material was extracted with 300 ml. of carbon tetrachloride and washed with three 100-ml. portions of water to remove all the salts. After the carbon tetrachloride was evaporated *in vacuo*, the reaction mixture was vacuum distilled at a pressure of 1 mm. Fraction A distilled at 24° and contained diethyl carbonate (1.04 g., 8.8 mmoles, 7.0%), ethyl pyruvate (VIII, 0.42 g., 3.6 mmoles, 2.9%), and ethyl α-diazopropionate (XIV, 2.0 mmoles, 1.6%). These volatile products were qualitatively identified by their infrared spectra and quantitatively by vapor phase chromatography. Since ethyl α-diazopropionate could not be passed through the columns without decomposition, the samples were first treated with hydrogen bromide, and the ethyl α-bromopropionate derivative was analyzed. The ethyl pyruvate could be isolated unchanged from the column. The less volatile fractions (B, $n^{24}D$ 1.4450; C, $n^{24}D$ 1.4451; and D, $n^{24}D$ 1.4453; lit.,[5] for nitrocarbamate IIb, $n^{24.5}D$ 1.4445) distilled at 70–74° (1 mm.) and gave infrared spectra which were identical with the infrared spectrum of ethyl N-carbethoxy-N-nitroalanate (IIb). The yield of nitrocarbamate IIb was 24.9 g. (0.106 mole, 85%). These samples of the nitrocarbamate gave only one peak when tested by vapor phase chromatography. The nonvolatile residue weighed 0.559 g. (principal infrared bands at 5.73, 6.45, and 6.50 μ). Thin layer chromatography indicated that several components were present. No ethyl acrylate, ethyl 1-carbethoxyethyl carbonate, or nitrous oxide was detected in this run.

Other Acylation Reactions with Ethyl Chloroformate.—In a similar manner ethyl N-nitroglycinate, potassium salt XIa, was treated with ethyl chloroformate to give 85% of ethyl N-carbethoxy-N-nitroglycinate (IIa), 3.6% of diethyl carbonate, and 2.2% of ethyl diazoacetate. This run was conducted without pyridine and 7 days at 0° were required for completion. A higher yield of ethyl diazoacetate was obtained when the reaction was conducted in the presence of sodium carbonate or sodium bicarbonate. Similar results were obtained with the respective sodium salts.

The reaction of the silver salt of ethyl N-nitroglycinate (XIIa) with ethyl chloroformate also led to predominantly N-acylation as determined from infrared spectra of the products.

Reaction of 3,5-Dinitrobenzoyl Chloride with the Silver Salt of Ethyl N-Nitroglycinate (XIIa).—3,5-Dinitrobenzoyl chloride (1.3 g., 5.6 mmoles) dissolved in 10 ml. of anhydrous methylene chloride was added dropwise to 1.5 g. (5.9 moles) of the silver salt XIIa suspended in 15 ml. of anhydrous methylene chloride containing a microdrop of pyridine. The reaction solution was stirred for 2.5 hr. at −80°, after which time it was pressure filtered at −80°. An infrared spectrum taken at −80° of the reaction solution at this time suggested that ethyl N-(3,5-dinitrobenzoyl)-N-nitroglycinate (VIIa) was the major product. Distillation of the volatiles left 0.82 g. (2.4 mmoles, 43%) of crude nitroamide VIIa (m.p. 104–107° dec.); after three recrystallizations from methylene chloride–hexane solutions, the melting point became 110–111° dec.

Anal. Calcd. for $C_{11}H_{10}N_4O_9$: C, 38.60; H, 2.95; N, 16.36. Found: C, 38.59; H, 2.82; N, 16.06.

Treatment of the methylene chloride insoluble material with 3 *N* hydrochloric acid, gave 0.30 g. of 3,5-dinitrobenzoic acid (1.4 mmoles, 25%, m.p. 201–203°, lit.[23a] m.p. 204–205°).

As with all the silver salt runs, the reaction proceeded at a negligible rate in the absence of pyridine.

Other "Salt" Reactions.—The silver salt of methyl N-nitroglycinate (XIIc) was similarly treated with 3,5-dinitrobenzoyl chloride at 25° to give 65% of methyl N-(3,5-dinitrobenzoyl)-N-nitroglycinate (VIIc) which melted at 142–143° after recrystallization from a mixture of methylene chloride and hexane.

Anal. Calcd. for $C_{10}H_8N_4O_9$: C, 36.60; H, 2.46; N, 17.07. Found: C, 36.73; H, 2.59; N, 16.81.

Also detected in this run were methyl diazoacetate, methyl N-nitroglycinate, 3,5-dinitrobenzoic acid, and 3,5-dinitrobenzoic anhydride.

Likewise, the silver salt of ethyl N-nitroalanate (XIIb) gave, at −10° with 3,5-dinitrobenzoyl chloride, 47% of the light yellow ethyl N-(3,5-dinitrobenzoyl)-N-nitroalanate (VIIb, m.p. 94–95.5° after recrystallization from methylene chloride–hexane).

Anal. Calcd. for $C_{12}H_{12}N_4O_9$: C, 40.45; H, 3.40; N, 15.73. Found: C, 40.43; H, 3.55; N, 15.11.

Also isolated was 43% of 3,5-dinitrobenzoic acid (m.p. 203–204°, lit.[23a] m.p. 204–205°).

At −80°, the sodium salt of ethyl N-nitroalanate (XIb) gave, with 3,5-dinitrobenzoyl chloride, 53% of nitroamide (VIIb), m.p. 94–95.5°.

The reaction of benzoyl chloride with the sodium salt of ethyl N-nitroglycinate (XIa) at −10° gave mainly ethyl N-benzoyl-N-nitroglycinate, as determined from the infrared spectrum. Ethyl diazoacetate and 44% of benzoic acid (m.p. 119–120°, lit.[23b] m.p. 121.7°) were also detected.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health (CY 3554).

(23) (a) N. A. Lange, "Handbook of Chemistry," 7th Ed., Handbook Publishers Inc., Sandusky, Ohio, 1949, p. 487; (b) p. 589.

On the Mechanism of the Conversion of β-Iodo Carbamates to Aziridines[1]

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Received November 1, 1963

The facile conversion of β-iodo carbamates with strong base to aziridines is shown to proceed *via* an intermediate N-carboalkoxy aziridine. The kinetics of the cyclization indicate abstraction of the proton from the carbamate nitrogen followed by a rate-determining ring closure made possible by neighboring group participation. Differences in rate of cyclization are explained on conformational grounds.

We have recently shown that *trans*-β-iodo carbamates can be converted to aziridines in good yield on treatment with alcoholic potassium hydroxide.[2] Since β-iodo carbamates are readily available from olefins, this represents a useful synthesis of fused aziridines from cyclic olefins. For instance, methyl (3α-iodo-2β-cholestane)carbamate (I), obtainable in 75% from 2-cholestene, is transformed in 90% yield[3] to cholesten(2β,3β)-imine (V) on refluxing for 1 hr. with 1.5 *N* methanolic potassium hydroxide. Three reaction paths, A, B, and C, come under consideration for the conversion of I to V in basic solution.

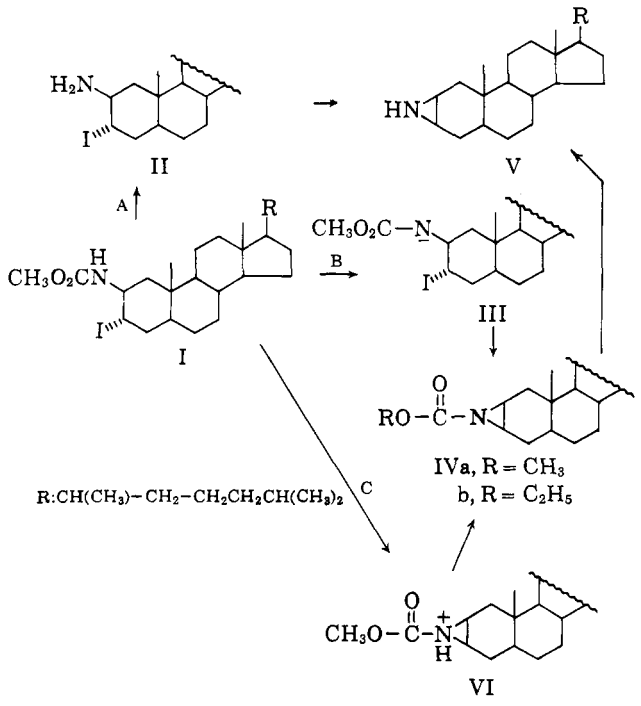
A rate-determining ring closure of I to VI (path C) can be eliminated by the fact that mild bases such as pyridine or sodium bicarbonate do not effect the conversion of I to V. Iodo amine II can in fact be readily converted to aziridine V but a facile hydrolysis of carbamate I to amine II would be unexpected in view of the known inertness of carbamates in basic medium.[4] We found, for example, that, on refluxing ethyl cyclohex-

(1) (a) Paper IV on Chemistry of Carbamates. For paper III see ref. 2. (b) This investigation was supported by U. S. Public Health Service Grant CY-4474 from the National Cancer Institute. (c) Presented in part before the Organic Division of the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April, 1964. (d) National Science Foundation Fellow, 1961–1963.

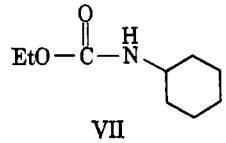
(2) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

(3) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 393 (1963).

(4) S. Rovira, *Ann. chim.* (Paris), *Ser. 11*, **20**, 660 (1945).

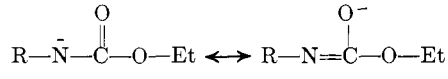


anecarbamate for 100 hr. in 0.85 *N* methanolic potassium hydroxide, no cyclohexylamine is formed.

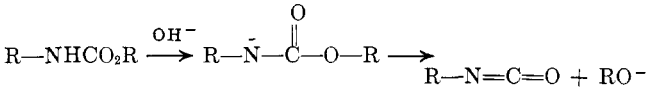


VII

The detailed mechanism of hydrolysis of carbamates is not yet well understood. However, the lack of hydrolysis of VII to cyclohexylamine in basic medium, contrasted with the fact that ester exchange in VII with methoxide ion takes place readily,[5] makes it unlikely that hydrolysis of such carbamates involves an attack of hydroxide ion on the carbamate carbonyl. The slow reactivity of carbamates, by comparison with carboxylic esters or amides, can then be attributed to a relatively high acidity of the carbamate NH giving rise to a resonance-stabilized anion that resists attack by negative hydroxide ion. It has previously been suggested that



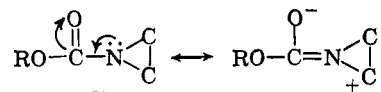
the hydrolysis of monosubstituted carbamates of type R-NHCO$_2$R proceeds by proton abstraction followed



by very slow decomposition into an alkoxide ion and an isocyanate.[6]

If abstraction of a proton from I can be fast, then facile ring closure of the resulting ion III to IVa, with expulsion of iodide ion, should be preferred over hydrolysis of I to an amine II, *via* an isocyanate and a carbamic acid. It might then become possible to isolate the N-carbomethoxyaziridine IVa and to study its conversion to V. Indeed, when iodo carbamate I was treated at room temperature with 0.1 *N* methanolic potassium hydroxide for 4.5 hr. it was possible to obtain the ring-closed product IVa in 64% yield. The structure of IVa was proved by its independent synthesis in quantitative yield from aziridine V with methyl chlorocarbonate. N-Carbethoxy aziridine (IVb) can be similarly prepared, and both IVa and IVb are hydrolyzed on 15-min. reflux with 1.5 *N* alcoholic potassium hydroxide to aziridine V. These results are compatible with the formation of an intermediate such as IVa in the conversion of I to V (path B). We have also determined that intermediate IVa is stable in the presence of iodide ions, indicating that in our case step III → IVa is essentially irreversible.

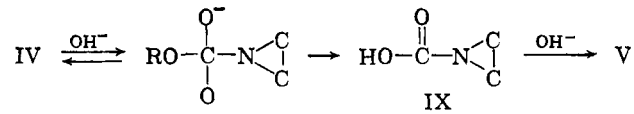
In order to account for the unusually facile hydrolysis of the steroidal aziridinyl carbamates IVa and IVb, one can extend to carbamates the arguments that were used by Brown[7] to explain the high reactivity of aziridinyl amides towards nucleophiles. Stabilization of carbamates by resonance structures such as VIII, which are



IV VIII

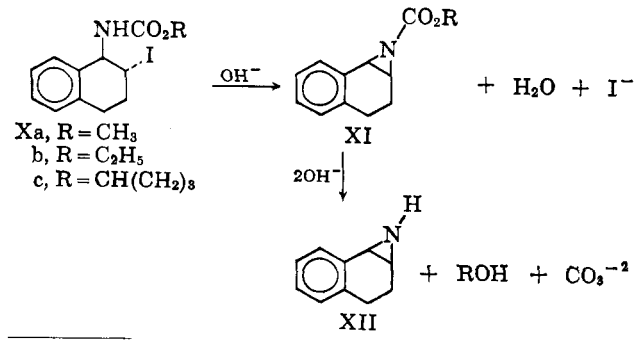
probably responsible for the inertness of carbamates to attack by basic reagents, is very unfavorable in the case of IVa, owing to the strain involved in placing a double bond *exo* to the three-membered ring.

It is now possible to postulate the mechanism of conversion of β-iodo carbamates to aziridine as a fast equilibrium step (I ⇄ III) followed by a slow cyclization step (III → IVa). This would be followed by a slow attack of hydroxide on the intermediate IVa and a rapid decomposition of the ortho ester intermediate to a carbamic acid IX. The latter is then decarboxylated irreversibly to ethylenimine V.



IX

In the hydrolysis of iodo carbamates Xa–Xc to 1,2,-3,4-tetrahydronaphthalene(1,2)imine XII, an N-carbomethoxy aziridine intermediate XI was not isolated, but its presence can be demonstrated in an indirect manner. In the first step (X → XI), 1 mole of base is consumed to give intermediate XI, water, and iodide. In the second step (XI → XII), 2 moles of base are consumed. However, 3 equiv. of base are produced in this step, namely aziridine XII and carbonate ion. The



(5) A. Hassner and E. G. Nash, unpublished results.

(6) T. Mukaiyama and M. Iwanami, *J. Am. Chem. Soc.*, **79**, 73 (1957).

(7) H. C. Brown, *ibid.*, **82**, 2016 (1962).

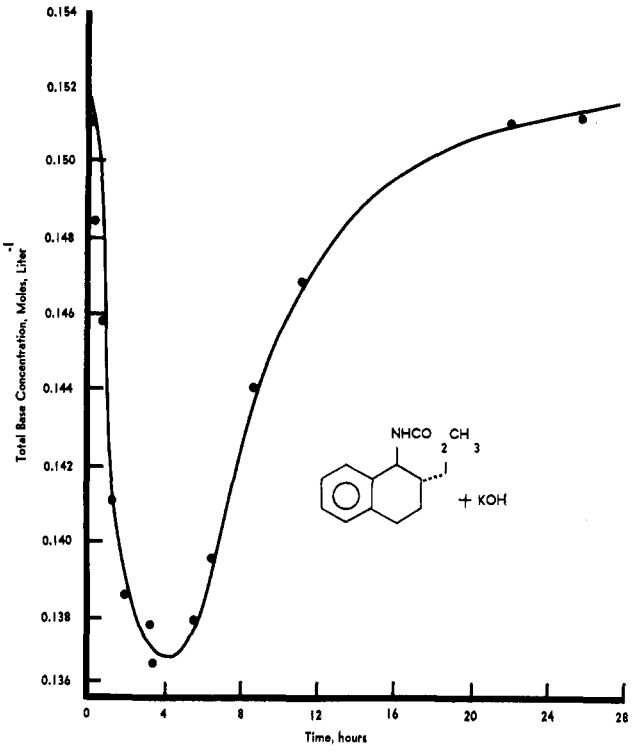


Fig. 1.—Reaction of methyl (*trans*-2-iodo-1-tetralin)carbamate (X) with methanolic potassium hydroxide. Initial carbamate concentration, 0.050 mole/l.; initial potassium hydroxide concentration, 0.1522 mole/l.

total base concentration at the beginning and at the end of the reaction is the same; yet, any accumulation of intermediate XI in the reaction will be accompanied by a temporary decrease in the total base concentration. In order to test this hypothesis, iodo carbamate Xa was allowed to react with 3 equiv. of methanolic potassium hydroxide and the total amount of base present was titrated at intervals. The results displayed in Fig. 1 indicate a decrease in total base concentration to a minimum after about 4 hr., followed by a rise until the base concentration again reaches the initial level. The maximum concentration of intermediate XI under these conditions is thus *ca.* 0.02 *M*. Apparently, in this system, the rate of formation of the intermediate N-carbomethoxy aziridine XI is of the same order of magnitude as its rate of consumption.

The rate of cyclization of iodo carbamate I can be measured by following the disappearance of I in the ultraviolet, and the rate law may be formulated as $d[C]/dt = k[C][OH^-]$, where [C] is the concentration of carbamate. Kinetic measurements, carried out with a tenfold excess of base, indicate that the disappearance of I follows pseudo-first-order kinetics. The reaction is first order with respect to hydroxide ion as determined by measuring the rate of cyclization at two different base concentrations (see Table I).

The *trans*-diaxial configuration of the iodine and carbamate groups[8] in III represent the most favorable stereochemical arrangement for ring closure to an aziridine. It was of interest to compare the cyclization rates of *trans*-iodo carbamates with different stereochemical arrangements of the participating groups. The results of kinetic measurements on five iodo urethanes are summarized in Table I. The second-order

(8) A. Hassner and C. Heathcock, *Tetrahedron Letters*, 1125 (1964).

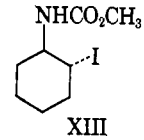
TABLE I

RATES OF CYCLIZATION OF β-IODO CARBAMATES[a] WITH POTASSIUM HYDROXIDE[b]

Compd.	$k_1 \times 10^5$, sec.$^{-1}$[e]	$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$	Relative rates
I[c]	16.9	16.9	6.5
Xa	12.1	12.1	4.7
Xb	10.05	10.05	3.9
Xc	7.32	7.32	2.8
XIII	2.69	2.69	1
XIII[d]	3.78	2.52	

[a] Carbamate concentration was 0.010 *M* except where otherwise noted. [b] Potassium hydroxide concentration was 0.01 *M*; temperature was 24 ± 0.5°. [c] Carbamate concentration was 0.001 *M*. [d] Base concentration was 0.150 *M*. [e] The errors in rate constants are less than 10%.

rate constant k_2 was determined from the pseudo-first-order constant k_1 and the base concentration. Methyl (3α-iodo-2β-cholestane)carbamate (I), in which the groups are *trans* diaxial, cyclizes 6.5 times faster than does methyl (*trans*-2-iodocyclohexane)carbamate XIII, in which the functional groups are predominantly diequatorial.[9] By a simple ring inversion, compound



XIII

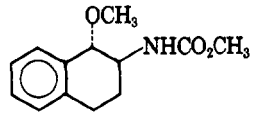
XIII may achieve a *trans*-diaxial geometry necessary for cyclization. The difference in rate between I and XIII probably reflects the activation energy needed to place the two functional groups in the diaxial arrangement.

Methyl carbamate Xa cyclizes at a rate intermediate between that of I and XIII This is probably due to the fact that the presence of two trigonal carbons in the ring allows compound Xa to invert to a conformation with iodo and carbamate groups axial more readily than compound XIII. The difference in cyclization rate between the methyl, ethyl, and isopropyl carbamate Xa, Xb, and Xc may be a ponderal effect.[10] Methyl (*trans*-2-iodoindane)carbamate, in which a *trans*-coplanar arrangement of groups is not likely, cyclizes to indenimine with concomitant formation of 1-indanone, the latter presumably resulting from a competing *cis* elimination of hydrogen iodide.[2]

Iodo carbamates Xa Xb, and Xc on hydrolysis with methanolic base give, in addition to aziridine XII, a neutral product, $C_{13}H_{17}NO_3$, in 5–10% yield. The infrared spectrum of this material was characteristic of a carbamate (3300, 3090, 1712, 1694, and 1560 cm.$^{-1}$). The n.m.r. spectrum showed sharp singlets at τ 6.45 (methyl ester) and 6.73 (aliphatic methoxy) in addition to peaks of aromatic and alicyclic protons found in Xa, indicating a tetralin nucleus in which the iodine from Xa has been replaced by a methoxy group. This and the following evidence led to the tentative assignment of structure XIV to this by-product. Since only

(9) The decoupled n.m.r. spectrum of XIII in deuteriochloroform or in pyridine shows at low field an AB quartet with J = 10 c.p.s., indicative of axial protons. We are grateful to Dr. J. L. McClanahan for the n.m.r. studies.

(10) For other examples, see E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p. 275.



XIV

the methyl carbamate is formed regardless of which of the three iodo carbamates, Xa, Xb, or Xc, is hydrolyzed, compound XIV probably arises from an intermediate, N-carboalkoxy aziridine XI, which may either react with hydroxide to give aziridine XII or may be opened by methoxide to give a methoxy carbamate in which ester interchange with methanol takes place to yield XIV.[11] The fact that no β-hydroxy carbamate is obtained as a product reflects the greater nucleophilicity of methoxide compared with hydroxide, as well as the fact that, in a solution of methanolic hydroxide, the main base species present is methoxide. Yet, the main fate of intermediate XI is hydrolysis by hydroxide, indicating that the rate for this reaction (XI → XII) is much faster than that for ring opening (XI → XIV). This suggests that the yield of the methoxy carbamate XIV should be dependent on the amount of water in the reaction mixture because of the mass action law.

$$\overset{+}{K}OH^{-} + CH_3OH \rightleftarrows \overset{+}{K}O\bar{C}H_3 + H_2O$$

This prediction was tested by carrying out the hydrolysis of iodo carbamate Xa in methanolic potassium hydroxide solutions containing various amounts of water. The results are summarized in Table II, and

TABLE II

EFFECT OF WATER ON THE HYDROLYSIS OF IODO URETHAN X IN 1.5 *N* METHANOLIC POTASSIUM HYDROXIDE[a]

	Yield, %		
Vol. % H_2O	XII	XIV	XII + XIV
0	74.7	5.2	14
10	73.5	2.6	28
20	77.5	1.5	50

are reproducible to 2% of XII, and 0.5% of XIV. The ratio of aziridine XII to methoxy carbamate XIV increases from 14 to 50 as the amount of water in the reaction mixture is increased from 0 to 20%. When the hydrolysis of carbamate Xa was carried out in 1.0 *N* methanolic potassium methoxide, methoxy carbamate XIV was isolated in 10% yield. The placing of the two functional groups in XIV as *trans* is justified on the basis of the known *trans* ring opening of ethylenimines.[3,12] The methoxy group was placed on C-1 by analogy with the ammonolysis of *trans*-2-bromo-1-tetralol to 1-amino-2-tetralol, which has been shown to proceed by ring opening at C-1 of an intermediate epoxide.[13]

Experimental[14]

Preparation of Urethans.—**Methyl (α-iodo-2β-cholestane)carbamate (I)**, m.p. 160–162°, was synthesized from 2-cholestene as reported[2]; λ_{max} 260 mμ (ε 500).

Methyl (*trans*-2-iodocyclohexane)carbamate (XIII), m.p. 130–131°, was obtained from cyclohexene as previously described[2]; λ_{max} 260 mμ (ε 760).

Methyl (*trans*-2-iodo-1-tetralin)carbamate (Xa), m.p. 129–131°, was prepared from 1,2-dihydronaphthalene[2]; λ_{max} 274 mμ (ε 1100).

Ethyl (*trans*-2-iodo-1-tetralin)carbamate (Xb), m.p. 138–140° from ethanol (lit.[15] m.p. 138–139°), was obtained in 60% yield from 1,2-dihydronaphthalene; λ_{max} 274 mμ (ε 900) and 267 mμ (ε 1100).

Isopropyl (*trans*-2-iodo-1-tetralin)carbamate (Xc) was obtained in 54% yield from 1,2-dihydronaphthalene by addition of iodine isocyanate[2] followed by heating with isopropyl alcohol; m.p. 106–108° from acetone–water, λ_{max} 274 mμ (ε 880) and 267 mμ (ε 1020).

Anal. Calcd. for $C_{14}H_{18}INO_2$: C, 46.81; H, 5.05; N, 3.90. Found: C, 46.58; H, 5.26; N, 3.85.

N-Carbomethoxycholesten(2β,3β)imine (IVa). A. From Cholesten(2β,3β)imine (V).—Imine V[2] (500 mg.) was dissolved in 30 ml. of dry ether and 0.7 ml. of triethylamine was added. Methyl chlorocarbonate was added dropwise (8 drops) until no more precipitate appeared. The solid was filtered off and the resulting solution was concentrated to dryness *in vacuo*. The product was obtained as a white solid weighing 554 mg. (96%), m.p. 120–123°. On recrystallization from acetone–water, the carbamate melted at 124–127°.

B. From Methyl (3α-Iodo-2β-cholestane)carbamate (I).—Carbamate I (525 mg.) was suspended in 200 ml. of 0.10 *N* methanolic potassium hydroxide. The slurry was stirred at 26° for 4.5 hr., at which time all of the material had dissolved. The clear solution was poured into 500 ml. of water and filtered. After drying over phosphorus pentoxide, the product weighed 300 mg. (64%) and melted at 99–105°. The infrared spectrum of this crude material was identical with that of the analytically pure material. An analytical sample, m.p. 128–129°, was obtained by two recrystallizations from methanol.

Anal. Calcd. for $C_{29}H_{49}NO_2$: C, 78.50; H, 11.13; N, 3.16. Found: C, 78.52; H, 11.11; N, 3.05.

This material was identical by mixture melting point (127–128.5°) and infrared spectra with the material prepared from cholesten(2β,3β)imine and methyl chlorocarbonate; ν_{max} 1732, 1720, 1415, 1280, 1230, and 793 cm.$^{-1}$.

N-Carbethoxycholesten(2β,3β)imine (IVb).—Cholesten(2β,3β)-imine[2] (V, 317 mg.) was dissolved in 30 ml. of dry ether and 0.5 ml. of triethylamine was added. Ethyl chlorocarbonate was added dropwise until no more precipitate was formed. After 15 min., the slurry was filtered through a layer of Filter Cel. The solvent was removed *in vacuo* to yield 375 mg. of the carbethoxyimine (100%): m.p. 107–109°, ν_{max} 1725 sh, 1711, 1430 sh, 1300, 1230, and 790 cm.$^{-1}$; $\nu_{max}^{CCl_4}$ 1724, 1418, 1275, 1220 cm.$^{-1}$. The analytical sample, m.p. 112–113°, was obtained by two recrystallizations from methanol–water.

Anal. Calcd. for $C_{30}H_{51}NO_2$: C, 78.72; H, 11.23. Found: C, 78.50; H, 11.10.

Hydrolysis of N-Carbethoxycholesten(2β,3β)imine (IVb).—The N-carbethoxyimine (360 mg.) was dissolved in a mixture of 12.5 ml. of ethanol and 1.5 ml. of water containing 1.25 g. of potassium hydroxide. The solution was refluxed for 15 min. and then poured into water. The suspension was extracted with ether. After the ether extracts were washed with water and dryed over magnesium sulfate, removal of solvent gave 277 mg. of cholesten(2β,3β)imine (19%), m.p. 101–102° (lit.[2] m.p. 103–105°). Similar results were obtained using N-carbomethoxycholesten(2β,3β)imine (IVa).

Attempted Basic Hydrolysis of Ethyl Cyclohexanecarbamate.—Ethyl cyclohexanecarbamate (3.0 g.) was dissolved in 100 ml. of 0.85 *N* methanolic potassium hydroxide. The solution was refluxed on a steam bath. At intervals specified in Table III, 10-ml. aliquots were withdrawn and analyzed in the following manner. The aliquot was partitioned between 20 ml. of water and 10 ml. of ether. After separation of the two phases, the aqueous layer was extracted twice more with 10-ml. portions of ether. The combined ether extracts were washed twice with 10-ml. portions of 10% hydrochloric acid, then with 20 ml. of water. After the solution was dried over anhydrous magnesium sulfate and ether was removed, the product was weighed and analyzed

(11) Alternatively ester interchange may take place with XI followed by ring opening by methoxide to XIV.

(12) R. Ghirardelli and H. J. Lucas, *J. Am. Chem. Soc.*, **77**, 106 (1955).

(13) J. von Braun and K. Weissbach, *Ber.*, **63**, 3052 (1930).

(14) All melting points are uncorrected and were determined on a Fisher-Johns melting block. Infrared spectra were determined in KBr pellets. Nuclear magnetic resonance spectra were obtained on a Varian A-60 instrument in dilute solutions (*ca.* 10% by weight) in deuteriochloroform with tetramethylsilane as an internal standard. Ultraviolet spectra were determined in methanol on a Cary 14 instrument. Microanalyses were performed by A. Bernhardt, Mülheim, Germany.

(15) G. Drefahl and K. Ponsold, *Ber.*, **93**, 519 (1960).

TABLE III

Time, hr.	Mole fraction: Methyl carbamate	Mole fraction: Ethyl carbamate	Amine	Recovery, %
4	4.3	95.7	0	88.4
12	12.1	87.9	0	82.5
23	22.7	77.3	0	90.5
33	34.7	65.3	0	90.8
48	54.4	45.6	0	92.8
59	66.8	33.2	0	80.0
100	81.8	18.2	0	90.0

by nuclear magnetic resonance. The peak heights of the methoxy singlet (τ 6.46) were used for the analysis.

The hydrochloric acid extracts were made basic and extracted with ether. The ether solution was dried and then evaporated in a tared flask to determine the amount of amine formed. Results are summarized in Table III.

The product from the last aliquot was recrystallized twice from pentane to give 110 mg. of pure methyl cyclohexanecarbamate as flat white needles, m.p. 74.5–75.5° (lit.[16] m.p. 75°).

Procedure for Kinetic Measurements.—The solvent used was Baker analyzed reagent grade methanol. Methanolic potassium hydroxide solutions were prepared immediately prior to use by diluting a stock solution of the reagent with methanol. In each case, the base was standardized against 0.01 *N* hydrochloric acid before being used.

β-Iodo carbamate solutions were prepared by weighing the correct amount of the compound into a volumetric flask and diluting to the mark with methanol. In most cases, the carbamate solutions were made to be 0.02 *M*, so that dilution with an equal volume of the base solution gave a substrate concentration of 0.01 *M* in the reaction mixture.

The base solutions were correspondingly made to be 0.200 *M* so that, in the actual reaction mixture, the base concentration was 0.100 *M*. In one case, a 0.300 *M* base solution was used in order to check the reaction order in base.

The reactions were run at 24.0 ± 0.2°. Each reaction was started by pipeting the base solution into an equal volume of the substrate solution, while swirling the reaction flask gently. Zero time was taken as the time the pipet was one-half drained.

At appropriate intervals, 1-ml. aliquots were removed from the reaction mixture and quenched by adding rapidly to a 10-ml. volumetric flask containing 8 ml. of methanol. The solution was diluted to the mark with methanol and analyzed in a Cary 14 recording spectrophotometer. Spectral measurements were made within 5 min. after the sample was taken.

With methyl (*trans*-2-iodo-1-cyclohexane)carbamate (XIII) and methyl (3α-iodo-2β-cholestane)carbamate (I) the rate of disappearance of the 260-mμ peak was measured. Infinity measurements shows that the peak completely disappeared.

With the esters of (*trans*-2-iodo-1-tetralin)carbamate (Xa, Xb, and Xc), the band at 267 mμ was used. The final product of the reaction, 1,2,3,4-tetrahydronaphthalen(1,2)imine, also absorbs at this wave length (ϵ 260). In the case of the imine, this band is doubtless due to the benzene ring chromophore. A similar absorption was assumed for the intermediate N-carboalkoxyimines. It was assumed that the 267-mμ band in the starting β-iodo carbamates contains, in addition to the contribution of the iodo group, a contribution with ϵ 260 from the benzene ring. Thus, in each analysis, the apparent extinction coefficient was diminished by 260 to correct for the contribution of this chromophore, present in both starting material and product.

With methyl (3α-iodo-2β-cholestane)carbamate (I), it was necessary to employ a substrate concentration of only 0.0010 *M*, due to the low solubility of the compound in methanol. In this case, after mixing of the reactants, an aliquot of the reaction mixture was placed in a cuvette and the reaction was allowed to proceed in the sample compartment of the spectrophotometer. Readings were taken at the appropriate intervals without the necessity of sampling.

Rate constants were calculated in the following manner. The pseudo-first-order rate constant was determined from the slope of the straight line obtained by plotting the log of the carbamate concentration at a given time against the elapsed time in seconds. Division of this value by the base concentration gave the second-order rate constant. The data are summarized in Table I.

Detection of N-Carbomethoxy-1,2,3,4-tetrahydronaphthalen-(1,2)imine (XI).—Methyl (*trans*-2-iodo-1-tetralin)carbamate (Xa, 3.3248 g.) was dissolved in absolute methanol in a 100-ml. volumetric flask. The flask was filled up to the mark with methanol to give a solution 0.1004 *M* in the carbamate. This solution and a 0.3044 *M* methanolic potassium hydroxide solution were placed in a constant-temperature bath at 19.2°. After temperature equilibrium had been reached, equal volumes of the two solutions were mixed in the reaction flask, also maintained at 19.2°. At appropriate intervals, 2-ml. aliquots were withdrawn and added to 25 ml. of distilled water. The total base was titrated using methyl orange indicator. The graphical presentation of the data is found in Fig. 1.

Methyl (*trans*-1-Methoxy-2-tetralin)carbamate (XIV).—Ethyl (*trans*-2-iodo-1-tetralin)carbamate (Xb, 3.45 g.) was dissolved in 50 ml. of 1.0 *N* methanolic potassium methoxide. The solution was refluxed for 4 hr., then poured into 100 ml. of water and extracted with ether. The ether layers were washed well with water and then dried over anhydrous magnesium sulfate. Removal of solvent left 1.35 g. of clear oil. Trituration with hexane gave 229 mg. (10%) of white needles: m.p. 85–102°; ν_{max} 3300, 3090, 1712, 1694, 1560, 1247, 1089, 1070, and 1044 cm.$^{-1}$; n.m.r. spectrum (CCl_4) had bands at τ 2.95 (aromatic protons), 6.45 (ester methyl), and 6.73 (methoxy). An analytical sample, m.p. 104.5–105.5°, was obtained by two recrystallizations from acetone–hexane.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 65.87; H, 7.30; N, 6.04.

The remaining oil was shown by n.m.r. to consist of a mixture of the above methoxy methyl carbamate and of the imine XII.

Basic Hydrolysis of Methyl (*trans*-2-Iodo-1-tetralin)carbamate (Xa). A. Isolation of N-(Phenylcarbamoyl)-1,2,3,4-tetrahydronaphthalen(1,2)imine.—From 3.31 g. of the carbamate Xa on warming with methanolic potassium hydroxide,[2] there was obtained 1.12 g. of crude 1,2,3,4-tetrahydronaphthalen(1,2)imine (XII), m.p. 44–48°. This material was dissolved in hexane and 1 ml. of phenyl isocyanate was added. The white precipitate, which resulted, after drying weighed 1.48 g. (56%) and melted at 156–157.5°. The material was identified by comparison of its infrared spectrum with that of authentic material.[2]

B. Isolation of Methyl (*trans*-1-Methoxy-2-tetralin)carbamate (XIV).—Three experiments were run using identical procedures, except that the amount of water in the solvent was varied from 0% to 20%. The general procedure was as follows.

Methyl (*trans*-2-iodo-1-tetralin)carbamate (Xa, 3.31 g., 0.01 mole) was dissolved in 100 ml. of 1.5 *N* methanolic potassium hydroxide. The solution was refluxed for 1 hr., then poured into 200 ml. of water and extracted with ether (three 100-ml. portions), dried, filtered, and evaporated to obtain the crude product. This material was weighed and a portion was removed for spectral examination. In each case, the infrared spectrum indicated that the crude mixture was essentially imine XII contaminated with a small amount of a carbamate.

The remaining material was dissolved in 30 ml. of ether and washed with 10% hydrochloric acid (two 20-ml. portions) to remove the basic material. The ether solution was dried and evaporated in a tared flask to obtain the neutral fraction. In each case, the neutral material was identical by infrared spectra with the methyl (*trans*-1-methoxy-2-tetralin)carbamate (XIV) prepared as mentioned above.

The yield of the imine XII was calculated by subtracting the weight of the neutral fraction from the weight of the total crude product, before hydrochloric acid extraction. The results of the three experiments are summarized in Table IV.

TABLE IV

H_2O, %	Crude product: Wt., g.	Crude product: M.p., °C.	After HCl extraction[a]: Wt., g.	After HCl extraction[a]: M.p., °C.	Yield, %: XII	Yield, %: XIV
0	1.233	36–44	0.151	95–99	74.7	5.2
10	1.142	44–47	0.076	98–100	73.5	2.6
20	1.161	45–50	0.038	95–98	77.5	1.5

[a] Corrected for the amount of crude material removed for spectral analysis.

Basic Hydrolysis of Isopropyl (*trans*-2-Iodo-1-tetralin)carbamate (Xc). A. Isolation of N-(Phenylcarbamoyl)-1,2,3,4-tetrahydronaphthalen(1,2)imine.—A solution of the isopropyl car-

(16) M. Barker, L. Hunter, and N. G. Reynolds, *J. Chem. Soc.*, 874 (1948).

bamate Xc (3.58 g.) in 100 ml. of 1.5 *N* methanolic potassium hydroxide was refluxed for 2 hr. The solution was poured into water and worked up as usual. There was obtained 1.01 g. of crude imine (XII) as a semisolid. This material was dissolved in ether–hexane and 1 ml. of phenylisocyanate was added. The resulting white precipitate was filtered off, washed with hexane, and dried. The yield of product was 1.01 g., m.p. 157–160°. The material was identified by comparison of its infrared spectrum with that of the authentic material.

B. Isolation of Methyl (*trans*-1-Methoxy-2-tetralin)carbamate (XIV).—A solution of 6.18 g. of the isopropyl carbamate Xc in 200 ml. of 1.5 *N* methanolic potassium hydroxide was refluxed for 1.5 hr., then worked up as usual. There was obtained 2.353 g. of crude semisolid. The infrared spectrum of this material showed that it was mostly imine XII, contaminated with a small amount of a carbamate.

The crude product was dissolved in ether (50 ml.) and washed with 1 *N* sulfuric acid (40 ml.). After drying over magnesium sulfate, the solution was evaporated to dryness to yield 288 mg. (5.8%) of the product, m.p. 73–83°. Several recrystallizations from hexane gave pure methyl (*trans*-1-methoxy-2-tetralin)-carbamate (XIV), m.p. 103–104°, identical by mixture melting point and infrared spectrum with a sample of the authentic material.

2-Deoxy-D-*arabino*-hexonic Acid 6-Phosphate and Methyl 2-Deoxy-β-D-*arabino*-hexopyranoside 4,6-(Monophenyl phosphate)

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Treatment of methyl 2-deoxy-β-D-*arabino*-hexopyranoside (I) with diphenyl phosphorochloridate under mild conditions yielded sirupy methyl 2-deoxy-β-D-*arabino*-hexopyranoside 6-(diphenyl phosphate) (II). Catalytic removal of the phenyl residues resulted in isolation of crystalline methyl 2-deoxy-β-D-*arabino*-hexopyranoside 6-[bis(cyclohexylammonium) phosphate] (IIb). Hydrolysis and oxidation with barium hypoiodite gave the crystalline bis(cyclohexylammonium) salt of 2-deoxy-D-*arabino*-hexonic acid 6-phosphate (V). Treatment of a phosphorylation mixture with base produced the crystalline methyl 2-deoxy-β-D-*arabino*-hexopyranoside 4,6-(monophenyl phosphate) (III), obtained also from methyl 2-deoxy-β-D-*arabino*-hexopyranoside and phenyl phosphorodichloridate; III formed a crystalline hexylammonium salt. 3,4,5-Tri-*O*-benzoyl-2-deoxy-6-*O*-trityl-D-*arabino*-hexose diethyl dithioacetal is recorded.

Selective phosphorylations of primary hydroxyl groups in carbohydrates employing diphenyl phosphorochloridate have been noted in the literature. Maley and Lardy[2] synthesized 2-amino-2-deoxy-D-glucose 6-phosphate by selective phosphorylation of 2-amino-*N*-anisylidene-2-deoxy-D-glucose with diphenyl phosphorochloridate. Tener and Khorana[3] phosphorylated benzyl β-D-ribofuranoside with diphenyl phosphorochloridate. Mild alkali hydrolyzed any secondary phosphate ester formed and they isolated benzyl β-D-ribofuranoside 6-(diphenyl phosphate). Ukita and Nagasawa[4] reported the phosphorylation of an anomeric mixture of methyl 2-deoxy-D-*erythro*-pentofuranosides with diphenyl phosphorochloridate. The sirupy mixture isolated was identified as the 5-(diphenyl phosphate) ester and the 3,5-bis(diphenyl phosphate) diester. Remizov[5] has reported the selective phosphorylation of methyl 2-deoxy-α-D-*arabino*-hexopyranoside with diphenyl phosphorochloridate at reduced temperature. Remizov was able to correlate the selective phosphorylation with a synthesis in which the primary hydroxyl group was protected as a trityl ether.

It was our desire to synthesize 2-deoxy-D-*arabino*-hexonic acid 6-phosphate for use as a possible metabolic blocking agent in the pentose phosphate pathway.[6] 3-Deoxy-D-*ribo*-hexonic acid 6-phosphate has been reported by Dahlgard and Kaufmann.[7] Several unsuccessful reports of the chemical synthesis of 2-deoxy-D-*arabino*-hexose 6-phosphate[8] had preceded Remizov's report. Enzymic syntheses of 2-deoxy-D-*arabino*-hexose 6-phosphate are known[9]; however, it did not appear that this route would provide the quantity of material needed.

The report by Inglis, Schwarz, and MacLaren[10] of the methoxy mercuration of tri-*O*-acetyl-D-glucal provided a ready route to methyl 2-deoxy-β-D-*arabino*-hexopyranoside (I). Phosphorylation of (I) with an equivalent amount of diphenyl phosphorochloridate using Remizov's method[5] yielded 80% of the expected amount of material as a sirup which was converted to a crystalline bis(cyclohexylammonium) salt, $[\alpha]_D$ −30°. Using Remizov's value of $[\alpha]_D$ +42.8° for the corresponding α-D-anomer and Hudson's isorotation rules, a value of $[\alpha]_D$ −29° was calculated.

Removal of the glycosidic methyl group had been achieved by Remizov by heating the bis(cyclohexylammonium) salt on a boiling water bath with a slight excess of 0.5 *N* hydrobromic acid. Paper chromatography of the resulting product had demonstrated the presence of inorganic phosphate. We circumvented this by using a lower temperature (68°) for the hydrolysis of the β-D-anomer (II) by its own acidity. The oxidation used was a modification[7] of the barium hypoiodite oxidation method of Goebel.[11] A crystalline bis(cyclohexylammonium) salt of 2-deoxy-D-*arabino*-hexonic acid 6-phosphate was obtained and attempts to obtain the tris(cyclohexylammonium) salt were unsuc-

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