Anal. Calcd for $C_{22}H_{41}O_4N$ (383.3): C, 68.87; H, 10.78; N, 3.65. Found: C, 68.99; H, 10.72; N, 3.75.

2,4-Dinitrophenylhydrazone.—Compound VI, 34 mg, was refluxed 5 min with 30 mg of 2,4-dinitrophenylhydrazine in 4 ml of methanol containing 0.1 ml of 6 *N* HCl. After cooling to room temperature the reaction mixture was centrifuged. The precipitate was crystallized from methanol, yield 27 mg, mp 138–141°.

Anal. Calcd for $C_{24}H_{42}O_5N_5Cl$ (515.3): C, 55.86; H, 8.22; N, 13.58. Found: C, 55.55; H, 8.21; N, 13.43.

Compound VII, 51 mg, treated in the same manner as compound VI with 2,4-dinitrophenylhydrazine, yielded 38 mg of derivative, mp 165°. The anticipated hydrazone corresponding to $C_{26}H_{43}O_6N_5$ (521.3) with calculated values for C, 59.85, H, 8.31, and N, 13.43 was not obtained; instead, the values for C, 55.37, H, 6.53, and N, 17.59 were found suggesting an empirical formula of $C_{26}H_{36}O_7N_7$ (557.3). The product showed one component on thin layer chromatography.

D-1-Hydroxy-2-carbobenzoxamido-3-ketooctadecane-4,5-^{3}H (VIII).—To 1.4 mg (22.8 mC) of N-carbobenzoxydihydrosphingosine-4,5-$^3H^8$ in 50 ml of methanol were added 434 mg of N-carbobenzoxydihydrosphingosine; the solution was concentrated and the residue was dried over phosphorus pentoxide. The product was dissolved in 30 ml of pyridine, chilled and treated with 435 mg of dry chromic anhydride. The remainder of the procedure, including column chromatography on silicic acid, was the same as that employed in the preparation of compound V, yield 138 mg (32%), mp 63°; recovered radioactivity 3.5 mCi, 15%; specific activity 25.5 μCi/mg (11.1 mCi/mmol).

The yield of N-carbobenzoxydihydrosphingosine-4,5-^{3}H recovered from the 1% methanol in chloroform was 150 mg (35%), mp 105–106°. Radioactive yield 5.4 mCi, 24%; specific activity 35.9 μCi/mg.

D-1-Hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H Hydrochloride.[17]—Compound VIII, 138 mg, was hydrogenated and the product was isolated in the same manner as that described for the preparation of compound VI, yield 93.4 mg (87%), mp 96–98°; Recovered radioactivity 3.3 mCi, 14%; specific activity 35.7 μCi/mg (11.9 mC/mmol). The product was stored in the dark *in vacuo* over phosphorus pentoxide.

Registry No.—I, 25515-49-5; II, 25515-50-8; dihydrosphingosine, 764-22-7; III, 25515-52-0; IV, 25515-53-1; V, 25515-54-2; VI (2,4-dinitrophenylhydrazone), 25515-57-5; dihydrosphingosine acetate (diastereoisomers), 25528-34-1; VII, 25515-55-3; VII (3-hydroxy diastereoisomers), 13552-12-0; VII (O,N-diacetyl), 25515-56-4; VIII, 25568-74-5; D-1-hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H (HCl), 25515-58-6.

(17) Preliminary studies showed that this compound was an efficient precursor in the biosynthesis of phytosphingosine by growing cultures of the yeast *Hansenula ciferrii*.

Carbodiimide–Sulfoxide Reactions. VIII.[1] Reactions of Oximes and Hydroxylamines[2]

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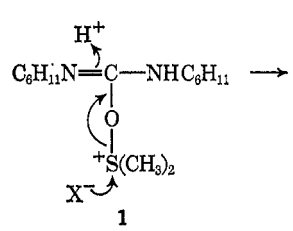
The reaction of benzophenone oxime with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of trifluoroacetic acid leads to formation of α,α-diphenyl-*N*-(thiomethoxymethyl)nitrone (**5**) and the isomeric *O*-(thiomethoxymethyl)benzophenone oxime (**6**). The relative amounts of **5** and **6** depend upon the reaction conditions and, using pentadeuterio-**5**, intramolecular rearrangement into pentadeuterio-**6** has been demonstrated. Similar formation of a nitrone and oxime ether occurred using fluoren-9-one oxime, but certain aliphatic oximes led to complex reaction mixtures. Reactions of several 17-oximino steroids led to the formation of D-homolactams and of unsaturated nitriles *via* first- and second-order Beckmann rearrangements, the latter being unusual with these compounds. Both *syn* and *anti* isomers of *p*-bromobenzaldoxime gave *p*-bromobenzonitrile and α-*p*-bromophenyl-*N*-(thiomethoxymethyl)nitrone in different proportions. *N*-Phenylhydroxylamine gave azoxybenzene, presumably *via* oxidation to nitrosobenzene, and *N*,*N*-dibenzylhydroxylamine gave α-phenyl-*N*-benzylnitrone in high yield. Mechanisms for these reactions are presented.

Previous papers in this series have described mild acid-catalyzed reactions of dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) with alcohols,[4] phenols,[5] and active methylene compounds.[1] In each case the observable reactions can be explained by nucleophilic attack of the functional group upon an initial DMSO–DCC adduct (**1**), giving an oxysulfonium salt, or related derivative, (**2**) which can readily lose a proton



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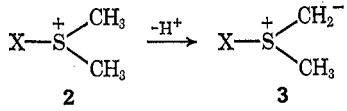


2 **3**

giving a sulfonium ylide (**3**). The latter can then directly rearrange or undergo further reactions.

The mildness of these reactions suggests that other nucleophilic functional groups might also react with **1** leading to many possible types of reaction. In this paper we describe the reactions of several different types of oximes and hydroxylamines while in subsequent publications a wide range of other functional groups are considered.[6]

Benzophenone oxime (**4**) was found to react rapidly with DMSO and DCC in the presence of 0.5–1.0 equiv of anhydrous orthophosphoric acid, omission of any of these reagents blocking the reaction. Unlike the reactions described previously, however, free trifluoro

(1) For part VII, see A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **90**, 740 (1968).

(2) This and related work was presented as part of the Eleventh National Medicinal Chemistry Symposium of the American Chemical Society, Quebec, Canada, June 1968.

(3) Syntex Postdoctoral Fellow, 1964–1965.

(4) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965); (b) A. H. Fenselau and J. G. Moffatt, *ibid.*, **88**, 1762 (1966).

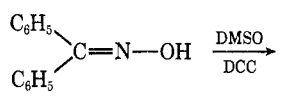
(5) (a) M. G. Burdon and J. G. Moffatt, *ibid.*, **88**, 5855 (1966); (b) M. G. Burdon and J. G. Moffatt, *ibid.*, **89**, 4725 (1967).

(6) U. Lerch and J. G. Moffatt, unpublished results.

acetic acid (TFA) gave a somewhat cleaner reaction mixture with no necessity for adding pyridine.

A preparative reaction between **4** and 3 mol equiv of DCC in a 1:1 mixture of DMSO and benzene containing 0.5 mol equiv of trifluoroacetic acid rapidly gave one major, polar product and one minor, nonpolar product together with traces of unreacted **4** and benzophenone. Chromatography on a column of silicic acid quite readily separated these components and led to the isolation, in crystalline form, of the two new products in yields of 74 and 3%. Both compounds gave elemental analyses corresponding to the molecular formula $C_{15}H_{15}NOS$ and their monomeric nature was confirmed by mass spectrometry. On the basis of the evidence presented below these compounds are shown to be α,α-diphenyl-*N*-(thiomethoxymethyl)nitrone (**5**) and *O*-(thiomethoxymethyl)benzophenone oxime (**6**), respectively.

The structure of **5** was deduced from its spectral properties and by degradation.[7] Its nmr spectrum clearly demonstrated the presence of a thiomethoxymethyl group and, unlike the oxime ether, two of the aromatic protons are deshielded by roughly 0.7 ppm due to the proximity of the polar oxygen atom. In addition, the ultraviolet spectrum closely resembles that of an authentic sample of α,α-diphenyl-*N*-methylnitrone (**7**)[8] which showed λ_{max} 234 mμ (ϵ 12,100) and 295 (11,200) and the infrared spectra of **5** and **7** showed very similar N → O stretching frequencies at 1250 cm^{-1}.



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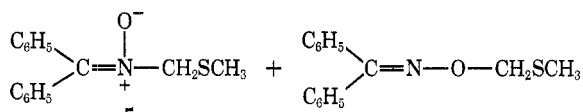
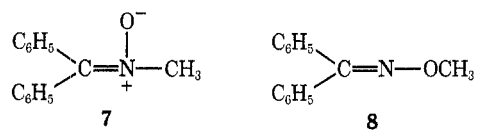


5 **6**



7 **8**

Treatment of **5** with very dilute hydrochloric acid in aqueous methanol led to rapid hydrolysis giving benzophenone, formaldehyde, and an odoriferous sulfur compound, presumably methyl mercaptan. A rough kinetic study by following changes in the ultraviolet spectrum indicated that the hydrolysis of **5** is about six times as fast as that of *N*-methylnitrone **7**. Desulfurization of **5** with a sponge nickel catalyst[9] gave the known crystalline *N*-methylnitrone **7** in 20% yield together with 37% benzophenone (presumably *via* simply hydrolysis of **5** or **7**) and 34% unreacted **5**.

The isomeric *O*-(thiomethoxymethyl) oxime (**6**) was also characterized by its nmr spectrum and by the similarity of its ultraviolet spectrum to that of *O*-methylbenzophenone oxime[8] **8** (λ_{max}^{MeOH} 231 mμ, ϵ 13,200; λ_{max} 260 mμ, ϵ 10,800) which was prepared from benzophenone and methoxylamine. Final proof of the structures of **5** and **6** came from an independent synthesis of both compounds *via* alkylation of the sodium salt of benzophenone oxime with chloromethyl methyl sulfide. Alkylation of such ambident anions is known to lead to both nitrones and *O*-alkyl oximes[7] and a systematic study of the factors affecting the site of alkylation has been made.[10] In most cases *O*-alkylation is somewhat favored[10] but in the above reaction roughly equal amounts of **5** (38%) and **6** (47%) were obtained. This ratio is, however, in marked contrast to that obtained in the DMSO–DCC reaction in which the nitrone was the preponderant product. Very recently Kerr and Wilson[11] have briefly reported the formation of **5** from benzophenone oxime with DMSO and DCC but **6** was apparently not obtained.

A number of small experiments were carried out in order to determine the effects of controlled variations in reaction conditions. The product distributions, as estimated by thin layer chromatography are recorded in Table I. From Table I it can be seen that, as in the oxidation of alcohols,[4] optimal results require the use of more than 1 mol equiv of DCC (experiments 1–3) and a larger than stoichiometric amount of DMSO (experiments 4 and 5). The nature of the cosolvent and the reaction time are also reflected in the relative proportions of **5** and **6**, the relative proportion of the ether **6** being lower in the presence of nonpolar diluents such as benzene or ether (reactions 3 and 7). An increase in the proportion of the oxime ether at the expense of the nitrone is also apparent when the reaction time is prolonged (reactions 8–10 and 12–13), especially when using phosphoric acid, but it is not significant under the standard conditions using TFA and benzene as a diluent (reaction 3). The same products are formed, although in somewhat different proportions, in reactions using TFA, anhydrous phosphoric acid,

TABLE I

PRODUCT DISTRIBUTION USING DIFFERENT REACTION CONDITIONS[a]

Expt	Variable feature	Oxime **4**	Benzophenone	Nitrone **5**	Oxime ether **6**
1	1 equiv, DCC (16 hr)	32	24	42	2
2	2 equiv, DCC (16 hr)	6	8	79	7
3	3 equiv, DCC (16 hr)	9	11	75	5
4	1 equiv, DMSO (3 hr)	81	4	12	3
5	2 equiv, DMSO (3 hr)	58	6	31	5
6	Pure DMSO (3 hr)	22	18	39	21
7	DMSO–ether (1:1) (1 hr)	5	11	67	9
8	DMSO–DMF (1.5 hr)[b]	13	11	67	9
9	DMSO–DMF (5 hr)[b]	14	14	52	20
10	DMSO–DMF (20 hr)[b]	20	13	30	37
11	1.0 equiv, H_3PO_4 (1.5 hr)	4	20	41	34
12	0.5 equiv, H_3PO_4 (1.5 hr)	4	19	59	18
13	0.5 equiv, H_3PO_4 (24 hr)	6	16	31	47

[a] Standard conditions used 3 mol equiv of DCC and 0.5 equiv of trifluoroacetic acid in DMSO–benzene (1:1). Only deviations from this standard mixture are indicated in the Table. The product distributions (%) were determined by quantitative tlc using chloroform–ethyl acetate (4:1) followed by measurement of ultraviolet absorption. [b] 0.8 mol equiv of trifluoroacetic acid was used.

(7) The chemistry of nitrones has recently been reviewed: (a) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); (b) G. R. Delpiene and M. Lamchen, *Quart. Rev. (London)*, **19**, 329 (1965).

(8) L. Semper and L. Lichtenstadt, *Ber.*, **51**, 928 (1918).

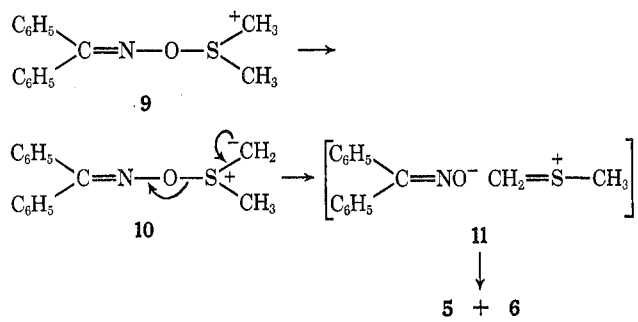
(9) Davidson Chemical Division of W. R. Grace and Co., Cincinnati, Ohio.

(10) P. A. S. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, **84**, 1197 (1962).

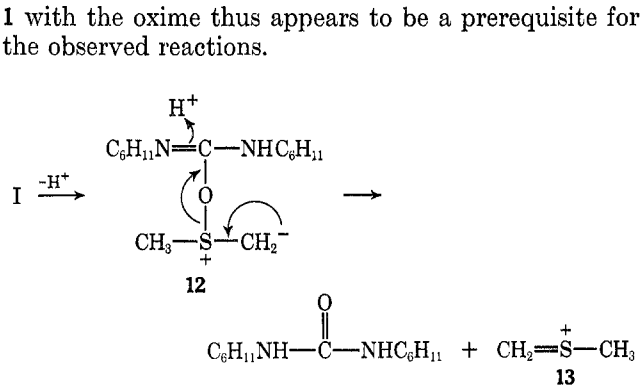
(11) D. A. Kerr and D. A. Wilson, *Tetrahedron Lett.*, 2885 (1968).

pyridinium trifluoroacetate, and dichloroacetic acid. No reaction, however, was observed using toluenesulfonic acid.

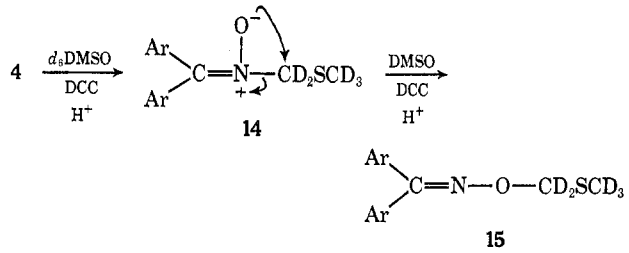
The most probable mechanism of the reactions above appears to involve nucleophilic attack of the oxime oxygen upon the DMSO–DCC adduct (1) with formation of an oxysulfonium salt (9) which readily loses a proton with formation of the sulfonium ylide (10). There is no proton in 10 available for abstraction in the oxidation of alcohols[4b] and the nature of the products precludes an intramolecular rearrangement with attack by the carbanion on carbon or nitrogen as in the reactions of phenols.[5] The ylide 10 appears, rather, to dissociate into the ion pair (11) which then recombines into the nitrone (5) and the ether (6) *via* alkylation by the electrophilic methylene methyl sulfonium ion at nitrogen or oxygen, respectively.



The alternate possibility that the methylene methyl sulfonium ion (13) arises *via* decomposition of the ylide (12) derived by proton loss from the DMSO–DCC adduct (1) appears unlikely. In previous work it has been shown that the ion 13, generated by different reactions, is indeed a powerful electrophile which rapidly alkylates phenols and phenol ethers.[5b,12] Anisole, however, undergoes no observable reaction with DMSO, DCC, and anhydrous phosphoric acid[5a] which indicates that the conversion 1 → 12 → 13 does not take place under the usual reaction conditions. Initial reaction of 1 with the oxime thus appears to be a prerequisite for the observed reactions.

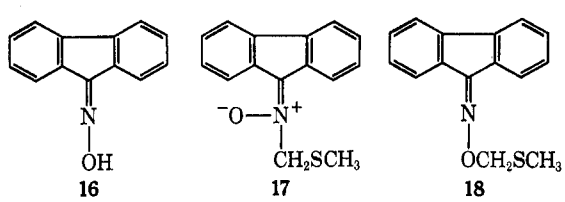


The observed increase with time of the relative proportion of oxime ether relative to nitrone suggests the possibility of a direct interconversion of these isomers. The thermal rearrangement of certain nitrones to the isomeric oxime ethers has been described by Cope, *et al.*,[13] and indeed it was found that heating a sample of 5 under nitrogen at 150° for 2 hr led to the formation of a mixture of benzophenone, benzophenone oxime, and the oxime ether (6) as judged by thin layer chromatography. A direct chemical isomerization of the nitrone to the oxime ether was also directly demonstrated. Thus, reaction of the crystalline nitrone 5 with DMSO, DCC, and anhydrous phosphoric acid for 40 hr at room temperature was shown to lead to the formation of 38% of the isomeric oxime ether (6) as well as 32% unreacted 5 and 30% benzophenone presumably arising from simple hydrolysis of 5. The conversion 5 to 6 appears to absolutely require the presence of DMSO, DCC, and acid since in the absence of any one of these reagents greater than 90% of the nitrone remained unchanged and only a little benzophenone was formed. When the pentadeuterionitrone (14) from 4, DMSO-d_6, DCC, and TFA was reacted with nondeuterated DMSO, DCC, and anhydrous phosphoric acid as above, the resulting oxime ether (15) was still predominantly deuterated; integration of the nmr signals at 5.23 and 2.22 ppm indicating the presence of only 9 and 18% protons in the $-NCH_2S$ and $-SCH_3$ groups, respectively. It is thus clear that the conversion of 5 to 6 is an essentially intramolecular process which could be explained by the type of mechanism (14 → 15) that has been used for the equivalent thermal rearrangement.[13] A radical dissociation–recombination mechanism has also been recently proposed for the thermal rearrangement of certain nitrones.[14] A mechanism that explains the necessary roles of DMSO, DCC, and a proton source remains obscure.



It might also be mentioned that α,α-diphenyl-*N*-methylnitrone (7) did not undergo any noticeable rearrangement under comparable conditions, only starting material and a little benzophenone being formed. The oxime ether (6) was completely stable under these conditions.

Fluoren-9-one oxime (16) underwent a very similar reaction with DMSO, DCC, and TFA giving the thiomethoxymethylnitrone (17) and the oxime ether (18) in yields of 71 and 5%, respectively. Some unreacted oxime was also recovered and traces of a very unstable, rather polar product were isolated but not examined further. Unlike 5, the nitrone (17) showed very little tendency to rearrange into the oxime ether (18) upon reaction with DMSO, DCC, and acid.



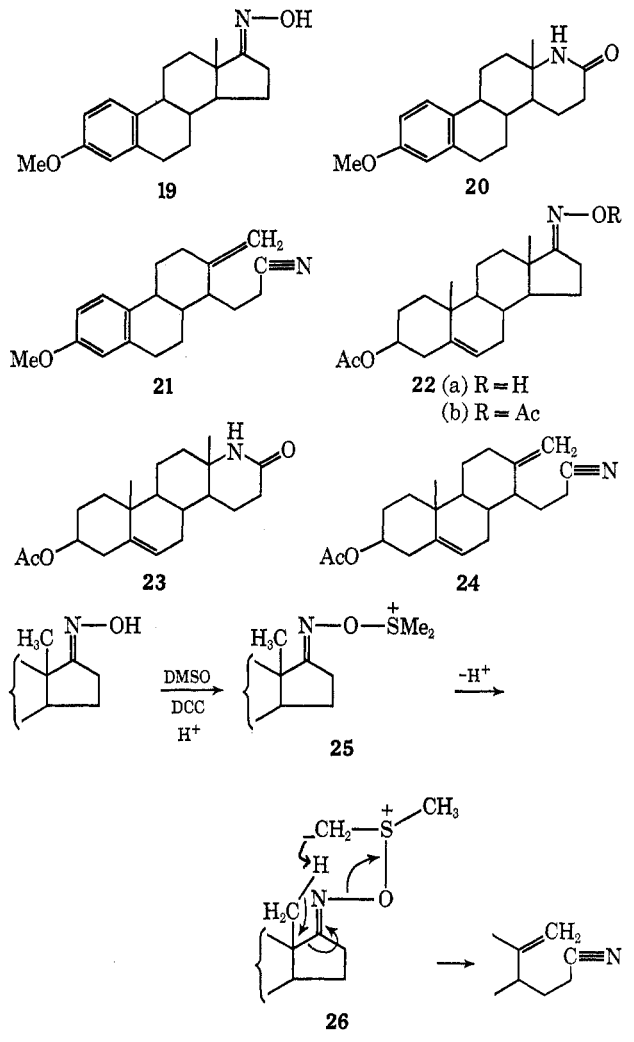
(12) K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *J. Amer. Chem. Soc.*, **87**, 4658 (1965).

(13) A. C. Cope and A. C. Haven, *ibid.*, **72**, 4896 (1950).

(14) E. J. Grubbs, J. A. Villaneal, J. D. McCullough, and J. S. Vincent, *ibid.*, **89**, 2234 (1967).

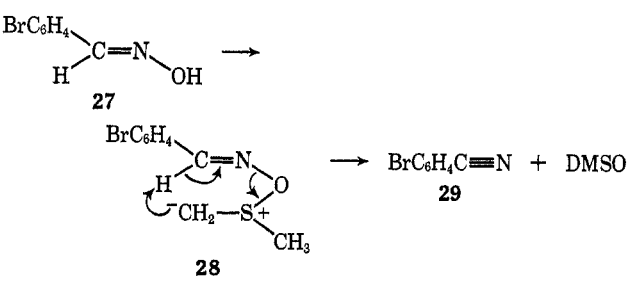
Several oximes containing aliphatic residues were also examined (*e.g.*, cyclohexanone, acetophenone, and tetralone oximes) and shown by tlc to lead to complex, and difficulty separable, mixtures containing six or more compounds including those expected from Beckmann rearrangements. Thus, acetanilide was shown to be a major product from the reaction of acetophenone oxime. More clear-cut examples of Beckmann rearrangements were found using several 17-oximino steroids as models. Reaction, for example, of estrone methyl ether oxime (**19**) with DMSO, DCC, and TFA led to the very rapid formation of two products in roughly equal amounts. Following chromatography on silicic acid, these were shown to be the known 13α-amino-3-methoxy-13,17-secoestra-1,3,5(10)-trien-17-oic-13,17-lactam (**20**)[15] which was isolated in 39% yield, and 3-methoxy-13,17-secoestra-1,3,5(10),13(18)-tetraenoic nitrile (**21**), the result of a second-order Beckmann rearrangement,[16] in 41% yield. The structure of **21** is based upon its elemental analysis, the presence of a nitrile band at 2250 cm^{-1} in its infrared spectrum, its nmr spectrum which shows the absence of an 18-methyl group and the presence of the methylene group as two 1-proton singlets at 4.56 and 4.85 ppm. The formation of equal amounts of lactam **20** and nitrile **21** is interesting since a number of 17-oximino steroids have been subjected to Beckmann rearrangement under a variety of conditions with formation, generally in high yield, of only the corresponding lactams. The only mention of second-order products that we have found was the formation of a 6% yield of a seco nitrile from adrenosterone 17-oxime upon rearrangement with 4-acetamidobenzenesulfonyl chloride in pyridine[17] and the very recent report of the formation in 9% yield of the $\Delta^{13(14)}$ tetrasubstituted olefin isomer of **21** from **19** and chlorosulfonic acid.[18] We suggest that the formation of the oxysulfonium salt (**25**), which provides an excellent leaving group for a normal Beckmann rearrangement, is followed by ylide formation (**26**) in the usual way. The availability of the ylide anion for an intramolecular proton abstraction from C_{18} then explains the anomolous formation of the unsaturated nitrile. Even though such a cyclic mechanism requires an eight-membered cyclic transition state, molecular models suggest that such an intermediate is readily accommodated. A similar reaction with 3-β-acetoxy-17-oximinoandrost-5-ene (**22a**) led to the formation of the lactam (**23**)[19] and the unsaturated nitrile (**24**) in yields of 21 and 61%, respectively.

Once again the requirements for these reactions have been checked and it was shown that the formation of **20** and **21** from **19** proceeded rapidly (within 30 min) only in the presence of DMSO, DCC, and TFA. The acid could be replaced by anhydrous orthophosphoric or by dichloroacetic acids but in both cases the reaction was less satisfactory. Reactions in which DMSO was replaced by DMF or benzene led to the formation of *traces* of lactam **20** but no nitrile, suggesting that some activation of the oxime, presumably *via* formation of an isourea ether, is possible with DCC and acid alone.



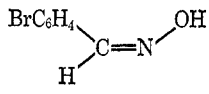
In the absence of DCC or of acid, however, no detectable reaction occurred. As has been reported earlier for the case of benzophenone oxime,[11] reaction of **22a** with DMSO and acetic anhydride led only to the quantitative formation of the *O*-acetyl oxime (**22b**).

Aldoximes behaved in quite a different way. Thus, the *syn* (**27**) and *anti* (**30**) isomers of *p*-bromobenzaldoxime were prepared in crystalline form by the isomerization method of Brady and Dunn[20] and separately subjected to the usual reaction. In both cases two products were rapidly formed and shown to be *p*-bromobenzonitrile (**29**) and α-*p*-bromophenyl-*N*-thiomethoxymethylnitrone (**31**). The *syn*-oxime (**27**) gave



crystalline nitrile and nitrone in yields of 68 and 39% while the *anti*-oxime gave a larger proportion of nitrile (84% isolated) with relatively little nitrone. This result is perhaps somewhat surprising since formation of

(15) B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, **78**, 639 (1956).
(16) (a) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **2**, 1 (1960); (b) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).
(17) W. Nagata, M. Narisada, and T. Sugasawa, *J. Chem. Soc. C*, 648 (1967).
(18) A. Cervantes, P. Crabbé, J. Iriarte, and G. Rosenkrantz, *J. Org. Chem.*, **33**, 4294 (1968).
(19) S. Kaufman, *J. Amer. Chem. Soc.*, **73**, 1779 (1951).
(20) O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, **123**, 1785 (1923).



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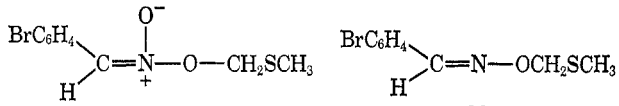


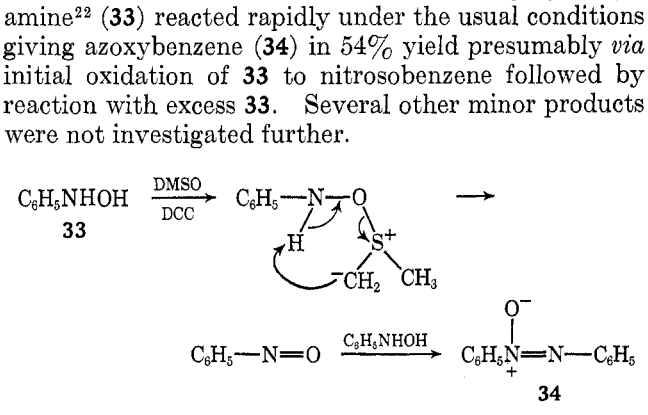
31 32

the nitrile could be expected to occur *via* an intramolecular proton abstraction mechanism (**27** → **30**) *via* the ylide **28**, a process that would be favored by *syn* stereochemistry. Formation of the nitrone (**31**, for which no stereochemical assignment can be made since only a single isomer has been isolated) presumably involves a dissociation and recombination mechanism *via* an ion pair similar to **11** and might be expected to be favored by *anti*-stereochemistry.

The assignment of configurations to **27** and **30** is based upon the usual preferential formation of the *syn* isomer which can then be transformed into the less stable, higher melting *anti* form[20] and is confirmed by nmr spectroscopy, the vinyl proton of **27** occurring at lower field (8.19 ppm) than that of **30** (7.46 ppm).[21] Alkylation of both **27** and **30** with chloromethyl methyl sulfide and sodium hydride in benzene gave roughly equal amounts of the nitrone **31** identical with that from the DMSO–DCC reaction, and the isomeric oxime ether **32**. In neither case was there any indication of geometrical isomers, presumably the thermodynamically more stable form being formed. Hydrolysis of **31** with hydrochloric acid in methanol gave mainly the *syn*-oxime (**27**) rather than the parent carbonyl compound as had been found with **5**.

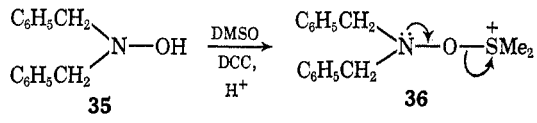
While quantitative experiments have not been done, owing in part to the volatility of the products and the lability of the isomeric oximes, benzaldehyde oxime has been shown to react in a similar way giving mainly benzonitrile and a small amount of α-phenyl-*N*-thiomethoxymethylnitrone.

Reactions of a few hydroxylamines with DMSO and DCC have also been studied. *N*-Phenylhydroxylamine[22] (**33**) reacted rapidly under the usual conditions giving azoxybenzene (**34**) in 54% yield presumably *via* initial oxidation of **33** to nitrosobenzene followed by reaction with excess **33**. Several other minor products were not investigated further.

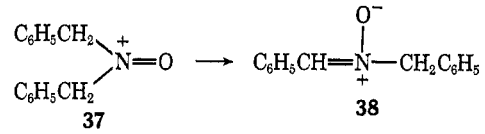


34

The reaction of *N*,*N*-dibenzylhydroxylamine (**35**) with DMSO, DCC, and TFA took a different course giving crystalline α-phenyl-*N*-benzylnitrone (**38**) in 84% yield together with minor amounts of benzaldehyde (isolated as its dinitrophenylhydrazone) and *N*-benzylbenzamide. We suggest that the initially formed



35 36



37 38

oxysulfonium ion (**36**) collapses with intervention of the unshared electrons on nitrogen to give the nitroso cation (**37**) and dimethyl sulfide. A prototropic shift then converts (**37**) into the protonated nitrone which is isolated as the free base (**38**). A very similar conversion of a nitroso compound into a nitrone by alklyation with an oxonium salt has recently been described by Baldwin, *et al.*[23]

The formation of both benzaldehyde and *N*-benzylbenzamide could result from hydrolysis or rearrangement of the nitrone **38**, both types of reaction being well known.[7]

Experimental Section

General experimental methods are as previously described.[1]

Reactions of Benzophenone Oxime.—Trifluoroacetic acid (0.75 ml, 10 mmol) was added to a cooled solution of benzophenone oxime (2.00 g, 10.1 mmol) and DCC (6.2 g, 30 mmol) in anhydrous DMSO (20 ml) and benzene (20 ml) under nitrogen. After 2 hr at 25°, the mixture was poured into ice water and the resulting precipitate was well washed by trituration with benzene. The combined filtrates and benzene washings were extracted several times with water, dried (Na_2SO_4), and evaporated leaving 3.39 g of a yellow semisolid which was chromatographed on a column containing 150 g of Merck silicic acid. Elution with benzene gave 80 mg (3%) of *O*-(thiomethoxymethyl)benzophenone oxime (**6**) with mp 49–49.5° from benzene–hexane: λ_{max}^{MeOH} 231 mμ (ε 14,600), 261 (12,000); nmr ($CDCl_3$) 2.20 ppm (s, 3, SCH_3), 5.22 (s, 2, OCH_2S), 7.4 (br s, 10, Ar); mass spectrum (70 eV) *m/e* 257 (M^+), 211 (M − CH_2S), 194, 180 (M − C_6H_5), 77 (C_6H_5), 61 (CH_3SCH_2).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.88; N, 5.43; S, 12.46. Found: C, 70.19; H, 5.97; N, 5.44; S, 12.63.

Continued elution with chloroform–ethyl acetate (4:1) gave small amounts of benzophenone (8%) and unreacted **4** (8%) and elution with ethyl acetate gave **5** contaminated with some dicyclohexylurea (2.66 g). The solid was triturated with benzene and the soluble portion crystallized from aqueous methanol giving 1.85 g (74%) of α,α-diphenyl-*N*-(thiomethoxymethyl)-nitrone (**5**): mp 92–92.5°; λ_{max}^{MeOH} 236 mμ (ε 13,200), 300 (12,400); ir (KBr) 1250 cm^{-1} (C=N^+–O^-); nmr ($CDCl_3$) 2.43 ppm (s, 3, SCH_3), 4.75 (s, 2, NCH_2S), 7.3 (m, 8, Ar), 8.0 (m, 2, Ar); mass spectrum (70 eV) *m/e* 257 (M^+), 196 (M − CH_2SCH_3), 62 (CH_2SCH_3).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.88; N, 5.43; S, 12.46. Found: C, 70.17; H, 5.87; N, 5.43; S, 12.61.

Alkylation of Benzophenone Oxime.—Benzophenone oxime (5.0 g, 25.4 mmol) and a suspension of pentane washed sodium hydride (from 1.6 g, 35 mmol of a 53% suspension in mineral oil) were stirred in benzene at 80° under nitrogen for 20 min. After cooling, chloromethyl methyl sulfide (5.1 g, 53 mmol) was added, and the mixture was refluxed for 30 min. The mixture was filtered and the filtrate was evaporated to dryness leaving 6.51 g of a yellow oil that was chromatographed on a column containing 270 g of Merck silicic acid. Elution with benzene gave 3.04 g (47%) of **6** with mp 49–49.5° from benzene–hexane and identical spectral properties with those above. Elution with chloroform and with chloroform–ethyl actate (1:1) gave 0.47 g (10%) of benzophenone and 2.3 g (38%) of **5** of mp 92–92.5° and identical with that above.

Acidic Hydrolysis of 5.—A solution of 139 mg (0.54 mmol) of **5** in 3.5 ml of 85% methanol containing 0.05 ml of concentrated

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(22) O. Kamm, "Organic Syntheses," Coll. Vol. I, 2nd ed, Wiley, New York, N. Y., 1956, p 445.

(23) J. E. Baldwin, R. G. Pudussery, B. Sklarz, and M. K. Sultan, *Chem. Commun.*, 1361 (1968).

hydrochloric acid was kept at 35° for 30 min. Evaporation of the solvent left a solid residue that was sublimed (50°, (0.1 mm)] giving 85 mg (91%) of benzophenone of mp 48° and giving a 2,4-dinitrophenylhydrazone of mp 235–238°. A similar hydrolysis mixture was directly treated with acidic 2,4-dinitrophenylhydrazine solution giving a mixture of the dinitrophenylhydrazones of benzophenone and formaldehyde which were separated and identified by tlc using chloroform.

Desulfurization of 5.—A mixture of 281 mg of **5** and 0.5 g of Davidson sponge nickel[10] was stirred in benzene at 50° for 5 hr. Chromatography of the filtered and evaporated mixture on a column of silicic acid using benzene–chloroform(4:1) gave 81 mg (41%) of benzophenone, and elution with chloroform–ethyl acetate (4:1) gave 95 mg (34%) of unreacted **5** followed by 46 mg (20%) of α,α-diphenyl-*N*-methylnitrone: mp 101.5–102° from hexane (lit.[8] mp 102–103°); λ_{max}^{MeOH} 234 mμ (ε 12,100), 295 (11,200); ir (KBr) 1250 cm^{-1}; nmr ($CDCl_3$) 3.7 ppm (s, 3, NCH_3), 7.4 (m, 8, Ar), 8.0 (m, 2, Ar).

α,α-Diphenyl-*N*-(pentadeuteriothiomethoxymethyl)nitrone (14).—The reaction between **4** (196 mg, 1 mmol), DCC (168 mg, 3 mmol), and TFA (0.04 ml, 0.5 mmol) in a mixture of d_6-DMSO (0.25 ml) and benzene (0.25 ml) was carried out essentially as with nondeuterated DMSO. Preparative tlc using chloroform–ethyl acetate (4:1) gave three main bands corresponding to **5**, unreacted **4**, and a little benzophenone. Elution of the slowest band gave 0.17 g of crystalline solid which was dissolved in benzene leaving 60 mg of dicyclohexylurea. Crystallization of the benzene soluble portion from hexane gave 96 mg (37%) of **14**: mp 93–95°; ir (KBr) almost identical with that of **6**; nmr ($CDCl_3$) 7.4 ppm (m, 8, Ar), 8.0 (m, 2, Ar), no resonance below 7 ppm; mass spectrum (70 eV) *m/e* 262 (M^+), 196 ($Ar_2C{=}NO^+$), 66 ($CD_2SCD_3^+$).

Reaction of 14 with DMSO–DCC–H_3PO_4.—The pentadeuterionitrone (**14**, 84 mg, 0.33 mmol), DCC (206 mg, 1 mmol), and anhydrous orthophosphoric acid (0.15 mmol) were dissolved in DMSO (0.2 ml) and ethyl acetate (0.2 ml). After 16 hr at 25°, the mixture was worked up with ethyl acetate and purified by preparative tlc using benzene. Elution of the fastest uv-absorbing band (same mobility as **6**) gave 15 mg of chromatographically homogeneous **15**: ir ($CDCl_3$) 1490, 1445, 1325, 1305, 980, 695 cm^{-1} almost identical with **6**; nmr ($CDCl_3$) 7.35 ppm (br s, 10, Ar), 5.23 (s, 0.2, OCH_2S), 2.12 (s, 0.4, SCH_3).

Reaction of Fluoren-9-one Oxime with DMSO–DCC.—A reaction between fluoren-9-one oxime (1.95 g, 10 mmol), DCC (6.18 g, 30 mmol), and TFA (0.375 ml, 5 mmol) in a mixture of DMSO (10 ml) and benzene (10 ml) for 24 hr at 25° was worked up with ethyl acetate. Evaporation and trituration of the residue with ether gave 1.22 g (48%) of pure crystalline **17** which was recrystallized from ethanol: mp 154–155°; λ_{max}^{MeOH} 238 mμ (ε 36,000), 256 (27,700), 341 (16,300), 356 (17,600); nmr ($CDCl_3$) 2.50 ppm (s, 3, SMe), 5.35 (s, 2, NCH_2S), 7.3 (m, 5, Ar), 7.6 (m, 2, Ar), 8.2 (m, 1, Ar); mass spectrum *m/e* 255 (M^+), 61 ($CH_2SCH_3^+$).

Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.72; H, 5.18; N, 5.34; S, 12.58.

The mother liquors from **17** were purified by preparative tlc using ether–hexane (3:1) giving four bands. The fastest band contained 135 mg (5%) of the oxime ether **18** as a homogeneous syrup that was crystallized from cold hexane with mp 49–50°: λ_{max}^{MeOH} 218 mμ (ε 22,600), 223 (22,600), 247 (36,100), 256 (47,100), 308 (10,500), 360 (1900); nmr ($CDCl_3$) 2.26 ppm (s, 3, SCH_3), 5.40 (s, 2, OCH_2S), 7.3 (m, 6, Ar), 7.7 (m, 1, Ar), 8.2 (m, 1, Ar).

Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.78; H, 4.97; N, 5.29.

The second band contained some unreacted **16** and the third band a further 0.60 g (total yield 1.82 g, 71%) of **17** identical with that above.

Reaction of Estrone Methyl Ether Oxime (19).—Estrone methyl ether oxime[15] (0.96 g, 3.2 mmol), DCC (1.85 g, 9 mmol), and TFA (0.15 ml, 2 mmol) were reacted for 16 hr in a mixture of DMSO (10 ml) and benzene (10 ml). The worked-up mixture was purified by chromatography on a column containing 200 g of silicic acid. Elution with benzene gave 430 mg (48%) of nitrile **21** that was homogeneous by tlc[24] and vpc but which has not been obtained in crystalline form: λ_{max}^{MeOH} 277 mμ (ε 1800), 286 (1700); nmr ($CDCl_3$) 3.71 ppm (s, 3, OCH_3), 4.56 (s, 1, $C{=}CH_2$), 4.85 (s, 1, $C{=}CH_2$), 6.58 (s, 1, C_4H), 6.74 (q, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 2 Hz, 1, C_2H), 7.13 (d, $J_{1,2}$ = 9 Hz, 1, C_1H), no methyl singlet in 1.1–1.2 ppm range; ir (neat) 2250 cm^{-1} ($C{\equiv}N$).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.95; H, 8.22; N, 5.15.

Continued elution with chloroform gave 120 mg (12%) of unreacted **19** and elution with chloroform–ethyl acetate (3:1) gave 370 mg (40%) of lactam **20**: mp 218–220° (lit.[15] mp 222–224°); λ_{max}^{MeOH} 277 mμ (ε 2000), 287 (1800); ir (KBr) 1665 cm^{-1} (CONH); nmr ($CDCl_3$) 1.17 ppm (s, 3, $C_{19}H$), 3.74 (s, 3, OCH_3), 6.64 (s, 1, C_4H), 6.70 (br d, 1, C_2H), 7.20 (d, $J_{1,2}$ = 9 Hz, 1, C_1H), 7.32 (s, 1, NH).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.04; H, 8.64; N, 4.51.

Reaction of 3-β-Acetoxy-17-oximinoandrost-5-ene (22).—The reaction of **22** (1.04 g, 3 mmol, mp 177–179°),[19] DCC (1.85 g, 9 mmol), and TFA (0.15 ml, 2 mmol) in a mixture of DMSO (5 ml) and benzene (5 ml) was worked up as above and chromatographed on a column containing 200 g of silicic acid. Elution with chloroform gave 633 mg (61%) of the nitrile **24** as a syrup that slowly crystallized (mp 104–106°) on standing. After recrystallization from methanol the mp 105–106°: ir (KBr) 2245 cm^{-1} ($C{\equiv}N$), 1740 (OAc); nmr ($CDCl_3$) 0.93 ppm (s, 3, $C_{18}H$), 2.00 (s, 3, OAc), 4.55 (s, 1, $C{=}CH_2$), 4.85 (s, 1, $C{=}CH_2$), 5.40 (d, 1, C_6H).

Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.91; H, 9.22; N, 4.31.

Continued elution with a gradient of ethyl acetate in chloroform gave dicyclohexylurea followed by 218 mg (21%) of lactam **23** with mp 292–293° (lit.[19] mp 295–298°): ir (KBr) 1735 cm^{-1} (OAc), 1680 (CONH); nmr ($CDCl_3$) 1.01 ppm (s, 3, $C_{19}H$), 1.17 (s, 3, $C_{18}H$), 2.02 (s, 3, OAc), 4.6 (m, 1, C_3H), 5.40 (m, 1, C_6H), 7.35 (s, 1, NH).

Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.19; H, 9.14; N, 3.92.

Reaction of 22 with DMSO and Acetic Anhydride.—A solution of **22** (173 mg, 0.5 mmol) in DMSO (1.5 ml) and acetic anhydride (1.0 ml) was kept at room temperature for 24 hr during which time a crystalline product separated. The mixture was poured over ice giving the crystalline oxime acetate (172 mg, 90%) with mp 184–186° from methanol: ir (KBr) 1735, 1755, 1770 cm^{-1}; nmr ($CDCl_3$) 0.99 ppm (s, 3, $C_{18}H$), 1.02 (s, 3, $C_{19}H$), 2.00 (s, 3, OAc), 2.12 (s, 3, OAc), 5.4 (m, 1, C_6H).

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.14; H, 9.06; N, 3.61.

Reaction of *syn*-*p*-Bromobenzaldoxime (27).—The *syn* oxime (**27**) (2.74 g, 13.7 mmol), with mp 112–113° (lit.[25] mp 110–111°), DCC (4.5 g, 22 mmol), and TFA (0.2 ml, 2.7 mmol) were reacted for 2.5 hr in a mixture of DMSO (15 ml) and benzene (20 ml). The mixture was worked up with benzene giving 2.85 g of a yellow solid which was sublimed [50° (0.1 mm)] giving 1.70 g (68%) of pure *p*-bromobenzonitrile (**29**) of mp 111–112° (lit.[26] mp 112.5°): λ_{max}^{MeOH} 240 mμ (ε 20,800); ir (KBr) 2230 cm^{-1} ($C{\equiv}N$). Upon raising the temperature of the sublimation[27] to 90°, 1.02 g (29%) of the pure nitrone **32** was obtained with mp 102.5–103.5°: λ_{max}^{MeOH} 302 mμ (ε 23,100); nmr ($CDCl_3$) 2.32 ppm (s, 3, SCH_3), 4.85 (s, 2, NCH_2S), 7.76 (s, 1, $HC{=}N$), 7.52 (d, J = 8 Hz, 2, Ar), 8.15 (d, J = 8 Hz, 2, Ar).

Anal. Calcd for $C_9H_{10}NOSBr$: C, 41.55; H, 3.88; N, 5.39; S, 12.33. Found: C, 41.74; H, 4.02; N, 5.26; S, 12.55.

Hydrolysis of 203 mg of **32** with 90% methanol (5 ml) containing 0.1 ml of 2 *N* hydrochloric acid at 25° for 4 hr gave mainly the *syn* oxime (**27**) which was isolated by thin layer chromatography using chloroform.

***anti*-*p*-Bromobenzaldoxime (30).**—Hydrogen chloride was bubbled for 15 min through a vigorously stirred solution of the *syn* oxime (**27**) (4.0 g) in ether. The resulting precipitate was collected by filtration, washed with ether, and dissolved in water. A 2 *N* solution of sodium hydroxide was then added until the mixture was pH 9 and the resulting crystalline residue (3.1 g, 78%) was collected by filtration and washed with water. Thin layer chromatography using $CHCl_3$–ethyl acetate (4:1) showed a single spot with a mobility smaller than that of **27**: mp 134–135°

(24) The product was distinctly different from the isomeric $\Delta^{13(14)}$ compound recently described by Cervantes, *et al.*[19] We are grateful to Dr. Crabbé for a sample of their compound.

(25) A. Hantzsch, *Z. Phys. Chem.*, **13**, 510 (1894).

(26) A. Korczynski and B. Fandrich, *C. R. Acad. Sci.*, **183**, 421 (1926).

(27) Alternatively, the reaction was worked up by chromatography on silicic acid, **29** and **32** being eluted with benzene and with chloroform–ethyl acetate (1:3), respectively. After crystallization from benzene–hexane, the products were identical with those above.

(lit.[28] mp 157° by a different method); nmr (DMSO-d_6) 7.46 ppm (s, 1, HC=N), 7.63 (d, J = 9 Hz, 2, Ar), 7.97 (d, J = 9 Hz, 2, Ar), 11.82 (s, 1, OH).

Reaction of *anti*-*p*-Bromobenzaldoxime (30).—A mixture of **30** (2.74 g), DCC (4.5 g), and TFA (0.20 ml) was reacted for 2.5 hr in DMSO (20 ml) and benzene (20 ml). After the usual work-up sublimation at 50° (0.1 mm) gave 2.10 g (84%) of nitrile **29** identical with that above. The residue (400 mg) contained a roughly 5:3 mixture of *p*-bromobenzaldehyde and nitrone **32** by quantitative tlc but isolation was not attempted.

Alkylation of *p*-Bromobenzaldoxime with Chloromethyl Methyl Sulfide. A.—Pentane washed sodium hydride (65 mg) was added to a stirred solution of the *syn* oxime (**27**) (417 mg) in benzene (20 ml). After 10 min at 25° the mixture was heated to 70° for 10 min, and cooled while chloromethyl methyl sulfide (1 ml) was added in several portions. After 15 min at 50° the yellow solution was filtered and evaporated *in vacuo* leaving 520 mg of a yellow oil which was purified by chromatography on a column of silicic acid. Elution with benzene–chloroform (4:1) gave 225 mg (42%) of *O*-(thiomethoxymethyl)-*p*-bromobenzaldoxime (**32**) which was sublimed at 70° (0.1 mm) with mp 61–62°: λ_{max}^{MeOH} 267 mμ (ε 19,100); 298 (3400); nmr ($CDCl_3$) 2.27 ppm (s, 3, SCH_3), 5.24 (s, 2, OCH_2S), 7.45 (s, 4, Ar), 8.04 (s, 1, HC=N).

Anal. Calcd for $C_9H_{10}NOSBr$: C, 41.55; H, 3.88; N, 5.39; S, 12.33. Found: C, 41.73; H, 3.97; N, 5.42; S, 12.57.

Traces (45 mg total) of unreacted oxime and *p*-bromobenzaldehyde were eluted with chloroform–ethyl acetate (1:1) and 217 mg (40%) of nitrone (**32**) was obtained with chloroform–ethyl acetate (1:5). After sublimation at 90° (0.1 mm) this material was identical with **32** obtained from the DMSO–DCC reaction.

B.—A reaction identical with A was carried out except that the *anti* oxime (**30**) was used. The products were identical with those from the *syn* oxime by melting point and by nmr and ir spectra.

Reaction of *N*-Phenylhydroxylamine (33).—Trifluoroacetic acid (0.075 ml, 1 mmol) was added to a solution of freshly prepared *N*-phenylhydroxylamine[22] (1.11 g, 10 mmol) and DCC (6.0 g, 29 mmol) in a mixture of DMSO (15 ml) and benzene (15 ml). The initially pale yellow solution rapidly became green, then yellow, and finally red. After 14 hr the mixture was diluted with benzene and excess DCC was destroyed by addition of oxalic acid (20 mmol). After filtration, the solution was extracted three times with water, dried, and evaporated leaving 1.06 g of an oil that was chromatographed on a column containing 100 g of silicic acid. The major product (540 mg, 54%) was eluted with a gradient of chloroform in benzene (20–80%) and was followed by small amounts of four unidentified compounds. The product crystallized upon storage giving *trans*-azoxybenzene as yellow needles of mp 34.5–35.5° (lit.[29] mp 36°): λ_{max}^{MeOH} 230 mμ (ε 9100), 259 (7800), 320 (14,700) (virtually identical with lit.[30] values); nmr ($CDCl_3$) 7.23–7.66 (m, 6, Ar), 8.01–8.41 (m, 4, Ar).

Reaction of *N*,*N*-Dibenzylhydroxylamine (35).—A solution of *N*,*N*-dibenzylhydroxylamine (2.13 g, 10 mmol), DCC (4.2 g, 20 mmol), and trifluoroacetic acid (0.1 ml, 1.3 mmol) in DMSO (10 ml) and ether (10 ml) was kept at 25° for 1 hr. The mixture was then diluted with chloroform, filtered, extracted several times with water, dried (Na_2SO_4), and evaporated leaving a clear syrup. Crystallization from benzene gave 1.76 g (84%) of α-phenyl-*N*-benzylnitrone (**38**) with mp 81–83° (lit.[31] mp 82–83°): λ_{max}^{MeOH} 294 mμ (ε 20,300), 222 sh (9800); nmr ($CDCl_3$) 5.03 ppm (s, 2, $ArCH_2N$), 7.2–7.6 (m, 9, Ar), 8.1–8.4 (m, 2, Ar and HC=N); ir (KBr) 1590 cm^{-1}.

Chromatography of the mother liquors in silicic acid gave benzaldehyde (310 mg, 10% as the 2,4-dinitrophenylhydrazone) and a small amount of *N*-benzylbenzamide of mp 102–104° which was identical in every way with an authentic sample.

Registry No.—**5**, 19133-01-8; **6**, 25056-49-9; **14**, 25056-50-2; **15**, 25055-75-8; **17**, 25055-76-9; **18**, 25055-77-0; **20**, 20678-99-3; **21**, 25062-42-4; **22b**, 7675-95-8; **23**, 2232-16-8; **24**, 25062-45-7; **29**, 623-00-7; **30**, 25062-46-8; **32**, 25055-79-2; **38**, 3376-26-9.

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(29) G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 2143 (1953).

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Carbodiimide–Sulfoxide Reactions. IX.[1] Synthesis of 2′- and 3′-Keto Derivatives of Cytidine

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Reaction of N^4-acetylcytidine with an excess of chlorotriphenylmethane in pyridine at 90° gives both the 2′,5- and 3′,5′-ditrityl derivatives and a small amount of N^4-acetyl-2′,3′,5′-tritritylcytidine. Each compound could be deacetylated and then related to the corresponding uridine derivatives by deamination. Efficient oxidation of the isomeric N^4-acetyl ditritylcytidines could be achieved using either the dimethyl sulfoxide–dicyclohexylcarbodiimide or the dimethyl sulfoxide–acetic anhydride methods giving the corresponding 2′- and 3′-ketocytidine derivatives. Subsequent detritylation using hydrogen chloride in chloroform gave N^4-acetyl-2′(or 3′)-ketocytidines. Oxidation of free 2′,5′- or 3′,5′-ditritylcytidines could also be accomplished using the DMSO–DCC method. Borohydride reduction of the various compounds was studied, the 2′ ketones giving nucleosides with the arabinose and ribose configurations in a ratio of 4:1 while the 3′ ketones gave xylosyl and ribosyl derivatives in a ratio of 3:2. Reduction of the free N^4-acetyl-2′- and -3′-ketocytidines with sodium borohydride-^{3}H provides a facile route to cytosine nucleosides with the arabinose, xylose, and ribose configurations containing a tritium label at specific positions of the sugar.

The development of mild methods for the oxidation of alcohols based upon the reactions of dimethyl sulfoxide (DMSO) activated by dicyclohexylcarbodiimide (DCC),[3] acetic anhydride,[4] or phosphorus pentoxide[5] has led to many syntheses of otherwise difficulty accessible keto sugar derivatives.[6] In an earlier paper in this series,[7] we have described the oxidation in good yield of 2′,5′-di-*O*-trityluridine (**1**) and of 3′,5′-di-*O*-

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(2) Syntex Postdoctoral Fellow, 1967–1968.

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