had mp 44–44.5°; the isotopic composition was 8% d_0, 91% d_1, and 1% d_2.

12,12-d_2-Δ^{24}-5β-Cholestene (XXXII).—Methyl 12-ketocholanate (1 g) was heated under reflux with ethylene glycol (200 mg) and *p*-toluenesulfonic acid (50 mg) in benzene for 24 hr using a water separator. The crude ketal was taken up in ether and then heated under reflux with lithium aluminum hydride (500 mg) for 4 hr. Work-up in the usual manner gave 12-ketocholan-24-ol ethylene ketal which was homogeneous by thin layer chromatography. Moffatt oxidation[6] of this compound gave 12-ketocholan-24-al ethylene ketal (ν_{max} 3.7 and 5.8 μ (–CHO)) which was immediately subjected to the Wittig reaction as described above. Chromatography on silica gel gave the crude Δ^{24}-5β-cholesten-12-one ethylene ketal (220 mg) which was taken up in ethanol and stirred with *p*-toluenesulfonic acid (50 mg) for 3 hr. Dilution with water and ether extraction gave after recrystallization from methanol–chloroform, Δ^{24}-5β-cholesten-12-one (XXXI, 200 mg) with mp 116–118° and $[\alpha]^{25}D$ +101 (*c* 1.0).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.38; H, 11.46; mol wt, 384. Found: C, 84.34; H, 11.54; mol wt (mass spectroscopy), 384.

Electrolytic reduction of a 10-mg sample in dioxane–deuteriosulfuric acid gave 12,12-d_2-Δ^{24}-5β-cholestene (XXXII) whose isotopic composition was 4% d_0, 27% d_1, 66% d_2, and 3% d_3.

12,12-d_2-Δ^{22}-5α-Cholestene (XXXVI).—A stirred dispersion of sodium hydride (20 mg) in dimethyl sulfoxide (5 ml) was heated at 70–75° for 45 min. The resulting solution was cooled to room temperature, tetrahydrofuran (5 ml) added and the mixture cooled further in an ice–salt bath. Trimethyl sulfonium iodide (145 mg) in dimethyl sulfoxide (2 ml) was added followed by 12,12-d_2,5α-pregnan-20-one[20] (XXXIII, 148 mg) in tetrahydrofuran (3 ml). After 1.5 hr at room temperature, dilution with water and ether extraction gave crude 12,12-d_2-20-methyl-20,21-oxido-5α-pregnane (XXXIV) which after recrystallization from methanol had mp 116–117°; ν_{max} 11.6, 12.2 μ; mol wt (mass spectroscopy) 316.

The epoxide (XXXIV, 140 mg) in benzene (5 ml) was stirred with boron trifluoride etherate (6 drops) for 10 min. Saturated sodium carbonate (5 ml) was then added and the organic layer separated and dried. Evaporation of the solvent gave crystalline 12,12-d_2-20-formyl-5α-pregnane (XXXV) (ν_{max} 3.7 and 5.8 μ) which was treated immediately with the phosphorane prepared from isoamyltriphenylphosphonium iodide (1.16 g) and sodium hydride (60 mg). Chromatography of the product on alumina gave an oil (117 mg) which on recrystallization from methanol gave 12,12-d_2-Δ^{22}-5α-cholestene (XXXVI), mp 52–56° (probably a mixture of isomers at C-20 and at the double bond); the isotopic composition was d_0 2%, d_1 20%, d_2 55%, d_3 18%, and d_4 4%.

14α-d_1-Δ^{22}-5α-Cholestene (XXXVIII).—14α-d_1-5α-Pregnan-20-one (XXXVII, 30 mg)[23] was treated with dimethyl sulfonium methylide[22] prepared from trimethyl sulfonium iodide (326 mg) and sodium hydride (39 mg) in dimethyl sulfoxide (3 ml) and tetrahydrofuran (4 ml) as described above for the preparation of 12,12-d_2-Δ^{22}-5α-cholestene (XXXVI). Without isolation the resulting epoxide, in benzene, was treated with boron trifluoride etherate (6 drops) and the aldehyde produced subjected immediately to the Wittig reaction. Chromatography on alumina gave 14α-d_1-Δ^{22}-5α-cholestene (XXXVIII, 18 mg) as an oil; its isotopic composition was 14% d_0 and 86% d_1.

Registry No.—VIII, 14949-23-6; VIIIa, 14949-24-7; X, 14949-25-8; XI, 4877-66-1; XII, 14949-12-3; XIV, 14949-11-2; XV, 14949-13-4; XVI, 15076-93-4; XVIa, 14949-14-5; XVIb, 14949-15-6; XVII, 14949-16-7; XVIII, 14949-17-8; XX, 14949-18-9; XXI, 14949-19-0; XXII, 14949-20-3; XXIV, 14949-21-4; XXVI, 14949-22-5; XXVII, 14949-26-9; XXVIII, 14949-27-0; XXIX, 14949-28-1; XXXI, 14949-29-2; XXXII, 14949-55-4; XXXIV, 15077-14-2; XXXVI, 14949-56-5; XXXVIII, 14949-57-6.

Ozone Oxidation of Primary Amines to Nitroalkanes

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Ozonation of primary amines produces nitroalkanes in modest yields (25–53% optimum), which are dependent on the structure of the amine, the solvent, and the temperature. About 3 mole equiv of ozone are required and the probable intermediates are N-alkylhydroxylamines and nitrosoalkanes. By-products include aldehydes, ketones, acids, and amides in relative amounts which also depend on the structure of the amine. N-Alkylhydroxylamines are ozonated to nitroalkanes in better yields (43%). Ketimines derived from primary amines give nitroalkanes in poorer yields (15%). Oximes do not yield nitroalkanes on ozonation. Ozone compares favorably with other oxidizing agents for converting primary amines into nitroalkanes, especially when the amine group is attached to a primary alkyl group.

Various oxidizing agents convert primary aliphatic amines into nitroalkanes, but ozone is reported to give other products but not nitroalkanes. Long[2] states that primary amines do not react with ozone, while Bailey[3] reports that methylamine gives formaldehyde, methyl nitrite and nitrate, and ammonium nitrite and nitrate. Florentine[4] claims the production of carboxylic acids by ozonation of primary amines in the presence of water and a Japanese patent[5] describes the production of 9-aminononanoic acid by ozonation of oleylamine, indicating preferential attack on the double bond rather than on the amino group by the ozone.

With the thought that the reported failures to ozonize primary amines to nitroalkanes may have depended on the N–H bonds present in such amines, we decided to attempt the ozonation of ketimines, $R^1R^2C{=}NR^3$, instead. Previous work in this area has been concerned primarily with Schiff bases in which R^3 is aromatic and R^2 is hydrogen. Bailey[6] reports traces of nitrobenzene from N-benzylideneaniline, while Miller[7] reports a 10% yield of *p*-chloronitrobenzene from N-benzylidene-*p*-chloroaniline and a 14% yield of 1,4-dinitrobenzene from N-benzylidene-*p*-nitroaniline. Belew and Person[8] obtained an oxa-

(1) Commercial Solvents Corp. Research Assistant, 1965.
(2) L. Long, Jr., *Chem. Rev.*, **27**, 437 (1940).
(3) P. S. Bailey, *ibid.*, **58**, 925 (1958).
(4) F. P. Florentine, Jr., U. S. Patent 2,793,221 (May 21, 1957); *Chem. Abstr.*, **51**, 17982*g* (1957).
(5) H. Otsuki and H. Funahashi, Japanese Patent 4117 (1956); *Chem. Abstr.*, **60**, 16522*b* (1957).
(6) A. H. Riebel, R. E. Erickson, C. J. Abshire, and P. S. Bailey, *J. Am. Chem. Soc.*, **82**, 1801 (1960).
(7) R. E. Miller, *J. Org. Chem.*, **26**, 2327 (1961).
(8) J. S. Belew and J. T. Person, *Chem. Ind.* (London), 1246 (1959).

TABLE I
OZONATION OF AMINES AND AMINE DERIVATIVES

Compound	Solvent	Temp., 0°C	Ozone, mole equiv	Nitro compd, % yield
$CH_3CH_2CH_2CH_2NH_2$	CH_2Cl_2	−78	2.52	26.3
	CH_2Cl_2	0	3.34	17.0
	CH_2Cl_2	45	Excess	9.5
	Pyridine	−30	2.50	9.0
	Ether	−20	5.00	13.5
	CH_3CN	−65	3.60	16.5
$CH_3(CH_2)_3N{=}C(CH_3)_2$	CH_2Cl_2	−78	4.00	15.0
$CH_3(CH_2)_5CH(CH_3)NH_2$	CH_2Cl_2	−78	3.25	26.0[a]
$(CH_3)_3CNH_2$	CH_2Cl_2	−78	Excess	33.4
	$CH_3CO_2C_2H_5$	−78	2.58	31.8
	Water	0	Excess	14.2
$(CH_3)_3CH_2C(CH_3)_2NH_2$	None	−40	3.00	53.0
$CH_3CH_2CH(NH_2)CH_2OH$	CH_2Cl_2	−78	2.37	14.4
$C_6H_5NH_2$	CH_2Cl_2	−78	2.78	16.4
	CH_3CO_2H	18	Excess	5.0
$CH_3(CH_2)_5C(=NOH)CH_3$	CH_2Cl_2	−78	2.60	None[b]
$CH_3CH_2CH_2CH{=}NOH$	CH_2Cl_2	−78	3.00	None[c]
$(CH_3)_2CHNHOH$	CH_2Cl_2	−78	1.75	43.0

[a] 2-Octanone (4%) was also formed. [b] 2-Octanone (70%) formed. [c] Butyraldehyde (20%) and butyric acid (30%) formed.

zirane from N-isobutylidene-*t*-butylamine but no *t*-nitrobutane. The nearest approach to a true aliphatic ketimine investigated appears to be N-cyclohexylidene-*t*-butylamine which is reported[6] to give cyclohexanone and peroxidic materials but no *t*-nitrobutane on ozonation. The oxidation of ketimines with peracetic acid has been shown by Emmons[9] to give oxaziranes and nitrosoalkane dimers but not nitroalkanes.

N-Isopropylidenebutylamine gave 1-nitrobutane when ozonized (Table I). Various conditions were investigated, but the best yield (15%) was obtained in methylene chloride solution at −78° using 4 moles of ozone. The green coloration present throughout most of the reaction may have been due to the presence of nitrosobutane, a probable intermediate in the oxidation. A small amount of *n*-butylammonium chloride was also formed, indicating attack on the solvent.

n-Butylamine also gives 1-nitrobutane on ozonation. Yields of 25% were obtained under the conditions described above. Lower yields resulted in basic solvents and no reaction occurred in acetic acid, in which the amine was doubtless protonated.

For comparison, primary amines in which the alkyl group attached to the amino group was secondary, tertiary, or substituted with other groups were also studied. The secondary alkylamine, 2-octylamine, gave a similar yield (26%) and the tertiary alkylamine, *t*-butylamine, gave a higher yield (33%) of the corresponding nitroalkane. Aminoacetic acid and its ethyl ester did not react with ozone, but 2-amino-1-butanol gave 2-nitro-1-butanol in 14% yield.

Discussion

The oxidation of primary amines by ozone may be considered to be initiated by attack at the amine group leading initially to an alkylhydroxylamine (eq 1). When ozonation is interrupted after 1 mole equiv of ozone is introduced, a positive Tollens test may be obtained, indicative of an alkylhydroxylamine.[10] Furthermore, when N-isopropylhydroxylamine is ozonized under similar conditions, 2-nitropropane is formed in 43% yield.

$$RCH_2NH_2 \xrightarrow{O_3} RCH_2NHOH + O_2 \qquad (1)$$

Further ozonation probably produces nitrosoalkanes (eq 2), since there is a greenish blue color formed which

$$RCH_2NHOH \xrightarrow{O_3} RCH_2NO + H_2O + O_2 \qquad (2)$$

is characteristic of such compounds.[11] This color varies in intensity and shade with the nature of the amine, being strongest and bluest with tertiary alkylamines and weakest and greenest with primary alkylamines. Interruption of the reaction after addition of 2 moles of ozone and attempts to isolate either nitrosoalkanes or their dimers failed. These mixtures contained nitroalkanes and -amines, showing that nitrosoalkanes, if formed, are more rapidly oxidized than their amine or alkylhydroxylamine precursors. The possibility that the nitrosoalkanes may have isomerized rapidly to oximes and these may have been oxidized to nitroalkanes was excluded by the observation that oximes do not yield nitroalkanes on ozonation but are converted into aldehydes and carboxylic acids (aldoximes) or ketones (ketoximes). Since such products are by-products in the ozonation of amines, it is attractive to assume that nitrosoalkanes are intermediates in the reaction and that they isomerize in part to oximes and are converted into by-products to the extent that this occurs. Since the nitroso derivatives of tertiary alkyl groups can not isomerize in this fashion, it would be expected that the yields of nitroalkanes in these cases would be higher. This was observed to be true. *t*-Butylamine yielded half again as much nitroalkane as did *n*-butylamine.

The final step in the oxidation requires a third mole of ozone (eq 3). In general the best yields of nitro-

$$RNO \xrightarrow{O_3} RNO_2 + O_2 \qquad (3)$$

(9) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 6522 (1957).

(10) N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," Interscience Publishers, Inc., New York, N. Y., 1957, p 242.

(11) B. G. Gowenlock and W. Luttke, *Quart. Rev.* (London), **12**, 321 (1959).

alkanes were obtained when 2.5–3.0 mole equiv of ozone were used, although more was required when solvents were present that are attacked by ozone, *e.g.*, alcohols, ethers, and tertiary amines.

In addition to the by-products already mentioned, water and amides are formed. From *n*-butylamine ozonations N-butylbutyramide was isolated by distillation and identified by comparison with an authentic sample. Undistillable tars were also formed, but were not identified.

Attempts to improve the yields of nitroalkanes by inverse addition of amine to saturated solutions of ozone in methylene chloride, by adding a dehydrating agent ($MgSO_4$) to remove water as it formed, by adding a possible catalyst (I_2), and by adding a scavenger for oxides of nitrogen (urea) were unsuccessful. The process therefore can not be recommended as a preparation of nitroalkanes, but it remains a method of converting primary amines into nitroalkanes when necessary that compares favorably with methods using other oxidizing agents, such as hydrogen peroxide,[12] Caro's acid,[13] percarboxylic acids,[14] and permanganates,[12] especially where primary alkyl amines are involved.

Experimental Section

General Procedure.—Ozonations were conducted in a 40 × 270 mm vertical glass tube sealed at the lower end and immersed in a vacuum-jacketed bottle which served as a temperature control bath container. The reaction tube was fitted at the top with a ground glass closure through which passed (1) a 10-mm glass tube reaching to the bottom of the reactor and fitted at the bottom with a sintered glass bubbler and (2) an exit tube which led to a glass wash bottle containing 2% aqueous potassium iodide and from there to a wet test meter. Ozone from a Welsbach T-23 generator was passed through the empty apparatus to set the rate of flow with the aid of the wet test meter and to determine the ozone concentration by titration of the oxidized potassium iodide with standardized thiosulfate solution. The usual concentration of ozone used was 0.003 mole/l.

The compound to be ozonized (*ca.* 2 g in 30 ml of solvent) was introduced into the reactor, fresh potassium iodide solution was introduced into the wash bottle, and the ozone flow was continued until (1) a predetermined amount had passed, (2) a blue color was observed in the reaction vessel, or (3) the contents of the wash bottle became brown. The ozone stream was stopped, the reaction product removed from the bath, the solvent largely removed by distillation, and the product analyzed with the aid of an Aerograph A-350-B gas chromatograph fitted with a 6.0 ft × 0.25 in. column packed with 5% SF-96 on Chromosorb G (Wilkens Instrument and Research, Inc.) and equipped for small sample collection.

All gas chromatographic analyses were conducted with the aid of internal standards and predetermined thermal conductivity factors.[15] The standards used with each product were bromobenzene for the 2-nitropropane and nitrobutanes, *o*-nitrotoluene for 2-nitrooctane, 2-octanone, and nitrobenzene, 1,2-dichlorobenzene for butyraldehyde and butyric acid, 1-chloronaphthalene for 2-nitro-1-butanol, and synthetic N-butylbutyramide for itself. Samples collected from the gas chromatographic apparatus were analyzed chemically for the elements and their infrared spectra were measured on a Perkin-Elmer Model 21 instrument.

N-Isopropylidenebutylamine.—Acetone and *n*-butylamine were condensed[16] with the aid of potassium carbonate and the product was isolated by distillation: bp 127°; $n^{20}D$ 1.4235; d^{20}_4 0.7955; yield 81%; conversion 53%.

Anal. Calcd for $C_7H_{15}N$: N, 12.40. Found: N, 12.49.

Preparative-Scale Ozonations of Amines.—Amines (0.5 mole quantities) were ozonized to determine the yields obtainable by fractional distillation. In the case of *n*-butylamine, methylene chloride was used as solvent (3.0 moles) and the temperature was maintained at −78°. The yield of purified 1-nitrobutane, bp 45–48° (15 mm), was only 10.4%. N-Butylbutyramide was also isolated in 12.0% yield, bp 98–101° (1 mm).

With *t*-butylamine neat, a 22% yield of 2-methyl-2-nitropropane, bp 121–124°, was obtained. Ozonation was started at −78°, but the temperature had to be raised, eventually to 0°, as the water formed froze and interfered with passage of the gas through the mixture.

With *t*-octylamine (2,4,4-trimethyl-2-aminopentane) neat, a 53% yield of 2,4,4-trimethyl-2-nitropentane was obtained: bp 83–86° (18 mm); $n^{27}D$ 1.4332. The temperature was programmed as with *t*-butylamine. The absence of solvent leads to increased losses of the more volatile amines through evaporation into the gas stream.

Registry No.—N-Isopropylidenebutylamine, 6700-95-4; 1-nitrobutane, 627-05-4; 2-methyl-2-nitropropane, 594-70-7; 2,4,4-trimethyl-2-nitropentane, 5342-78-9; N-butylbutyramide, 10264-61-1.

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(16) The procedure used was that of D. C. Norton, V. E. Haury, F. C. Davis, L. J. Mitchell, and S. A. Ballard, *J. Org. Chem.*, **19**, 1054 (1954).