum m/e (rel intensity) 333 (42, M^+), 305 (19, M − CO), 276 (100, M − C_4H_9), 260 (56, M − OC_4H_9).

Anal. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.56; H, 8.31; N, 12.46.

2,12-Dioxo-7-hydroxy-3,11,15-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (6).—A mixture of **5** (60.8 mg, 0.182 mmol) and 20 ml of anhydrous trifluoroacetic acid was swirled for 5 min, at which time a solution was obtained. The trifluoroacetic acid was quickly removed *in vacuo* at 25–35°, 2 ml of chloroform and 1 ml of methanol were added, and the solution was allowed to crystallize at 0°. The insoluble precipitate was isolated by filtration, washed three times with a total of 1 ml of methanol, and dried to afford 39.6 mg (78%) of **6**, mp 316–318° dec. Recrystallization from methanol afforded pure (tlc) **6**: R_f 0.15 (silica, 50% chloroform, 40% acetone, 10% diethylamine); mp 320–323° dec; ν_{max}^{KBr} 3100–3600 (NH, OH), 1663 (sh), and 1640 cm^{-1} (C=O); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.9–1.4 (m, 3 H, pyridine H), 1.7–2.2 (m, exchangeable with D_2O/OD^-, 2 H, NH), 6.2–7.4 (m, 5 H, CH_2N and CHOH); mass spectrum m/e (rel intensity) 277 (4, M^+), 260 (9, M − OH), 249 (25, M − CO), 105 (100, M − C_4H_5NCO).[17]

15-Benzyl-2,12-dioxo-7-hydroxy-3,11,15-triazoniumbicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide (1).—A solution of **6** (27.7 mg. 0.10 mmol), freshly vacuum distilled benzyl bromide (170 mg, 1.00 mmol), and 10 ml of dimethylformamide (distilled from CaH_2) was stirred under a nitrogen atmosphere at 75–85° for 2.5 hr. Dimethylformamide and excess benzyl bromide were removed *in vacuo* at 60°, 20 ml of methyl ethyl ketone was added, and the resulting solid was isolated by filtration to afford 47.7 mg of a light brown solid, mp 242–244° dec. This material was dissolved in water, decolorized with Norit, and recrystallized from methanol–methyl ethyl ketone (1:4) to afford 30.7 mg (68%) of **1**, mp 236–241° dec.

The analytical sample was prepared by two recrystallizations from ethanol–acetone: mp 239–241° dec; ν_{max}^{KBr} 3250–3550 (OH, NH), 3140 (NH), 1670 (C=O); $\tau_{D_2O}^{TMS}$ 0.6–0.8 (m, 2 H, pyridine H-2 and H-6), 1.36 (broad s, 1 H, $W_{1/2}$ = 6 Hz, pyridine H-4), 2.58 (s, 5 H, C_6H_5), 4.13 (s, 2 H, $CH_2C_6H_5$), 6.3–7.3 (m, 5 H, CH_2N and CHOR); $\lambda_{max}^{H_2O\ (pH\ 6)}$ 243 mμ (sh, ε 7.0 × 10^3).

Anal. Calcd for $C_{21}H_{26}N_3O_3Br$: C, 56.25; H, 5.86; N, 9.37; Br, 17.82. Found: C, 56.34; H, 6.14; N, 9.06; Br, 17.58.

2,12-Dioxo-3,11,15-triazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (7).—Following the procedure used for the preparation of **5**, dry 1,7-heptanediamine (1.300 g, 10 mmol, freshly vacuum distilled from CaH_2) was condensed under high dilution conditions with freshly sublimed 3,5-dicarbochloropyridine[16] (1.030 g, 5 mmol) to afford after continuous extraction ($CHCl_3$) and sublimation (250°, 1 Torr) 180 mg (6.9%) of **7**, mp 334–337° dec.

The analytical sample was prepared by recrystallization from methanol to afford platelets: mp 334–337° dec; ν_{max}^{KBr} 3265 (NH), 1654, and 1637 cm^{-1} (C=O); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.8–1.4 (m, 3 H, pyridine H), 1.6–1.8 (m, exchangeable with D_2O/OD^-, 2 H, NH), 6.3–7.2 (m, 4 H, CH_2N); mass spectrum m/e (rel intensity) 261 (83, M^+), 233 (11, M − CO), 204 (71, M − CO and/or CH_2=NH), 105 (100, M − C_5H_4NCO).

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.35; H, 7.33; N, 16.08. Found: C, 64.15; H, 7.42; N, 16.02.

15-Benzyl-2,12-dioxo-3,11,15-triazoniumbicyclo[11.3.1]heptadeca-1(17),13,15-triene Bromide was prepared from **7** in 79% yield following a procedure identical with that for the preparation of **1**. The analytical sample was prepared by two recrystallizations from ethanol–acetone: mp 261–262° dec; ν_{max}^{KBr} 3270 (NH), 1665 cm^{-1} (C=O); $\tau_{D_2O}^{TMS}$ 0.6–0.8 (m, 2 H, pyridine H-2 and H-6), 1.30 (s, 1 H, $W_{1/2}$ = 6 Hz, pyridine H-4), 2.53 (broad s, 5 H, C_6H_5), 4.03 (s, 2 H, $CH_2C_6H_5$), 6.4–7.4 (m, 4 H, CH_2N).

Anal. Calcd for $C_{21}H_{26}N_3O_2Br$: C, 58.34; H, 6.06; N, 9.72. Found: C, 58.49; H, 6.24; N, 9.50.

1-Benzyl-*N*′,*N*′′-dipropyl-3,5-dicarboxamidopyridinium Bromide (9).—A solution of reagent grade *n*-propylamine (0.84 ml, 10 mmol), 3,5-dicarbochloropyridine[16] (424 mg, 2.0 mmol), and 25 ml of distilled benzene was stirred at 25° under an atmosphere of nitrogen for 2 hr. The benzene was removed *in vacuo*, and the residue was washed with water and recrystallized from ethanol–water to afford 489 mg (95%) of *N*,*N*′-dipropyl-3,5-dicarboxamidopyridine, mp 180–181°.

Quaternization with benzyl bromide following the procedure used for the preparation of **1** afforded 745 mg (95%) of **9**, mp 236–238°. The analytical sample was prepared by two recrystallizations from ethanol–acetone: mp 233–234°; ν_{max}^{KBr} 3195 (OH, NH), 1670 cm^{-1} (C=O); $\tau_{DMSO\text{-}d_6}^{TMS}$ 0.20 (broad s, 2 H, pyridine H-2 and H-6), 0.45 (broad s, 1 H, pyridine H-4), 0.70 (s, J = 5 Hz, exchangeable with D_2O/OD^-, 2 H, NH), 2.15–2.65 (m, 5 H, C_6H_5), 3.93 (s, 2 H, $CH_2C_6H_5$), 6.41–6.83 (m, 4 H, CH_2N), 8.15–8.60 (m, 4 H, $CH_2CH_2CH_3$), 9.08 (unsymmetrical t, J = 7 Hz, 6 H, CH_3).

Anal. Calcd for $C_{20}H_{26}N_3O_2Br$: C, 57.14; H, 6.24; N, 10.00; Br, 19.01. Found: C, 57.04; H, 6.19; N, 10.08; Br, 18.68.

Treatment of 1 with Strong Bases under Anhydrous Conditions.[18] A. Aluminum Isopropoxide.—**1** (12.1 mg 0.027 mmol) was weighed into a predried nmr tube and under an argon stream 0.40 ml of dry HMPA[18a] was added *via* syringe. After the tube was filled with an argon atmosphere, the cap was sealed with Parafilm, and the tube was heated at 80° for 10 min until **1** dissolved. After the tube was allowed to cool to room temperature, freshly distilled aluminum isopropoxide[18c] (17.5 mg, 0.086 mmol) was added under an argon stream, and the tube was filled with an argon atmosphere and the cap sealed with Parafilm. The nmr[21] spectrum was nearly identical with that of **1** before the addition of aluminum isopropoxide and showed absorptions (downfield from HMPA) of 440–480 (broad m, 2 H, NH), 450 (s, ~1 H, $W_{1/2}$ = 8 Hz, pyridine H-4), 396 (broad s, $W_{1/2}$ = 17 Hz, 2 H, pyridine H-2 and H-6), 342–312 (m, 2 H, *o*-C_6H_5), 304–270 (m, 3 H, *m*- and *p*-C_6H_5), 240 Hz (s, 2 H, $CH_2C_6H_5$), and a peak assigned to the hydroxyl hydrogen of isopropyl alcohol at 161 Hz (d, J = 4 Hz, 1.3 H). Addition of 20 μl of isopropyl alcohol increased the peak at 161 Hz. After 12 hr the above sample was quenched by the addition of 1 drop of glacial acetic acid, and the nmr spectrum was unchanged except that the peak at 450 Hz was noticeably sharper having the same $W_{1/2}$ (5 Hz) as did the sample before the addition of aluminum isopropoxide.

B. Sodium Hydride.—Following the same procedure as described above in experiment A, **1** (12.1 mg, 0.024 mmol) was treated with sodium hydride[18b] (5 mg, 52.6% dispersion in oil) in 0.35 ml of dry HMPA.[18d] The nmr spectrum (downfield from HMPA) showed the complete absence of signals in the pyridine aromatic region (360–480 Hz), a poorly resolved increase in intensity in the C_6H_5 region (270–350 Hz), and the absence of the benzyl methylene hydrogens of **1** at 240 Hz. After 15 min the reaction was quenched by the addition of 1 drop of glacial acetic acid. The nmr spectrum was unchanged. HMPA was removed by vacuum sublimation at 60–70° (1 Torr) using a Dry Ice cooled cold finger, and the resulting yellow residue was triturated with 3 ml of hot chloroform. The absence of any dihydropyridine product in the concentrated chloroform extract (10 mg of a light red oil) was apparent from the absence of singlet absorption for the benzyl methylene of a dihydropyridine in the τ 4.5–5.5 region[22] and the absence of ketone carbonyl absorption (1680–1720 cm^{-1}) in the ir spectrum.

C. Potassium *tert*-Butoxide or Lithium Bis(trimethylsilyl)amide.[23]—Treatment of **1** (2×10^{-3} *M* in HMPA)[18a] for 10 min

(17) Correct analyses could not be obtained for this compound. All preparations analyzed approximately 1% low for carbon.

(18) The bases and solvents used were purified as follows. (a) Hexamethylphosphoroamide (HMPA) (Aldrich) was vacuum (5–10 Torr) distilled from CaH_2 directly into the reaction flask. The still was constructed such that the vacuum could be replaced by argon before the reaction flask was removed. (b) Sodium hydride (Metal Hydrides Inc.), a 52% dispersion in mineral oil, was washed twice with distilled pentane, covered with dry HMPA, and transferred into the reaction flask as a slurry in HMPA. (c) Aluminum isopropoxide (MCB) was distilled [bp 130–140° (7 Torr)] directly before use and stored under an argon atmosphere in a desiccator over P_2O_5. (d) Potassium *tert*-butoxide was prepared by the procedure of Johnson,[19] sublimed [220° (1 Torr)] directly before use, and stored under an argon atmosphere in a desiccator over P_2O_5. (e) Lithium bis(trimethylsilyl)amide was prepared by the procedure of Smith[20] [bp 115° (1 Torr)], sublimed [60° (1 Torr)] directly before use, and stored under an argon atmosphere in a desiccator over P_2O_5.

(19) W. S. Johnson and W. P. Schneider, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 132.

(20) E. H. Amonoo-Neizer, R. A. Shaw, D. O. Sklovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965).

(21) The nmr spectra of benzyl salts **1**, **8**, **9**, and **10** show considerable solvent variations. The most dramatic differences were observed for the C_6H_5 group which appeared as a sharp singlet ($W_{1/2}$ = 4 Hz) in D_2O and a complex multiplet in DMSO or HMPA.

(22) H. Dieckman, G. Englert, and K. Wallenfels, *Tetrahedron*, **20**, 281 (1964).

(23) These experiments were conducted in a drybox under an argon atmosphere.

at 25° with 1 equiv of potassium *tert*-butoxide[18d] afforded after quenching with acetic acid and chloroform isolation[13a] a yellow oil which contained no **1a** as judged by the absence of carbonyl absorption in the ir spectrum and the absence of a uv maximum at wavelength longer than 330 nm (observed λ_{max}^{EtOH} 328 and shoulder 260 nm).

Nearly identical results were obtained from similar experiments using lithium bis(trimethylsilyl)amide[18c] as the base.

Registry No.—**1**, 36612-02-9; **2**, 869-95-4; **3**, 36612-04-1; **4**, 36612-05-2; **5**, 36612-06-3; **6**, 36612-07-4; **7**, 36612-08-5; **8**, 36635-93-5; **9**, 36612-09-6.

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Reaction of Trialkyl Phosphites with Haloamides[1]

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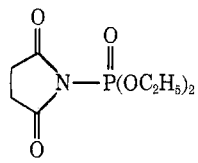
Synthetic routes to insecticidally active *O,S*-dialkyl *N*-acylphosphoramidothioates are multistep and often result in poor yields.[2] In seeking alternate routes to these compounds, the reactions between *N*-bromoacetamide (**1**) and triethyl phosphorothioite and between *N*-chlorobenzamide (**2**) and trimethyl phosphorothioite were investigated. In each case, no dialkyl *N*-acylphosphoramidothioate could be isolated although the starting materials were consumed and alkyl halides were evolved.

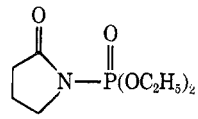
In an attempt to understand these reactions it was decided to investigate the reaction between *N*-haloamides and trialkyl phosphites, as the products from these reactions have not been fully elucidated.[3] *N*-Chlorosuccinimide[4] (**3**) and *N*-bromosuccinimide[5] (**4**) react with trialkyl phosphites to give the Arbuzov products. *N*-Chloro-*N*-alkylamides, on the other hand, react with trialkyl phosphites to give imidoyl chlorides and trialkyl phosphates.[6] Similarly, *N*-chloro-*N*-ethylbenzamide and triphenylphosphine react to give *N*-ethylbenzimidoyl chloride and triphenylphosphine oxide.[7] However, the action of triphenylphosphine on *N*-bromoamides results in the corresponding nitrile and triphenylphosphine oxide.[8]

This note describes the products obtained from the reaction between trialkyl phosphites and the following *N*-haloamides: *N*-bromoacetamide (**1**), *N*-chlorobenzamide (**2**), *N*-chlorosuccinimide (**3**), *N*-bromosuccinimide (**4**), *N*-bromo-2-pyrrolidinone (**5**), *N*-chloroacetamide (**6**), *N*-chloro-*N*-methylacetamide (**7**), and *N*-bromobenzamide (**8**).

The cyclic haloamides or imides (**3**–**5**) reacted with 1 equiv of triethyl phosphite to give ethyl halide and phosphoramidate **9** or **10**. The product **9**, which was



9

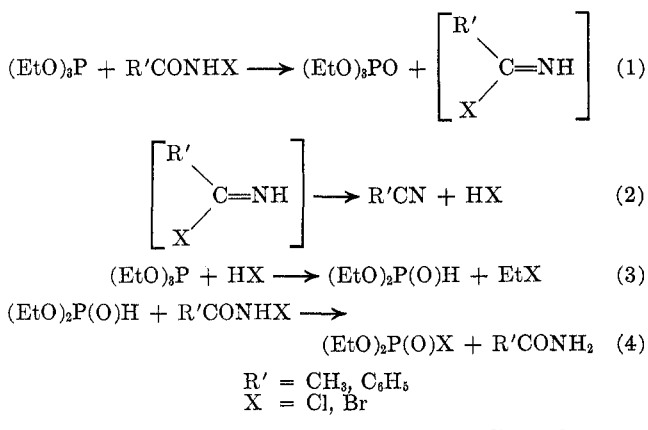


10

the same whether prepared from **3** or **4**, was identical with that reported previously.[5]

The acyclic primary haloamides (**1**, **2**, **6**, and **8**) did not give the expected Arbuzov products but instead reacted to give products (Table I) consistent with Scheme I.

SCHEME I[a]



$$(EtO)_3P + R'CONHX \longrightarrow (EtO)_3PO + \left[\begin{matrix} R' \\ \diagdown \\ C{=}NH \\ \diagup \\ X \end{matrix}\right] \quad (1)$$

$$\left[\begin{matrix} R' \\ \diagdown \\ C{=}NH \\ \diagup \\ X \end{matrix}\right] \longrightarrow R'CN + HX \quad (2)$$

$$(EtO)_3P + HX \longrightarrow (EtO)_2P(O)H + EtX \quad (3)$$

$$(EtO)_2P(O)H + R'CONHX \longrightarrow (EtO)_2P(O)X + R'CONH_2 \quad (4)$$

R′ = CH_3, C_6H_5
X = Cl, Br

[a] Square brackets are used to indicate intermediates that were never isolated.

When *N*-chloro-*N*-methylacetamide (**7**) and trialkyl phosphite were allowed to react, the only products were the trialkyl phosphate and *N*-methylacetimidoyl chloride,[6] analogous to step 1 in the scheme. For the primary haloamides, Scheme I is supported by the following evidence.

(1) Reaction of 1 equiv of primary haloamide with 1 equiv of triethyl phosphite led to the formation of approximately 0.5 equiv of ethyl halide, nitrile, amide, triethyl phosphate, and diethyl halophosphate (*cf.* Table I).

(2) The reaction was exothermic until almost 2 equiv of triethyl phosphite had been added. At this point, no triethyl phosphite could be isolated when it was introduced rapidly.

(3) Addition of 2 equiv of triethyl phosphite to 1 equiv of primary haloamide gave in good yields the products indicated in eq 5 (the summation of steps 1–3). Small amounts of amide and diethyl halophosphate (the products of step 4) also were isolated.

$$2(EtO)_3P + R'CONHX \longrightarrow (EtO)_2P(O)H + (EtO)_3PO + R'CN + EtX \quad (5)$$

(1) This investigation was supported in part by a Research-Training Grant from The Rockefeller Foundation and by Research Grant No. EP-00806 from the Environmental Protection Agency, Washington, D. C.

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