157–158°; reported[20] m.p. 97–99°, m.p. phenylurethan 152–154°.

(20) J. D. Roberts, E. R. Trumbull, W. Bennett and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

Acknowledgment.—This investigation was made possible by the award of a visiting studentship (to K. N.) from the Kao Soap Co., Ltd., Tokyo, Japan.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA, DAVIS, CALIFORNIA]

Amines Derived from Dihalopropenes. I. The Mechanism of Allenimine Formation[1a,b]

BY ALBERT T. BOTTINI AND ROBERT E. OLSEN[1c]

RECEIVED JULY 31, 1961

Treatment of N-(2-bromoallyl)-*n*-propylamine (Ia) with sodium amide in tritium-labeled liquid ammonia has been found to yield radioactive N-*n*-propylallenimine (IIa). No significant exchange with solvent of the hydrogens bonded to carbon of Ia and IIa occurred under the reaction conditions. Compound IIa was degraded and determination of the radioactivity of the degradation products showed that 99.8 ± 0.3% of the tritium was incorporated in IIa at the ring-methylene group. These results are consistent with the proposal that an N-alkylallenimine is formed *via* an elimination–addition mechanism involving an allenic amine intermediate (III).

When an N-(2-bromoallyl)-alkylamine (I) is treated with an alkali metal amide in liquid ammonia the principal product is the N-alkylallenimine (1-alkyl-2-methyleneaziridine, II).[2] A small amount of the corresponding N-alkylpropargylamine (IV) also is formed.

Several plausible mechanisms can be written to explain the formation of II from I.[3] Internal displacement of bromide ion can be envisaged as occurring by an SN2-type reaction (1) or an addition–elimination reaction (2). Formation of II can also be the result of an elimination–addition reaction (3) involving an allenic amine intermediate (III). The possibility of an analogous elimination–addition mechanism (4) involving IV is precluded by the high yields of N-alkylpropargylamines obtained from reactions of N-(2-chloroallyl)-alkylamines with alkali metal amides in liquid ammonia.[2b]

From consideration of these mechanisms, it appeared likely that a choice between paths 1, 2 and 3 could be made by examination of II obtained from an appropriate N-(2-bromoallyl)-alkylamine (I) and amide ion in tritium-enriched ammonia. The absence of tritium in II would indicate that 1 is the reaction path since intermediates V in 2 and VII in 3 would be expected to abstract a proton from the solvent. However, the absence of tritium in II could not be used to rule out 2 as the reaction mechanism since it is conceivable that loss of bromide ion from V to yield unlabeled II could occur at a much faster rate than the reaction of V with ammonia to yield radioactive VI. If I and II (aside from the amine hydrogen) do not undergo exchange with the solvent under the reaction conditions, presence of tritium in II would definitely rule out 1 as the exclusive reaction mechanism. A choice between 2 and 3 could be made by degrading II and determining the location of the incorporated tritium. Path 2 would yield II labeled at the exocyclic-methylene group; path 3 would yield II labeled at the ring-methylene group.

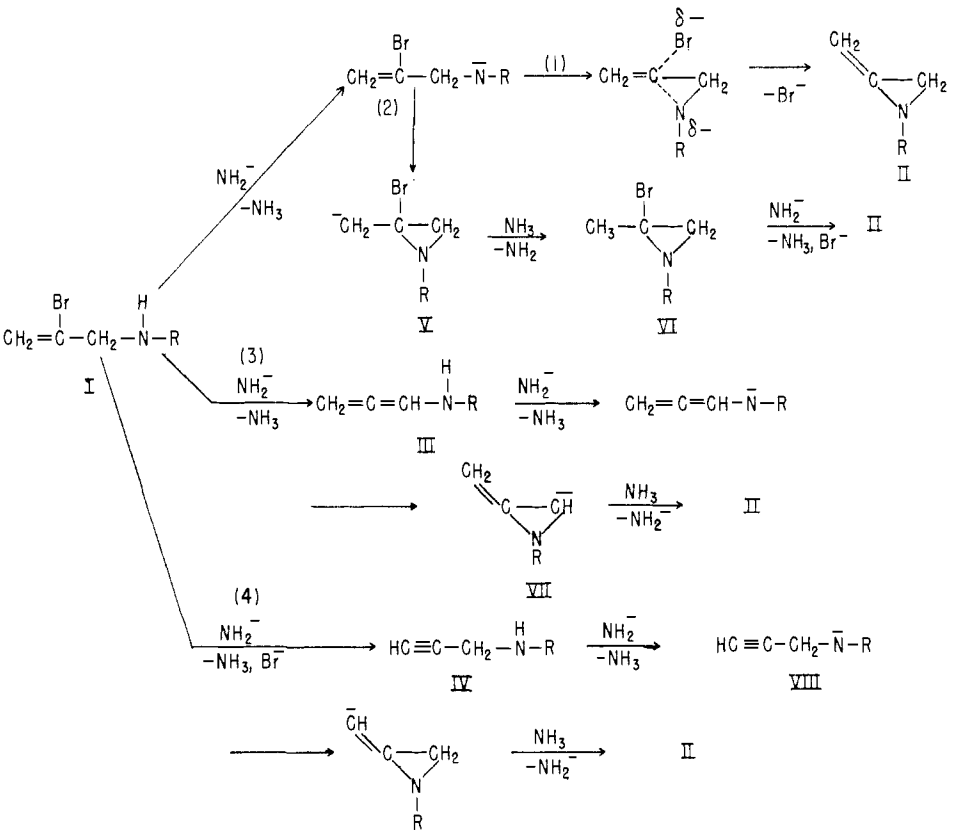
It was decided to treat N-(2-bromoallyl)-*n* propylamine (Ia, R = *n*-C_3H_7) with sodium amide in tritium-labeled liquid ammonia because it appeared likely that the N-*n*-propylallenimine (IIa, R = *n*-C_3H_7) obtained could be hydrogenated to di-*n*-propylamine in high yield[2a] and a convenient procedure for conversion of primary and secondary amines to the corresponding carbonyl compounds had been worked out in these laboratories.

Compound Ia was prepared in 81% yield by treatment of 2,3-dibromopropene with excess *n*-propylamine in water. Treatment of Ia with sodium amide in liquid ammonia which had been equilibrated with a small amount of tritium oxide gave IIa in 39% yield together with a small amount of N-*n*-propylpropargylamine (IVa, R = *n*-C_3H_7). Compound IIa was freed of the last traces of IVa by distillation from lithium aluminum hydride at reduced pressure. Determination of the radioactivity of purified IIa indicated that it had a specific activity equal to the calculated specific activity of the hydrogens of the ammonia, *i.e.*, one-third the specific activity of the ammonia. The hydrogens bonded to carbon of Ia and IIa did not undergo exchange with the solvent under the reaction conditions since treatment of excess Ia with sodium amide in tritium-enriched liquid ammonia and treatment of radioactive IIa with sodium amide in ordinary liquid ammonia caused no significant change in the specific activity of either compound. These results ruled out 1 as the exclusive mode of formation of IIa. The equal specific activities of the product and the hydrogens of the solvent, which is to be expected if a carbanion intermediate such as VII or, possibly, V is

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, Administered by the American Chemical Society, for partial support of this research. (b) Presented in part at the 140th National meeting of the American Chemical Society, Chicago, Ill., September, 1961. (c) American Chemical Society–Petroleum Research Fund Fellow, 1961.

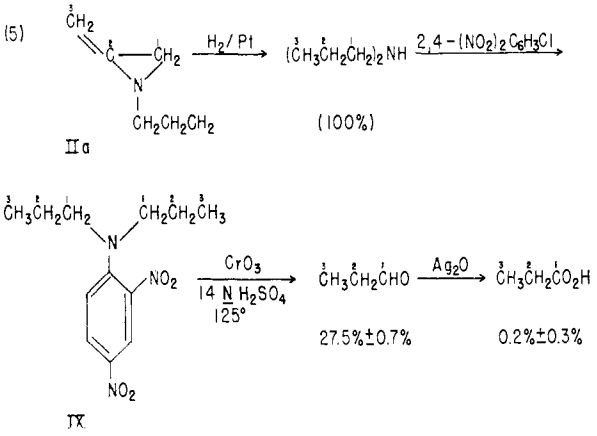
(2) (a) C. B. Pollard and R. F. Parcell, *J. Am. Chem. Soc.*, **73**, 2925 (1951); (b) A. T. Bottini and J. D. Roberts, *ibid.*, **79**, 1462 (1957); (c) unpublished work of A. T. Bottini, R. E. Olsen and B. J. King.

(3) *Cf.* S. I. Miller and P. K. Yonan, *J. Am. Chem. Soc.*, **79**, 5931 (1957), and D. E. Jones, R. O. Morris, C. A. Vernon and R. F. M. White, *J. Chem. Soc.*, 2349 (1960).



formed in the reaction,[4] indicate further that path 1 accounts for little, if any, of the IIa formed.[5]

Radioactive IIa was degraded to propionic acid in four steps. Liquid products were converted to colorless solid derivatives which were purified by several recrystallizations, and the specific activities of the derivatives were determined by the scintillation count technique. The activities of the degradation products are shown in 5 as percentages of the specific activity of IIa.



Several features of the degradation scheme should be noted before the results are discussed. There was no significant exchange of the ring-hydrogens of IIa with platinum hydride during the hydrogenation since the specific activities of IIa and di-*n*-propylamine (as the hydrochloride and as the *p*-bromobenzenesulfonamide) were the same within experimental error. No exchange of the aliphatic hydrogens of N,N-di-*n*-propyl-2,4-dinitroaniline (IX) with the solvent occurred during the chromic acid oxidation since oxidation of inactive IX with chromic acid in tritium-enriched 14 *N* sulfuric acid gave inactive propionaldehyde (isolated as the methone derivative). During the oxidation in the radioactive medium, some tritium oxide co-distilled with the propionaldehyde and some tritium was incorporated in the methone derivative. Virtually all of the tritium was removed from this derivative by recrystallization from ethanol whereas the radioactivity of the methone derivative of the propionaldehyde prepared from tritiated IX in ordinary 14 *N* sulfuric acid was not decreased by recrystallization from ethanol. These results are reasonable since the hydrogens attached to the cyclohexanedione rings of the methone derivative are expected to equilibrate rapidly with the hydrogens of the hydroxylic solvent, whereas the other hydrogens of the methone derivative are not expected to exchange with the solvent.

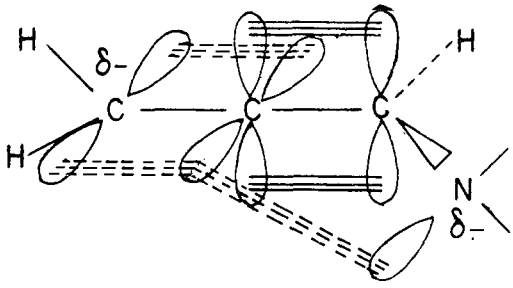
As can be seen from 5, the propionic acid, which should contain all the tritium incorporated at the exocyclic carbon (C_3) and none of the tritium incorporated at the ring carbon (C_1) during the formation of IIa, was found to have virtually no radioactivity. This and the nearly equal specific

(4) K. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(5) Treatment of N-(2-bromoallyl)-methylamine (Ib, R = C_4H_7) with sodium amide in liquid ammonia containing 0.408 μc./mmole of tritium yielded N-methylallenimine (IIb, R = CH_3) with a specific activity of 0.136 μc./mmole. Treatment of inactive IIb with sodium amide in liquid ammonia containing 1.0 μc./mmole yielded IIb with a specific activity of <0.002 μc./mmole. Details of these experiments are given by R. E. Olsen, Thesis, University of California, Davis, 1961.

activities observed for IIa and the hydrogens of the liquid ammonia are consistent only with the proposal that IIa and other allenimines prepared from N-(2-bromoallyl)-alkylamines are formed primarily, if not exclusively, *via* 3.[6]

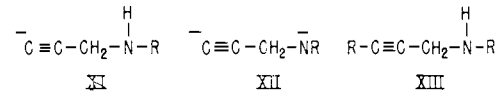
It seems likely that the transition state leading to formation of an allenimine is approximated by X, *i.e.*, the new bond formed by carbon and nitrogen during the reaction is formed by attack of nitrogen on the nearest *p*-orbital whose axis lies in the plane defined by the three allene carbons and the nitrogen atom. As bond formation proceeds, the incipient exocyclic carbon atom can be pictured as moving back from the line of the two other allenic carbons in a direction away from the incoming nitrogen atom. Also occurring during bond formation is rotation of the bond between the incipient exocyclic carbon atom and the ring carbon and lengthening of the bond between the two incipient ring carbons. This process leads to formation of an allylic carbanion of which VII is a resonance form.



X

An acetylenic carbon and the central carbon of an allene group have digonal (*sp*) hybridization and many examples of nucleophilic addition to acetylenes are known.[8] Surprisingly, though, there appears to be no straight-forward example of nucleophilic addition to the diagonal carbon of an allene. It is conceivable that the reaction of an allene with an alkoxide in alcohol to yield a vinyl ether[9] can occur by nucleophilic addition to an acetylene formed by prior, base-induced isomerization of the allene *via* intermediate carbanions.[10] The failure of III to isomerize completely to an acetylenic amine such as IV before ring closure to II indicates that the most acidic hydrogen of III is the amino hydrogen. The removal of a second proton from III necessary for rearrangement to an acetylenic amine is expected to be retarded by the presence of the negative charge on nitrogen, thereby favoring the competing ring closure to VII.

It is noteworthy that in the presence of amide ion virtually all of IV will be in the form of the carbanion XI rather than the amide ion VIII. Formation of III *via* mechanism 4 would therefore require an extremely large rate constant for the ring-closure reaction of VIII. Although 4 and nucleophilic additions to acetylides such as XI and XII were ruled out by the observed stability of alkylpropargylamines, the possibility of conversion of acetylenic amines such as XIII, which cannot form acetylides, to allenimines by treatment with an alkali metal amide in liquid ammonia remains to be tested. Such a test might provide the answer to the question of the relative rates of nucleophilic addition to an acetylenic carbon and the digonal carbon of an allene.



XI XII XIII

Mechanism 2 was considered because numerous examples of analogous addition–elimination reactions are known.[11] However, a vinyl chloride is expected to undergo an addition–elimination reaction with a nucleophilic reagent more rapidly than a vinyl bromide because chlorine is more electronegative than bromine, and the failure of N-(2-chloroallyl)-alkylamines to yield significant amounts of the corresponding allenimines[2b,c] seemed more consistent with the SN2-type mechanism (1) than with 2. Mechanism 2 could not be removed from consideration because of this inconsistency since it was conceivable that the ratio of the rates of dehydrohalogenation across the double bond of an N-(2-chloroallyl)-alkylamine and an N-(2-bromoallyl)-alkylamine was much greater than the ratio of the rates of internal nucleophilic addition to the vinylic carbon attached to chlorine and the vinylic carbon attached to bromine.

Experimental

Melting points and boiling points are uncorrected. Vapor phase chromatograms were obtained using a 2-m. column which contained a packing of nonyl phthalate on firebrick in a model 1 Chromat-O-Fex (Loe Engineering Co., Pasadena, Calif.). Microanalyses were performed by Mr. V. H. Tashinian, Berkeley, Calif., and Drs. Weiler and Strauss, Oxford, England.

N-(2-Bromoallyl)-*n*-propylamine (Ia).—In a 1-l., 3-necked flask equipped with a stirrer, reflux condenser and dropping funnel were placed 177 g. (3.0 moles) of *n*-propylamine and 54 g. (3.0 moles) of water. 2,3-Dibromopropene (200 g., 1.0 mole) was added dropwise in 75 min. to the stirred solution. When the addition was complete, stirring was continued for 6 hr. and the homogeneous solution was allowed to stand overnight. The solution was cooled in an ice-bath, 60 g. (1.5 moles) of sodium hydroxide was added with stirring, and the resulting mixture was extracted 3 times with 150-ml. portions of ether. The ether extracts were combined, dried over sodium hydroxide, and the *n*-propylamine and ether were removed by distillation. The residual oil was distilled at reduced pressure under nitrogen through a 20-cm. Vigreux column and 144 g. (81%) of Ia was collected at 53.0–53.5° (20 mm.), $n^{19}D$ 1.4759, $n^{25}D$ 1.4734.

Anal. Calcd. for $C_6H_{12}BrN$: C, 40.47; H, 6.79. Found: C, 40.30; H, 6.78.

(6) The specific activities of IIa and propionaldehyde indicate that an α-hydrogen of IX-1-*t* is removed 1.2 times faster than the α-tritium of IX-1-*t* in the rate-determining step of the oxidation with chromic acid in 14 *N* sulfuric acid at 125°. The observed kinetic isotope effect (k_H/k_T) = 1.2) is much less than the hydrogen–deuterium kinetic isotope effect observed in the oxidation of isopropyl alcohol with chromic acid,[7] although it should be noted that the reaction conditions were quite different and the kinetic isotope effect is expected to decrease with increasing temperature.[4]

(7) F. H. Westheimer and N. Nicolaides, *J. Am. Chem. Soc.*, **71**, 25 (1949).

(8) See W. E. Truce and J. A. Simms, *ibid.*, **78**, 2756 (1956), and references cited therein.

(9) A. Faworski, *J. prakt. Chem.*, [2] **44**, 208 (1891).

(10) T. L. Jacobs, R. Akawie and R. G. Cooper, *J. Am. Chem. Soc.*, **73**, 1273 (1951).

(11) See E. F. Silversmith and D. Smith, *J. Org. Chem.*, **23**, 427 (1958), and references cited therein.

During an attempt to distil the product from another run at atmospheric pressure, most of the Ia (b.p. 173–174°) polymerized in the column.

Compound Ia (0.70 g.) was converted to the *p*-bromobenzenesulfonamide derivative[12a] in 92% yield. After recrystallization from dilute ethanol, it had m.p. 58.0–59.0°.

Anal. Calcd. for $C_{12}H_{15}Br_2NO_2S$: C, 36.29; H, 3.81. Found: C, 36.60; H, 3.95.

N-*n*-Propylallenimine-3-*t* (**1-*n*-Propyl-2-methyleneaziridine-3-*t***).—In a 2-l., 3-necked flask equipped with a stirrer, gas inlet tube and Dry Ice reflux condenser protected with a soda lime tube was condensed 1500 ml. (lit.[13] $d^{-33.4}$ 0.6814, 1020 g., 60 moles) of anhydrous ammonia. The gas inlet tube was replaced with a dropping funnel and a small piece of freshly cut sodium was added to the ammonia. The blue color of the resulting solution did not fade in 2 min. Water (30 μl.) containing 3.0 mc. of tritium oxide (New England Nuclear Corp.) was added to the stirred solution. After 10 min., 100 mg. of dry ferric chloride was added with subsequent addition of 41.5 g. (1.80 moles) of freshly cut sodium in 1 hr. When the blue color disappeared (about 75 min. was required), Ia (258 g., 1.45 moles) was added dropwise in 75 min. to the stirred sodium amide slurry. After the mixture had stirred for an additional 6.5 hr. (about 500 ml. of liquid ammonia was allowed to evaporate), 500 ml. of ether was added followed by the dropwise addition of 50 ml. of water. The mixture was allowed to stand overnight and most of the ammonia evaporated. The ether solution was separated, dried over sodium hydroxide and distilled through a 250 × 13-mm. column packed with glass helices and equipped with a total reflux head. The fraction with b.p. 104–107°, $n^{20.5}D$ 1.4350, was collected. The fraction weighed 58.9 g. (42%) and vapor phase chromatographic (v.p.c.) analysis indicated that it consisted of 93% IIa and 7% IVa. A portion (10 g.) of the mixture was added to 25 ml. of *ca.* 0.3 *M* lithium aluminum hydride in ether. The resulting mixture, which contained a large amount of white, flocculent precipitate, was centrifuged and the supernatant liquid was distilled at <1 mm. into a receiver cooled in a Dry Ice–acetone-bath. The distillate was found by v.p.c. analysis to consist only of ether and IIa. The ether–IIa solution was redistilled through a 60-cm. Podbielniak-type column[14] and 6.5 g. (70%) of IIa was collected at 104–106°, $n^{22}D$ 1.4341.

Anal. Calcd. for $C_6H_{11}N$: C, 74.17; H, 11.14; N, 14.42. Found: C, 74.19; H, 11.29; N, 14.16.

Di-*n*-propylamine-1-*t*.—The purified IIa (1.8 g., 0.019 mole) was hydrogenated in 50 ml. of aqueous ethanol over platinic oxide under a hydrogen pressure of 20–30 p.s.i. for 6 hr. The catalyst was removed by filtration and the filtrate was acidified with 6 *N* hydrochloric acid. The acidic solution was evaporated to dryness and the residue was recrystallized from acetone to yield 2.0 g. (80%) of di-*n*-propylamine hydrochloride as white flakes. A mixture of 0.76 g. of *p*-bromobenzenesulfonyl chloride, 0.48 g. of the amine hydrochloride and 10 ml. of 10% sodium hydroxide solution was heated on a steam-bath for 45 min. to yield 0.72 g. (76%) of N,N-di-*n*-propyl-*p*-bromobenzenesulfonamide. After 2 recrystallizations from ethanol, the derivative had m.p. 55.0–55.7°. The melting point was not depressed when the derivative was mixed with an analytical sample of N,N-di-*n*-propyl-*p*-bromobenzenesulfonamide prepared from commercial di-*n*-propylamine.

Anal. Calcd. for $C_{12}H_{16}BrNO_2S$: C, 45.00; H, 5.66; N, 4.37. Found: C, 45.18; H, 5.74; N, 4.55.

N,N-Di-*n*-propyl-2,4-dinitroaniline-1-*t* (**IX-1-*t***).—A solution of 9.0 g. (0.044 mole) of 2,4-dinitrochlorobenzene, 6.66 g. (0.049 mole) of di-*n*-propylamine-1-*t* hydrochloride and 13.0 g. (0.094 mole) of sodium acetate trihydrate in 150 ml. of 70% aqueous ethanol was heated at reflux for 5 hr. The reaction mixture was allowed to stand overnight and the oil that settled out during the reflux period crystallized. The orange crystals weighed 11.3 g. (96%). A sample, after recrystallization from ethanol and from Skellysolve B, had m.p. 41–42° (lit.[15] m.p. 40°).

Chromic Acid Oxidation of IX-1-*t*.—A mixture of 0.50 g. (1.9 mmoles) of IX-1-*t* and 25 ml. of 14 *N* sulfuric acid was heated to boiling in a 50-ml. distillation flask. A solution of 0.50 g. (5.0 mmoles) of chromium trioxide in 25 ml. of 14 *N* sulfuric acid was added slowly in 10 min. as water and propionaldehyde were distilled from the reaction mixture into an aqueous solution containing 0.70 g. (5.0 mmoles) of methone. The propanal-1-*t*-dimethone (0.45 g., 36%) had m.p. 154.5–155.0° (lit.[12b] m.p. 155°) after recrystallization from dilute ethanol. A second recrystallization from dilute ethanol did not raise the melting point.

A 1.0-g. sample of IX-1-*t* was oxidized in the same manner and the distillate was made up to 30 ml. The solution was made slightly alkaline with dilute sodium hydroxide solution and 1.0 g. (4.3 mmoles) of silver oxide was added. The mixture was shaken intermittently during a 6-hr. period and allowed to stand overnight. The solids were removed by filtration and 30 ml. of ethanol and 1.0 g. (3.6 mmoles) of *p*-phenylphenacyl bromide were added to the filtrate. The mixture was heated at reflux for 3 hr. to yield 0.51 g. (25%) of *p*-phenylphenacyl propionate, m.p. 104.0–104.3° (lit.[12c] m.p. 103°) after 2 recrystallizations from dilute ethanol and 1 recrystallization from Skellysolve B.

Radioactivity Determinations.—Solutions of IIa-3-*t* and the solid derivatives of its degradation products, with the exception of di-*n*-propylamine-1-*t* hydrochloride, were prepared by dissolving samples of known weight in toluene containing 0.6% (by wt.) of DPO (2,5-diphenyloxazole) and 0.05% (by wt.) of POPOP (1,4-bis-2-(5-phenyloxyazolyl)-benzene). Samples of IIa-3-*t* and di-*n*-propylamine-1-*t* hydrochloride were dissolved in absolute ethanol and the solutions were diluted with equal volumes of toluene containing DPO and POPOP. The ethanol–toluene solvent had an efficiency of 9.2% of that of the toluene solvent. At least 3 solutions were prepared for each sample and the most concentrated solution was at least twice as concentrated as the least concentrated solution. Solutions of N,N-di-*n*-propyl-*p*-bromobenzenesulfonamide-1-*t* and propanal-1-*t*-dimethone exhibited self-quenching at concentrations above approximately 6.0 mg./ml. Radioactivity measurements were made using a Packard Tri-Carb model no. 314 Liquid spectrometer. The results are given in Table I.[16]

TABLE I

RADIOACTIVITY DETERMINATIONS OF DEGRADATION PRODUCTS OF N-*n*-PROPYLALLENIMINE-1-*t* OBTAINED FROM TRITIUM-ENRICHED AMMONIA

Compound	Specific activity, μc./mmole × 10^2	% total activity
N-*n*-Propylallenimine-1-*t*	1.62 ± 0.03	(100)
Di-*n*-propylamine[a]	1.59 ± .03	(100)
Di-*n*-propylamine[b]	1.58 ± .05	(100)
Propionaldehyde[c]	0.441 ± .012	27.05 ± 07
Propionic acid[d]	(3 ± 5) × 10^{-3}	0.2 ± 0.3

[a] As di-*n*-propylamine hydrochloride. [b] As N,N-di-*n*-propyl-*p*-bromobenzenesulfonamide. [c] As propanaldimethone. [d] As *p*-phenylphenacyl propionate.

Attempted Exchange of Ia with Sodium Amide in Tritiated Liquid Ammonia.—To 300 ml. (204 g., 12 moles) of liquid ammonia contained in a 500-ml., 3-necked flask equipped with a stirrer, dropping funnel and Dry Ice reflux condenser was added 30 μl. of water containing 3.0 mc. of tritium oxide (New England Nuclear Corp.). Sodium amide (3.9 g., 0.10 mole, Roberts Chemical Co, Inc.) was added after 10 min. followed by the dropwise addition of 50 g. (0.28 mole) of Ia in 20 min. After the mixture had been stirred for 1.5 hr., 100 ml. of ether and 7 ml. of water were added cautiously. The ammonia was allowed to evaporate and the ether solution was separated, dried over sodium hydroxide and distilled through the Podbielniak-type column. A 0.70-g. portion of the recovered Ia (28 g., 56%) was converted in 91% yield to the *p*-bromobenzenesulfonamide derivative, m.p. 58.0–59.0° after 2 recrystallizations from dilute ethanol, which had a specific activity of (9.6 ± 3.7)

(12) (a) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," 2nd Ed., Interscience Publishers, Inc., New York, N. Y., 1957, p. 412; (b) p. 583; (c) p. 553.

(13) J. M. Timmermans, *Bull. soc. chim. Belg.*, **32**, 299 (1923).

(14) J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1950, pp. 237–243.

(15) P. Van Romburgh, *Rec. trav. chim.*, **8**, 248 (1889).

(16) We are most grateful to Mr. L. Matsen who carried out the radioactivity determinations.

$\times 10^{-5}\mu$c./mmole, or approximately 0.1% of the calculated specific activity of the hydrogens in the ammonia used.

Attempted Exchange of IIa-3-*t* with Sodium Amide in Liquid Ammonia.—To a stirred slurry of 2.5 g. (0.064 mole) of sodium amide and 300 ml. of liquid ammonia was added dropwise in 30 min. 24 g. (0.25 mole) of IIa-3-*t*, b.p. 104–107°, containing 7% IVa. When the mixture had stirred for 2 hr., 100 ml. of ether and 5 ml. of water were added cautiously. The ammonia was allowed to evaporate and the ether solution was separated, dried over sodium hydroxide and distilled through the Podbielniak-type column. A 5.0-g. portion of the fraction (17.0 g., 71%) with b.p. 104–106° was freed of IVa by treatment with lithium aluminum hydride, as shown by v.p.c. analysis, and hydrogenated in 80% aqueous ethanol over platinic oxide. The di-*n*-propylamine was isolated as the hydrochloride (4.9 g., 69%). The hydrochloride (0.53 g.) was converted in 85% yield to the *p*-bromobenzenesulfonamide derivative, m.p. 55.0–55.7° after 2 recrystallizations from ethanol, which had a specific activity of $(1.64 \pm 0.03) \times 10^{-2}\mu$c./mmole.

Chromic Acid Oxidation of IX in Tritium-enriched 14 *N* Sulfuric Acid.—Compound IX (0.50 g., 1.9 mmoles) was oxidized with chromic acid as described earlier except the solvent contained 1.0 mc. of tritium oxide. About 5 ml. of water was allowed to co-distil with the propionaldehyde into a solution containing 0.75 g. (5.4 mmoles) of methone. The methone derivative, m.p. 154–155°, weighed 0.50 g. (40%) and had a specific activity of $(1.42 \pm 0.02) \times 10^{-3}\mu$c./mmole. After one recrystallization from dilute ethanol, the methone derivative, m.p. 154.5–155.0°, had a specific activity of $(1.5 \pm 1.5) \times 10^{-5}\mu$c./mmole.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE FOR MEDICINE AND CHEMISTRY, CAMBRIDGE, MASS.]

The Synthesis of 19-Noraldosterone Acetate and Related 19-Substituted Steroids[1]

BY D. H. R. BARTON AND J. M. BEATON

RECEIVED AUGUST 3, 1961

Corticosterone 3,20-bisethylene ketal 21-acetate 11β-nitrite affords on photolysis a mixture of isomeric 18- and 19-substituted oximes. By further processing the former has been converted into aldosterone acetate. The 19-oxime has been transformed into the 19-substituted isomer of aldosterone (XXIII), into 19-hydroxycorticosterone, into 19-norcorticosterone and finally into 19-noraldosterone acetate. 19-Substituted steroids bearing 11β-hydroxyl groups thus become readily available. Starting with cortisol 3,20-bisethylene ketal 21-acetate 11β-nitrite the derived 18- and 19-oxo-derivatives have been prepared through the oximes in the usual way. The former has been transformed into 17α-hydroxy-18,21-anhydroaldosterone; the latter into the 19-isomer of 17α-hydroxyaldosterone.

Recent work[2] has shown that the photochemically induced exchange of H and NO within nitrite esters, discovered in this Institute,[3] can provide a useful synthetic method for steroids as well as for other types of compound. We have applied[4] the reaction specifically to the synthesis of aldosterone acetate. Photolysis of corticosterone acetate 11β-nitrite (I) gave the C_{18}-oxime II which, on deoximation with nitrous acid, furnished aldosterone acetate III. The same procedure could not be used for the synthesis of the C_{19}-isomer of aldosterone. This was because that moiety of the photolysis product which involved formation of the C_{19}-carbon radical IV involved also intramolecular cyclization to V which, on capture by nitric oxide, afforded the oxime VI. The present paper describes experiments designed to overcome this difficulty. The success that we have attained also has enabled us to prepare 19-noraldosterone acetate.

We reasoned that the cyclization of radical IV to radical V must be facilitated by the fact that the latter radical is resonance stabilized through distribution over oxygen as well as carbon. If, therefore, the 4(5)-ethylenic linkage of I could be moved to 5(6)-, this facilitation would no longer be present and there might be a reasonable chance of securing the true 19-substituted compounds that we desired. This argument was found to be correct by the facts outlined in the sequel.

Corticosterone 3,20-bisethylene ketal 21-acetate[5] (VII, R = H) was converted to the nitrite (VII, R = NO) and photolyzed according to our general method.[3] This afforded two isomeric oximes[6] (VIII) and (X). The 18-oxime VIII was characterised by dehydration with phosphorus oxychloride and pyridine to the nitrile XII. Its constitution was proved by deoximation with nitrous acid to give aldosterone 21-acetate bisethylene ketal (IX) which, on hydrolysis with 90% aqueous acetic acid,[7] afforded aldosterone 21-acetate (III). This procedure amounts to an alternative partial synthesis of the latter.

The 19-oxime X, which at first[1] resisted crystallisation, was characterized by dehydration with phosphorus oxychloride and pyridine which furnished, instead of the expected nitrile, the iminolactone XI. The latter may, of course, have been formed by the working up procedure. Deoximation of the 19-oxime X with nitrous acid afforded the expected masked aldehyde XIII which, on chromic acid oxidation, gave the γ-lactone XIV. Treatment of the latter with dioxane-hydrochloric acid at room temperature gave the mono-ketal XV. This compound was also obtained by similar acid treatment of the bis-ketal XIII under the same conditions to give the monoketal masked aldehyde XVI which on chromic acid oxidation afforded XV.

(1) This paper is Communication No. 14 from the Research Institute for Medicine and Chemistry. For a preliminary report see D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 750 (1961). The article by M. Akhtar and D. H. R. Barton, *ibid.*, **83**, 2213 (1961), is Communication No. 13.

(2) For summary see A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, in press (1961).

(3) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961).

(4) D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960); **83**, 4083 (1961).

(5) S. Bernstein and R. H. Lenhard, *ibid.*, **77**, 2331 (1955).

(6) For convenience we write these compounds as true oximes, but without commitment on our part as to whether this constitution or the alternative cyclized hydroxylamino-tautomer is correct. We have made this reservation[4] before in analogous compounds.

(7) J. Schmidlin, G. Anner, J.-R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta*, **40**, 2318 (1957).