Cholestan-3β-ol-22-one (XXXVII) (A. Ercoli), R.D. (Fig. 4) in methanol (*c* 0.090): $[\alpha]_{700}$ −20°, $[\alpha]_{589}$ −14° $[\alpha]_{310}$ −305°, $[\alpha]_{270}$ +400°; acid study (40 min.), $[\alpha]_{700}$ +5°, $[\alpha]_{589}$ +2°, $[\alpha]_{310}$ −180°, $[\alpha]_{302.5}$ +87°: at 310 mμ, 35 min. = −180°.

Cholestan-3β-ol-23-one (XXXVIII) (A. Ercoli), R.D. in methanol (*c* 0.121): $[\alpha]_{700}$ + 10°, $[\alpha]_{589}$ +10°, $[\alpha]_{310}$ −317°, $[\alpha]_{265}$ +870°, $[\alpha]_{262.5}$ +830°; acid study (20 min.), $[\alpha]_{312.5}$ −294°: at 310 mμ, 3 min. = −301°, 10 min. = −227°, 15 min. = −231°.

3-Methyl-3-phenylhexan-4-one (XXXIX) (D. J. Cram),[39] R.D. in methanol (*c* 0.14): $[\alpha]_{700}$ +56°, $[\alpha]_{589}$ +61°, $[\alpha]_{315}$ +1588°, $[\alpha]_{307.5}$ +1176°; acid study (98 min.), $[\alpha]_{700}$ +46°, $[\alpha]_{589}$ +57°, $[\alpha]_{315}$ +1349°, $[\alpha]_{310}$ +1278°: at 315 mμ, 94 min. = +1349°.

3,4,6-Trimethyl-5-oxoheptanoic acid (XL) (R. H. Eastman),[40] R.D. in methanol (*c* 0.110): $[\alpha]_{700}$ +36°, $[\alpha]_{589}$ +43°, $[\alpha]_{315}$ +914°, $[\alpha]_{300}$ +393°; acid study (20 min.), $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +40°, $[\alpha]_{315}$ +930°, $[\alpha]_{310}$ +836°: at 315 mμ, 17 min. = +930°.

Acknowledgment.—We are greatly indebted to the various authors listed in the Experimental section for gifts of samples.

DETROIT, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MASSACHUSETTS]

O-Acylhydroxylamines. I. Synthesis of O-Benzoylhydroxylamine[1]

BY LOUIS A. CARPINO, CHESTER A. GIZA AND BARBARA A. CARPINO

RECEIVED AUGUST 27, 1958

O-Benzoylhydroxylamine has been synthesized by taking advantage of the ease of cleavage of the carbo-*t*-butoxy group. The hydrochloride was obtained analytically pure whereas the free base was found to be an unstable oil which suffered O-to-N rearrangement of the benzoyl group.

Previously[2] it has been shown that oxidation of 1,1-dibenzylhydrazines by means of mercuric oxide yields bibenzyls. The reaction has been postulated[3] to proceed through intermediates such as I. Because of the relationship between intermediates such as I and aliphatic diazo compounds, syntheses of the latter have been modified to provide new routes to bibenzyls. Alkaline deg-

$$\underset{\text{I}}{(C_6H_5CH_2)_2\overset{+}{N}{=}\overset{-}{N}} \qquad \underset{\text{II}}{(C_6H_5CH_2)_2NOH} \qquad \underset{\text{III}}{H_2NOSO_3H}$$

radation of 1,1-dibenzyl-2-benzenesulfonhydrazide gave, as expected, a high yield of bibenzyl.[4] A second synthetic route to diazo compounds has now been examined. Forster[5] found that certain ketone oximes such as benzil monoxime, on treatment with chloramine, yielded the corresponding diazo compounds. When aqueous solutions of chloramine were mixed with a suspension of N,N-dibenzylhydroxylamine (II) in aqueous alkali no evidence for bibenzyl formation was obtained. Furthermore numerous attempts to apply the Forster reaction to the synthesis of simple diazo compounds such as diazofluorene were unsuccessful. Since these difficulties may have been due to the nature of chloramine, an unstable gaseous substance most easily handled in dilute aqueous solution, attention was directed toward the synthesis of O-acyl and O-sulfonyl derivatives of hydroxylamine as substitutes for chloramine. Hydroxylamine-O-sulfonic acid[5,6] (III) has already been shown to undergo many reactions analogous to those of chloramine although its insolubility in organic solvents hinders its widespread utilization. Simple N-unsubstituted O-acylhydroxylamines are unknown except for the O-anthranoyl[7,8] and O-carbamoyl[9-13] derivatives. In this paper a synthesis of O-benzoylhydroxylamine (VIII) is reported. The method employed took advantage of the extreme ease of cleavage of the carbo-*t*-butoxy group.[14-16] Analogous preliminary attempts to use the carbobenzoxy group were unsuccessful.[17]

t-Butyl N-hydroxycarbamate (V) was obtained (80%) by treatment of a mixture of *t*-butyl azidoformate and aqueous hydroxylamine hydrochloride with sodium hydroxide. When the reaction was carried out by dropwise addition of the azide to the other reactants or at temperatures above that of the room the O,N-diacylated derivative *t*-butyl N-*t*-butyloxycarbonyloxycarbamate was formed. For preparative purposes a better yield of this compound was obtained by treatment of the hydroxamic acid V with the azide IV in a separate reaction. The hydroxamic acid V reacted normally

$$\underset{\text{IV}}{N_3COOCMe_3} \xrightarrow{NH_2OH} \underset{\text{V}}{NHOHCOOCMe_3} \xrightarrow{C_6H_5COCl} C_6H_5COONHCOOCMe_3$$

$$\underset{\text{VI}}{C_6H_5COONHCOOCMe_3} \xrightarrow{HCl} \underset{\text{VII}}{C_6H_5COONH_3Cl} \xrightarrow{HCO_3^-} \underset{\text{VIII}}{C_6H_5COONH_2}$$

(1) Supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under contract No. AF 18(603)-114. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2) M. Busch and B. Weiss, *Ber.*, **33**, 270 (1900).

(3) J. Kenner and E. C. Knight, *ibid.*, **69**, 341 (1936); see also C. G. Overberger and B. S. Marks, THIS JOURNAL, **77**, 4104 (1955); W. R. McBride and H. W. Kruse, *ibid.*, **79**, 572 (1957); and C. G. Overberger, J. G. Lombardino and R. G. Hiskey, *ibid.*, **80**, 3009 (1958).

(4) L. A. Carpino, *ibid.*, **79**, 4427 (1957).

(5) M. O. Forster, *J. Chem. Soc.*, **107**, 260 (1915).

(6) (a) F. Sommer, O. F. Schulz and M. Nasaau, *Z. anorg. u. allgem. Chem.*, **147**, 142 (1925); (b) G. Gever and K. Hayes, *J. Org. Chem.*, **14**, 813 (1949).

(7) A. W. Scott and B. L. Wood, *ibid.*, **7**, 508 (1942).

(8) J. E. Leffler and A. A. Bothner-By, THIS JOURNAL, **73**, 5473 (1951).

(9) G. Zinner, *Ber.*, **91**, 303 (1958).

(10) L. Francesconi and A. Parrozzani, *Gazz. chim. ital.*, **31**, II, 334 (1901).

(11) O. Exner, *Coll. Czech. Chem. Comm.*, **22**, 335 (1957).

(12) O. Exner, *ibid.*, **23**, 276 (1958).

(13) H. Kofod, *Acta Chem. Scand.*, **7**, 274, 938 (1953).

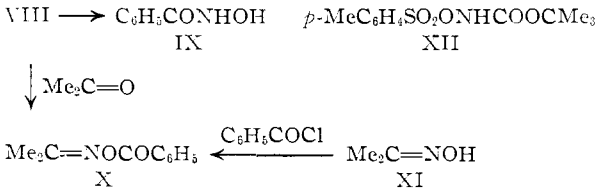
(14) L. A. Carpino, THIS JOURNAL, **79**, 98 (1957).

(15) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).

(16) F. C. McKay and N. F. Albertson, *ibid.*, **79**, 4686 (1957).

(17) Attempted cleavage of benzyl N-benzoyloxycarbamate [L. W. Jones and R. Oesper, *ibid.*, **36**, 2208 (1914)] by means of hydrogen bromide in nitromethane was accompanied by evolution of free bromine and consequent reduction of the desired linkage.

with benzoyl chloride in the presence of triethylamine yielding the O-benzoyl derivative VI. Cleavage of VI by means of hydrogen chloride in nitromethane yielded the hydrochloride VII. This proved to be somewhat unstable on continued standing, undergoing slow decomposition to O,N-dibenzhydroxamic acid. An aqueous solution of the hydrochloride VII upon treatment with sodium bicarbonate gave free O-benzoylhydroxylamine (VIII) as a water-white oil which on standing at room temperature for 4-5 hours was converted to solid materials, primarily the rearrangement product benzohydroxamic acid (IX). The O-benzoyl derivative was more stable in methylene dichloride solution; one sample underwent no



change in 10 hours as shown by infrared examination. The free base VIII was too unstable to allow purification for elemental analysis. Its structure was confirmed by reaction with acetone which gave O-benzoylacetoxime (X), a known compound which was obtained for comparison purposes from acetone oxime and benzoyl chloride.

The O-*p*-toluenesulfonyl derivative (XII) of V was also examined although it was not possible to cleave this compound by means of hydrogen chloride in nitromethane since the reaction was accompanied by evolution of chlorine and therefore reduction of the O–N linkage. From the cleavage reaction the expected reduction product, ammonium *p*-toluenesulfonate, was the only substance isolated.[18]

The O-acetyl derivative of V was also prepared but has not been subjected to cleavage. Several preliminary attempts to prepare the O-trifluoroacetyl derivative were unsuccessful.

The infrared carbonyl absorptions of compounds prepared during the course of this work which contain the O-acylhydroxylamine linkage are recorded in Table I. The absorption range (5.65 to 5.85 μ) confirms the ester-like structure of these derivatives.[19]

Experimental[20-22]

t-Butyl **Azidoformate.**—In view of the difficulties encountered by various workers in duplicating the high (80%) yield previously reported[4] for this key intermediate, the following detailed procedure is given. A solution of 100 g. of *t*-butyl carbazate, 88 g. of glacial acetic acid and 125 ml. of water was cooled in an ice-bath and with vigorous stirring 57.4 g. of solid sodium nitrite or a solution of the sodium nitrite in 80 ml. of water was added over a period of 50–60 min. keeping the temperature at about 9–13°. The mixture was allowed to stir in the ice-bath for 30 min. and 125 ml. of water was added. The golden-yellow azide layer was separated and the aqueous layer extracted with four 40-ml. portions of ether. The combined organic layers were washed three times with 50-ml. portions of water and three times with 40-ml. portions of 1 *M* sodium bicarbonate solution. The light yellow solution was dried over magnesium sulfate and the solvent removed from a water-bath at 40–45° and a water aspirator pressure of 140 mm. Raising the water bath temperature to 90–95° and distilling through a Claisen flask gave 88.8–94 g. (82–87%) of light yellow liquid, b.p. 73–76° (70 mm.), n^{24}D 1.4236.

t-Butyl **N-Hydroxycarbamate.**—A solution of 13 g. of hydroxylamine hydrochloride in 40 ml. of water was cooled in an ice-bath and 20 g. of *t*-butyl azidoformate added. While stirring vigorously, a cold solution of 22.4 g. of sodium hydroxide in 80 ml. of water was dropped in during 40–50 min. at 5–10°. The mixture was allowed to stir in the ice-bath for one hour and 100 ml. of water was added to dissolve a precipitated solid. The solution was extracted twice with 50-ml. portions of ether and the extracts discarded. The aqueous solution was cooled in an ice-bath and acidified to congo red with about 75 ml. of 6 *N* hydrochloric acid. The resulting mixture was extracted with five 40-ml. portions of ether, the solution dried (magnesium sulfate) and the solvent removed from a water-bath with the aid of a water aspirator. The thick oil solidified within several hours after placing in a vacuum desiccator giving 15.2 g. (81.7%) of white crystals, m.p. 55–57.5°. Recrystallization from 140 ml. of 60–90° ligroin gave 14.4 g. (77.5% of snow-white needles, m.p. 56–58°. The analytical sample had m.p. 58–59°.

Anal. Calcd. for $C_5H_{11}O_3N$: C, 45.10; H, 8.33. Found: C, 45.08; H, 8.23.

t-Butyl N-*t*-Butyloxycarbonyloxycarbamate.—A mixture of 2.66 g. of *t*-butyl N-hydroxycarbamate, 2.83 g. of *t*-butyl azidoformate and 25 ml. of water was stirred well at room temperature while a solution of 1.6 g. of sodium hydroxide in 15 ml. of water was added during 5–7 minutes. The clear solution was allowed to stir for 30 minutes during which time a small amount of the free diacylated material began to separate. The mixture was cooled in an ice-bath and acidified with dil. hydrochloric acid (1:1). An oil separated which soon crystallized to a white solid. The yield was 4.1 g. (88%), m.p. 65.5–68.5°. Recrystallization from 60–90° ligroin gave 3.55 g. (76%) of white needles, m.p. 67–69°.

Anal. Calcd. for $C_{10}H_{19}O_5N$: C, 51.49; H, 8.21. Found: C, 51.84; H, 8.09.

t-Butyl **N-Benzoyloxycarbamate.**—A solution of 26.6 g. of *t*-butyl N-hydroxycarbamate and 27.8 ml. of triethylamine in 100 ml. of methylene dichloride was cooled in an

TABLE I

CHARACTERISTIC CARBONYL ABSORPTIONS OF O-ACYLHYDROXYLAMINES AND RELATED COMPOUNDS

Compound	Phase[a]	Position, μ
VIII	F	5.80
VII	N	5.67
$C_6H_5CO_2NHCOC_6H_5$	N	5.65
VI	C	5.66, 5.86
$Me_3COCO_2NHCOOCMe_3$	C	5.66
$CH_3CO_2NHCOOCMe_3$	F	5.70
X	C	5.70
o-$H_2NC_6H_4CO_2NH_2$[b]	N	5.85
o-$H_2NC_6H_4CO_2N{=}CMe_2$[b]	N	5.85
p-$MeC_6H_4SO_2ONHCOOCMe_3$	N	5.85
V	N	5.79
$C_6H_5CH_2OCONHOH$[c]	N	5.80
IV[d]	C	5.67, 5.74
$NH_2CO_2NH_2$[e]	..	5.71
$C_2H_5CO_2N{=}CMe_2$[e]	..	5.66

[a] Nujol mull (N), thin film (F) or carbon tetrachloride solution (C). [b] Prepared by the method of J. E. Leffler and A. A. Bothner-By (ref. 8). [c] Prepared by the method of Jones and Oesper, ref. 17. [d] Shows a strong twin absorption at 4.56, 4.67 μ due to the azide group. [e] Reported by Zinner (ref. 9).

(18) The application to this cleavage of non-reducing acids such as hydrogen fluoride is being investigated.

(19) For a study of the "ester" carbonyl frequencies of O-acylhydroxylamines see J. P. Freeman, THIS JOURNAL, **80**, 5954 (1958).

(20) Melting and boiling points are uncorrected.

(21) Analyses are by Drs. Weiler and Strauss, Oxford, Eng.

(22) Infrared spectra were recorded linearly in wave length on a Perkin–Elmer model 21 spectrophotometer, sodium chloride optics. We are indebted to the National Science Foundation and the Research Corporation for funds with which to purchase the spectrophotometer.

ice-bath and stirred vigorously. There was dropped in over a period of one hour a solution of 23.2 ml. of benzoyl chloride in 50 ml. of methylene dichloride. The mixture was allowed to stir in the ice-bath for an additional three hours, 150–200 ml. of water was added and the two layers shaken well in a separatory funnel. The organic layer was drawn off into a flat dish and the aqueous layer extracted with one 25-ml. portion of methylene dichloride. Spontaneous evaporation of the combined organic layers left 46.5 g. (98%) of white solid, m.p. 81–84°. Recrystallization from 52 ml. of 60–90° ligroin gave 44.5 g. (94%) of snow-white crystals, m.p. 82–84°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.74; H, 6.37. Found: C, 60.75; H, 6.49.

O-Benzoylhydroxylamine Hydrochloride.—A solution of 15 g. of *t*-butyl N-benzoyloxycarbamate in 80 ml. of nitromethane was treated with a stream of dry hydrogen chloride for 5–7 min. The mixture became slightly warm and a white solid separated. The mixture was allowed to stand in an ice-bath for 15 min., filtered and washed twice with fresh nitromethane. The air-dried snow-white crystals amounted to 9.0 g. (82%), m.p. 70–100° dec. When freshly prepared the substance is completely soluble in cold water. On standing for several hours slow decomposition occurs since the solid no longer dissolves completely in water. The decomposition product proved to be O,N-dibenzhydroxamic acid, m.p. 164–166° (lit.[23] m.p. 161–162°) identified by comparison of its infrared spectrum with that of an authentic sample.[23] The crude hydrochloride was pure enough for conversion to the free base. An analytical sample was prepared by dissolving 3 g. in 10 ml. of methanol at room temperature, adding 40–50 ml. of nitromethane and cooling in an ice-bath which gave small white needles, m.p. 70–100° dec.

Anal. Calcd. for $C_7H_8NO_2Cl$: N, 8.07; Cl, 20.4. Found: N, 8.32; Cl, 20.4.

When the hydrochloride was first prepared (L.A.C.) it was obtained in the form of white needles which melted sharply at 120–122° with gas evolution, resolidified and then remelted at 190–196°. The compound was subsequently prepared several times by C.A.G. who observed the same melting point behavior but all subsequent preparations by L.A.C. led to the form described above, m.p. 70–100° dec.

NOTE.—The referee has pointed out that a description of the isolation of O-benzoylhydroxylamine has already been presented in a preliminary communication by W. P. Jencks [*Biochim. et Biophys. Acta*, **27**, 417 (1958)]. A full report of this work subsequently appeared [W. P. Jencks, THIS JOURNAL, **80**, 4581, 4585 (1958)].

O-Benzoylhydroxylamine.—A solution of 5 g. of O-benzoylhydroxylamine hydrochloride in the minimum amount of water (room temperature) was treated with 1 *M* sodium bicarbonate solution until effervescence stopped and the mixture was slightly basic. The precipitated oil was extracted with three 10-ml. portions of methylene dichloride. The solvent was removed from the dried (magnesium sulfate) solution by means of a water aspirator while immersing the liquid in a water-bath at room temperature (20–22°). The clear water-white oil which remained amounted to 3 g. (76%); major peaks (μ) in the infrared spectrum of a thin film of the liquid examined just after removal of methylene dichloride solvent: 3.07m, 5.80s, 6.25m, 6.40m-s (b), 6.89m-s, 7.61m-s, 7.85s (b), 8.35m (b), 8.47m (b), 9.21m-s, 9.38s, 9.75m-s, 14.20s (b) (m = medium, b = broad, s = strong). In methylene dichloride solution the carbonyl absorption occurred at 5.76 μ.

(23) W. B. Renfrow and C. R. Hauser, THIS JOURNAL, **59**, 2308 (1937).

Treatment of a portion of the oil with acetone yielded O benzoylacetoxime, m.p. 43–44°, shown by infrared spectra to be identical with an authentic sample, m.p. 43–44° (lit.[24] m.p. 43–44°), prepared from acetoxime, benzoyl chloride and triethylamine.

It was noted that a sample of O-benzoylhydroxylamine which had stood for 4–5 hours at room temperature began to deposit crystals. The major product of this decomposition was determined by allowing 1.5 g. of the freshly prepared oil to stand overnight until the white solid which formed was no longer tacky (about 18 hours). The solid (amount 1.45 g., m.p. 90–110°) was recrystallized from nitromethane which gave 1.15 g. of white flakes, m.p. 112–125°. This solid was dissolved in ethanol and water added until no further precipitation of flocky white crystals occurred. The mixture was filtered to remove an unidentified solid (amount 0.1 g., m.p. 126–136° dec.) and the filtrate evaporated by a stream of air which caused the deposition of 0.6 g. (40%) of benzohydroxamic acid, m.p. 128.5–130.5° (lit.[25] m.p. 126°). The infrared spectrum of this material was identical with that of an authentic sample.

t-Butyl **N-*p*-Toluenesulfonoxycarbamate.**—A solution of 2.5 g. of *t*-butyl N-hydroxycarbamate and 2.62 ml. of triethylamine in 10 ml. of dimethylformamide was cooled in an ice-bath and a solution of 3.58 g. of *p*-toluenesulfonyl chloride in 5 ml. of dimethylformamide was added during 8–10 minutes. After standing for 15 min. in the ice-bath the solution was treated with 50 ml. of water. Cooling and scratching caused solidification. The light yellow powder was washed with ethanol and amounted to 3.4 g. (63%), m.p. 101–102° dec. (followed by resolidification and m.p. 160–165°). The crude solid was recrystallized by solution in about 5 ml. of hot benzene, filtration and addition of two volumes of 60–90° ligroin to the cool filtrate. Cooling in the refrigerator gave 2 g. (37%) of tiny cream-white crystals, m.p. 97° dec. ("pops" with evolution of smoke at the mouth of the capillary).

Anal. Calcd. for $C_{12}H_{17}SO_5N$: C, 50.15; H, 5.96. Found: C, 49.95; H, 5.87.

Attempted Hydrogen Chloride Cleavage of *t*-Butyl N-*p*-Toluenesulfonoxycarbamate.—A solution of 1.0 g. of the carbamate in 12 ml. of nitromethane which was saturated with hydrogen chloride gas was allowed to stand for 10–15 min. The vapors at the mouth of the tube gave a positive test with moistened starch–iodide paper indicating the presence of chlorine. Filtration gave 0.45 g. of tiny white crystals, m.p. 345–347°. The analytical sample was recrystallized from nitromethane. Warming the solid with aqueous sodium hydroxide caused the evolution of ammonia. Apparently the desired O-sulfonacyl derivative is reduced by hydrogen chloride to the ammonium salt of *p*-toluenesulfonic acid.

Anal. Calcd. for $C_7H_9NSO_3$: C, 44.43; H, 5.86. Found: C, 44.19; H, 5.73.

t-Butyl **N-Acetoxycarbamate.**—A solution of 13.3 g. of *t*-butyl N-hydroxycarbamate and 10.1 g. of triethylamine in 40 ml. of ether was cooled in an ice-bath (6–10°) and treated slowly with a solution of 7.86 g. of acetyl chloride in 10 ml. of ether. After 0.5 hour of stirring the mixture was filtered and the filtrate washed with 50 ml. of saturated sodium bicarbonate solution and 50 ml. of water. Removal of solvent and distillation gave a colorless viscous liquid, b.p. 90° (2.8 mm.), $n^{26}D$ 1.4280, yield 66–80%. No attempt has yet been made to cleave this derivative.

Anal. Calcd. for $C_7H_{13}O_4N$: C, 47.99; H, 7.48. Found: C, 48.18; H, 7.63.

AMHERST, MASS.

(24) J. Schmidt, *Ber.*, **31**, 3225 (1898).

(25) E. Bamberger, *ibid.*, **33**, 1786 (1900).