Alkylation of *syn*- and *anti*-Benzaldoximes[1a]

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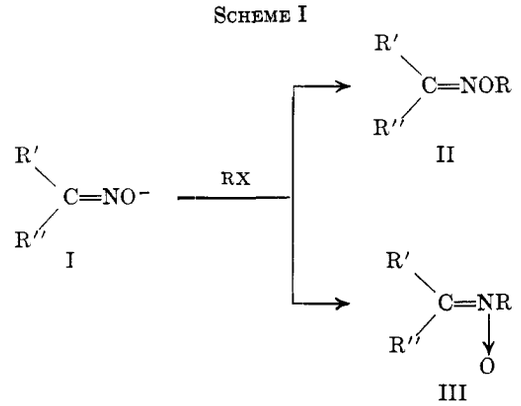
Geometrical isomerism and associated steric factors have been demonstrated to affect the site of alkylation of aldoximes. *anti*-benzaldoxime is readily N-alkylated by various alkyl halides, whereas *syn*-benzaldoxime is largely O-alkylated. This finding opens a convenient synthetic route to α-phenyl-N-substituted nitrones and O-alkyl benzaldoximes. The assignments of structure, geometrical isomerism, and determination of the ratios of O- and N-alkylation, have been derived from nuclear magnetic resonance (nmr) spectra.

It is well established that the alkylation of oxime anions I (Scheme I) results in mixtures of O-alkyl oximes II and -nitrones III.[2] Changes in the reaction conditions or variations in the alkyl halides or oximes employed have failed to affect the ratio of O- and N-alkylation significantly. Thus, the general applicability of this reaction for the synthesis of compounds of types II or III has suffered.[3]

SCHEME I



Since oximes are of ambifunctional nucleophilic character, alkylation of the many structural variations possible permits the establishment of structure–reactivity relationships. This has been done in a detailed study with a series of disubstituted *p,p'*-benzophenonoximes.[4] There have been few adequate studies of aldoximes, which represent the stronger nucleophiles[2a,b] and in which geometrical isomerism can be expected to exert some control on the reaction course.

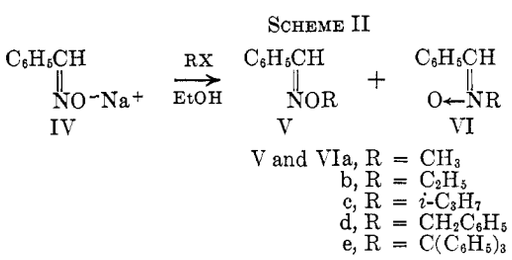
It has been reported[5a] that the methylation of sodium *syn*-benzaldoximate (IV) leads predominantly to O-methyl benzaldoxime (Va), whereas sodium *anti*-benzaldoximate (VII) yields more of the N-methylated isomer VIa. The conclusions of those authors[5,6] who postulate "ionic" and "nonionic" mechanisms for the different sites of methylation, have been seriously questioned.[4] However, their experimental findings regarding the predominant site of methylation[5a] remain valid, especially since corresponding results have been reported with allyl halides.[5b] The early literature on the synthesis of a few N-substituted hydroxylamines from nitrones reveals that a correlation between geometrical isomerism and predominant site of alkylation was used sporadically, though without complete understanding.[7] Those findings[7] have been neglected in modern investigations and review articles, probably because of the lack of knowledge at that time about geometrical isomerism in the aldoximes.[2a]

In view of the existing ambiguity and of the importance of nitrones[2,3,8] and N-substituted hydroxylamines[8] as synthetic intermediates, we have reinvestigated the course of alkylation of the sodium salts of the *syn*- and *anti*-benzaldoximes.

Results

Alkylations.—The alkylation of sodium *syn*-benzaldoximate (IV, Scheme II) differs from that of the

SCHEME II



V and VIa, R = CH_3
b, R = C_2H_5
c, R = i-C_3H_7
d, R = $CH_2C_6H_5$
e, R = $C(C_6H_5)_3$

anti-benzaldoximate VII in two ways: reaction time and ratio of O- to N-alkylation (O/N ratio in Table I). The reaction times and corresponding temperatures were obtained from standardized alkylation experiments. The *syn*- or *anti*-benzaldoxime with an equivalent amount of sodium ethoxide in ethanol and the alkyl halide in a small excess were stirred at room temperature until the pH was below 7 as shown by a wet pH paper. When the reaction was still incomplete after 4 days, the mixture was heated at 70–85° until the pH dropped. From the nmr the alkylations of IV and VII proceed quantitatively and lead exclusively to O- or/and N-alkylated benzaldoxime derivatives. The ratio of O- to N-alkylation was determined on the crude reaction mixtures by utilizing the difference in chemical shifts of corresponding protons in the nmr spectra. The integration of the CH=N proton of the component O-alkyl benzaldoxime (H_B in Table II) and -nitrone ($H_{B'}$

(1) (a) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA-03190-09 and 08748), and a fellowship, during 1965, from the Damon Runyon Memorial Fund. (b) Deceased Oct 10, 1966.

(2) (a) J. Meisenheimer and W. Theilacker, in "Stereochemie," Vol. 3, K. Freudenberg, Ed., Verlag Franz Deuticke, Wien, 1932, p 963; (b) L. I. Smith, *Chem. Rev.*, **23**, 222 (1938); (c) J. Hamer and A. Maculuso, *ibid.*, **64**, 474 (1964).

(3) G. R. Delpierre and M. Lamchen, *Quart. Rev.* (London), **19**, 329 (1965).

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

(5) (a) O. L. Brady, F. B. Dunn, and R. F. Goldstein, *J. Chem. Soc.*, 2386 (1926); (b) O. L. Brady and F. H. Peakin, *ibid.*, 226 (1930).

(6) O. L. Brady and R. F. Goldstein, *ibid.*, 2403 (1926).

(7) (a) E. Beckmann, *Chem. Ber.*, **22**, 429 (1889); (b) C. Kjellin, *ibid.*, **26**, 2377 (1893); (c) A. Hantzsch and W. Wild, *Ann.*, **289**, 285 (1896); (d) C. Kjellin, *Chem. Ber.*, **30**, 1892 (1897).

(8) P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin Inc., New York, N. Y., 1966, pp 1–107.

TABLE I

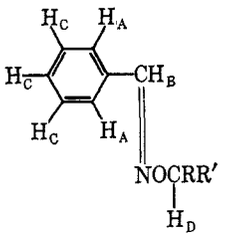
ALKYLATION OF SODIUM *syn*- AND *anti*-BENZALDOXIMATES WITH VARIOUS ALKYL HALIDES IN ETHANOL

	syn			*anti*		
Alkyl halide	Time	Temp, °C	O/N ratio[a]	Time	Temp, °C	O/N ratio[b]
CH_3I	30 hr	25	3	3.5 hr	25	<0.05
C_2H_5I	4 days	25+	5	24 hr	25	<0.05
	15 min	80				
i-C_3H_7I	4 days	25+	6	4 days	25+	>0.05[c]
	6.5 hr	85		1 hr	70	
$C_6H_5CH_2Cl$	4 days	25+	9	4 hr	25	<0.05
	40 min	80				

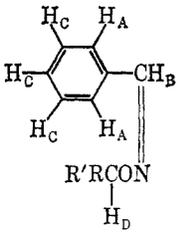
[a] These O/N ratios represent the rounded averages from at least two experiments. [b] Estimated. [c] See footnote 10.

TABLE II

CHEMICAL SHIFTS[a] OF *syn*- AND *anti*-BENZALDOXIMES AND THEIR O-ALKYL DERIVATIVES



syn-V



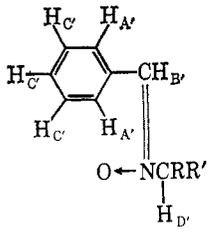
anti-IX

					τ values, ppm			
	R	R′	Configuration	$H_A:H_B:H_C:H_D$	H_A	H_B	H_C	H_D
Va	H	H	*syn*	2:1:3:3	2.31	1.74	2.54	6.05
IXa	H	H	*anti*		2.00	2.45	2.50[b]	
Vb	H	CH_3	*syn*	2:1:3:2	2.30	1.74	2.53	5.79
IXb	H	CH_3	*anti*		1.95	2.50[b]	2.50[b]	
Vc	CH_3	CH_3	*syn*	2:1:3:1	2.28	1.75	2.54	5.54
IXc	CH_3	CH_3	*anti*		1.94	2.48	2.50[b]	
Vd	H	C_6H_5	*syn*	2:1:3:2	2.30	1.63	2.58	4.74
α-Benzaldoxime			*syn*	2:1:3	2.28	1.70	2.52	
β-Benzaldoxime			*anti*	2:(4)	1.98	2.55	2.54	

[a] Measured downfield from tetramethylsilane (internal standard) in DMSO-d_6. [b] This figure is only approximate because the corresponding signal coincides with the H_C signal of the coexisting *syn* isomer. See footnote 17.

TABLE III

CHEMICAL SHIFTS[a] OF α-PHENYL-N-ALKYLNITRONES (VI)



			$H_A':H_B':$	τ values, ppm			
	R	R′	$H_C':H_D'$	H_A'	H_B'	H_C'	H_D'
VIa	H	H	2:1:3:3	1.66	2.10	2.49	6.14
VIb	H	CH_3	2:1:3:2	1.62	2.08	2.49	5.99
VIc	CH_3	CH_3	2:1:3:1	1.64	2.05	2.50	5.60
VId	H	C_6H_5	2:1:3:2	1.70	1.85	2.31	4.85

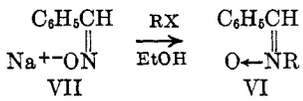
[a] Measured downfield from tetramethylsilane (internal standard) in DMSO-d_6.

in Table III), provided O/N ratios reproducible within 10–15%. A similar method has been used for the determination of *syn*/*anti* isomer ratios in various aliphatic aldoximes.[9]

The alkylation of the *syn*-benzaldoximate IV leads, as expected, to a mixture of the O-alkyl *syn*-benzaldoxime (V) and the isomeric nitrone VI. Compound V always predominates and the O/N ratio depends on the alkylating agent used (Table I). From these reaction mixtures the pure O-alkyl *syn*-benzaldoximes (Va–e) could be easily isolated in yields of about 50–70%.

Upon alkylation of the sodium *anti*-benzaldoximate (VII, Scheme III) under the same reaction conditions

SCHEME III



the O/N ratio is reduced sharply. In fact the presence of O-alkyl benzaldoximes[10] in the crude reaction mixtures is too low to permit a meaningful evaluation of the integration curves for O/N ratio determinations. The yields of pure nitrones VIa–e resulting from these alkylation reactions range from 50 to 80%. The synthesis of α-phenyl-N-triphenylmethylnitrone (VIe) presents an excellent example of the applicability of the selective alkylation of the benzaldoximates. The usual condensation reaction between benzaldehyde or its imino derivative and N-triphenylmethylhydroxylamine has repeatedly failed[11,12] to yield the expected nitrone VIe and furnished O-triphenylmethyl benzal-

(9) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 825 (1958).

(10) In the case of isopropylation the proportion of O-alkyl product was significant, although low. From the nmr the predominant configuration of this O-alkyl derivative seems to be *anti*.

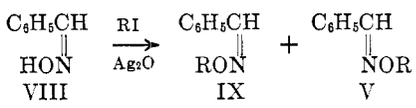
(11) A. C. Cope and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **72**, 4896 (1950).

(12) E. J. Grubbs, J. D. McCullough, Jr., B. H. Weber, and J. R. Maley, *J. Org. Chem.*, **31**, 1098 (1966).

doxime (Ve). The authors had little doubt[11,12] that during the condensation reaction the nitrone was formed but rearranged to the O-trityl derivative under the conditions applied. The tritylations of the *syn*- and the *anti*-benzaldoximates IV and VII, respectively, proceed smoothly in ethanol at room temperature and lead, respectively, to good yields of O-trityl benzaldoxime (Ve) and α-phenyl-N-tritylnitrone (VIe). Heat does rearrange the nitrone VIe to the corresponding O-alkyl oxime Ve thus confirming the thermal rearrangement postulated to occur during the condensation reaction.[11,12]

Treatment of various *syn*- or *anti*-benzaldoximes in methyl iodide in the presence of suspended silver oxide has been reported to yield exclusive O-methylation.[5a,13] We repeated this with the assumption that little interconversion of the *anti*-benzaldoxime VIII (Scheme IV)

SCHEME IV



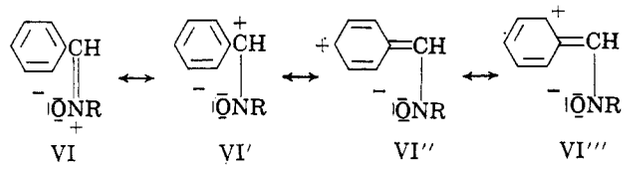
into the *syn* isomer would take place under these conditions, and that various O-alkyl *anti*-benzaldoximes (IXa–c) would be obtained to permit comparison of their nmr spectra with those of the pure *syn* isomers (Va–c). Exclusive O-alkylation was confirmed since the nitrones could not be detected by nmr.[14,15] However, interconversion of the original *anti* to the *syn* configuration took place to an increasing extent from methylation to isopropylation.[16] The *anti*/*syn* ratios of O-alkyl benzaldoximes (IX/V) found in these mixtures were 14 with CH_3I, 8 with C_2H_5I, and 7 with *i*-C_3H_7I as determined by nmr.[17] No separation into pure isomeric forms was possible. The nmr indicates that the *anti*/*syn* ratio is unaffected by fractional distillation in vacuum.

Structural Studies by Nmr.—The chemical shifts pertinent to the assignment of structures to the isomeric O-alkyl benzaldoximes (V and IX) are recorded in Table II. The assignment of the derivatives V to the *syn* series and of the derivatives IX to the *anti* series is based upon comparison of the chemical shifts of the H_A and H_B signals with those of *syn*- and *anti*-benzaldoximes (Table II).

The difference in the chemical shifts of the H_B protons in corresponding *syn*- and *anti*-O-alkyl benzaldoximes (see structure V and IX in Table II) follows closely the general pattern recently established for various types of *syn* and *anti* isomers.[9,18] The proton H_B is always deshielded in the *syn* form (structure V) and therefore useful for assigning *syn* and *anti* structures. The anisotropy of the alkyl-O-N function appears to be responsible for the deshielding effect on the proximate H_B proton in the *syn* isomers. A similar deshielding can be anticipated for the *ortho* protons (H_A) of the phenyl in the *anti* isomers IX, since they are then the ones in close proximity to the alkyl-O-N function. In fact, the nmr signals due to the phenyl protons of the *anti* isomers are clearly separated into two sets of multiplets.[19a] Integration accounts for two protons in the downfield and three protons in the upfield area.[19b] In view of this, the *ortho* protons (H_A) have been assigned to the downfield multiplet and the *meta* and *para* protons (H_C in Table II) to the upfield resonance. Corresponding assignments have been recently made on various substituted *syn*- and *anti*-benzaldoximes.[18d]

Geometrical isomerism, which is well established in the O-alkyl benzaldoximes series,[2a,20] is rarely reported from α-phenyl-N-alkylnitrones.[2,21] Therefore the presence of a CN double bond in the nitrones VI may be questioned. Several mesomeric forms (VI′–VI‴, Scheme V) can be considered to lessen the double-bond character of the CN bond in structure VI.

SCHEME V



According to the nmr spectra of the nitrones VIa–d (Table III), the mesomeric forms VI″ and VI‴ in which the positive charge is delocalized in the phenyl ring are of minor importance. This is indicated by the striking similarity of the nmr pattern of the phenyl protons in O-alkyl benzaldoximes and nitrones. The separation of the resonance of the phenyl protons is enhanced and the integration again assigns two protons ($H_{A'}$ in Table III) to the downfield multiplet and three protons ($H_{C'}$ in Table III) to the upfield resonance. The mesomeric form VI′, however, appears to be quite extensively involved. The chemical shift of the CH_3 singlet in nitrone VIa did not show any temperature dependence over the range of −60° (in $CDCl_3$) to 100° (in DMSO-d_6). This behavior of the methyl peak over the wide range of temperature suggests that there is little restriction around the CN bond in VIa. In view of this, it is interesting to find that the arithmetical mean of the chemical shifts (in τ values) of the H_B protons of the corresponding *syn*- and *anti*-O-alkyl benzaldoximes (ranging from 2.09 to 2.11 ppm) compare well with the chemical shifts of the corresponding $H_{B'}$ protons in the nitrones VIa–c (ranging from 2.05 to 2.10 ppm).

(13) H. Lindemann and K. T. Tschang, *Chem. Ber.*, **60**, 1727 (1927).

(14) It has been suggested that nucleophilic substitutions proceed under these conditions in an SN1- rather than an SN2-type mechanism,[15] which explains the preference of the substitution by the oxygen.

(15) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Am. Chem. Soc.*, **77**, 6269 (1955).

(16) Since each alkylation was carried out at the boiling point of the corresponding alkyl iodide, the decreasing *anti*/*syn* ratio reflects to some extent the temperature of the reaction and the tendency toward thermal isomerization.

(17) Determined by integrated intensity measurements utilizing the different chemical shifts of corresponding protons in the O-alkyl groups of the *anti* (IXa–c) and the coexisting *syn* isomers (Va–c). Since these signals are only 3–4 cps apart they were fivefold expanded (sweep width from 500 to 100 cps).

(18) (a) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961); (b) E. J. Poziomek, D. N. Kramer, W. A. Mosher, and H. O. Michel, *J. Am. Chem. Soc.*, **83**, 3916 (1961); (c) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *ibid.*, **85**, 2326, 2327 (1963); (d) I. Pejkovic-Tadic, M. Hranisavljevic-Jakovljevic, S. Nesic, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **48**, 1157 (1965).

(19) (a) A small separation of the phenyl proton resonance is also present in the *syn* isomers (H_A and H_C in Table II) indicating an anisotropic effect of the CN double bond.[20] (b) Integrates actually for four protons, since the H_B singlet is superimposed.

(20) H. Hjeds, K. P. Hansen, and B. Jerslew, *Acta Chem. Scand.*, **19**, 2166 (1965).

(21) W. D. Emmons, *J. Am. Chem. Soc.*, **70**, 5739 (1957).

Discussion

Consideration of the geometrical isomerism and the associated steric factors permits a reasonable and useful interpretation of the O- and N-alkylations of aldoximes, about which there have been numerous conflicting results and theories.[2,4,5,22] The important features of O- *vs.* N-alkylation can now be summarized. *anti*-Benzaldoximate VII is almost exclusively N-alkylated by all alkyl halides; *syn*-benzaldoximate IV is largely O-alkylated; and the O/N ratio (Table I) depends on the alkylating agent.

In the alkylation reaction of each geometrical isomer, the two competing nucleophilic sites, O and N, of the ambifunctional oximate cannot be regarded as sterically equivalent. In the *anti*-benzaldoxime the phenyl ring exerts a steric hindrance on the oxygen, whereas the electron pair of the nitrogen is completely free to participate in a nucleophilic attack on the carbon of the alkyl halide. In *syn*-benzaldoxime, however, the nitrogen site is sterically restricted by the phenyl ring, whereas the oxygen is free to execute a nucleophilic attack. From this consideration it must not be concluded that the proportion of O- *vs.* N-alkylation in the different geometrical isomers IV and VII are merely reversed. As a result of the conjugation of the nitrogen to the phenyl ring in either isomer, N-alkylation seems in principal to be facilitated, since it may proceed through a transition state (XI) whose activation energy is considerably lowered in comparison with that of the O-alkylation (*e.g.*, XII). In addition it is seen from consideration of models that the approach to the nitrogen in the *syn* isomer is considerably less hindered than is the approach to the oxygen in the *anti* isomer. Both arguments are consistent with our finding that the *anti*-VII is O-alkylated to a negligible extent, whereas the *syn*-IV alwayss hows some degree of N-alkylation (Table I).

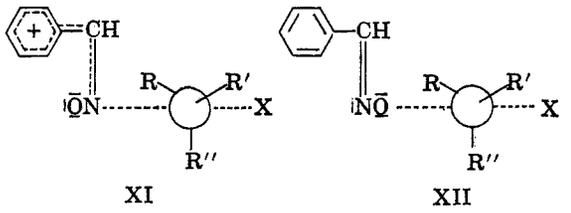
A secondary steric influence on the ratio of O- *vs.* N-alkylation of the *syn* benzaldoximate is attributable to the bulkiness of the alkylating agent. A similar influence of the alkylating agent has been found in the methylation and benzylation of benzophenonoximes.[4]

The increased time and temperature required with increasingly bulky alkyl iodides is correlated with the second-order process[4,23] of the alkylation of aldoximes.

The *anti* isomer VII is more reactive (Table I) than the *syn* isomer IV,[24,25] which would be expected since VII is under some steric strain[26] and undergoes almost exclusive N-alkylation.

For N-alkylation of the syn-IV and *anti*-VII isomers the transition state XI (Scheme VI) is proposed. With nucleophilic attack by the free electron pair of the nitrogen, the original CN double bond acquires single-bond character through the delocalization of the partial positive charge formed on the nitrogen during its nucleophilic attack. This delocalization should relieve the steric congestions in the *anti* isomer VII.

SCHEME VI



For O-alkylation of the *syn* isomer the transition state would be XII. Since the oxygen is involved in the nucleophilic attack, no delocalization of the partial charges is possible, and there is no steric strain to be relieved. Thus, the O-alkylation leaves the original geometrical conformation essentially unchanged. The formation of one and the same nitrone by N-alkylation of IV and VII is the result of the single-bond character of the CN bond in the transition state XI, or in the mesomeric ground state (VI and VI′ in Scheme V).

Detailed interpretation of the *anti/syn* ratios of the O-alkyl benzaldoximes obtained in the presence of silver oxide is not justified, particularly since the experimental conditions are not standardized.[16] The configurational stability[2a,27] reported for *cis*- and *trans*-O-alkyl oximes suggests that isomerization occurred before O-alkylation.[28]

Experimental Section

Melting and boiling points are uncorrected. The nmr spectra were obtained on a Varian Model A-60 spectrometer, and are, unless otherwise stated, measured in DMSO-d_6 downfield from tetramethylsilane (internal standard). The ultraviolet spectra were determined on a Cary 15 spectrophotometer. The analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Alkylation of Sodium *syn*-Benzaldoximate (IV).—A solution was prepared from 1.15 g (0.05 mole) of sodium and 6.05 g (0.05 mole) of *syn*-benzaldoxime[29] in 100 ml of absolute ethanol. To the magnetically stirred solution 0.053 mole of the alkyl halide were added in one portion and the reaction mixture was heated[30] in a bath (80–85°) until the pH was below 7 as shown by a wet pH paper. The reaction mixture was evaporated, the residue was treated twice with 50 ml of chloroform and the inorganic material was removed by filtration. The combined filtrates were evaporated and the remaining oils[31] were distilled under vacuum to give the O-alkyl *syn*-benzaldoximes as colorless oils in yields about *ca.* 50–70% (Table IV). In all distillations an oily residue remained which consisted chiefly of the corresponding nitrones.[31]

Alkylation of Sodium *anti*-Benzaldoximate (VII).[32]—The procedure is essentially the same as that for the sodium *syn*-benzaldoximate (IV), but only during isopropylation was external heating required. In all others room temperature (*ca.* 25°) was sufficient. Depending on the alkyl halide used, a solid or an oil remained after evaporation of the salt-free chloroform solutions. Recrystallization of the solids from ether or petroleum

(22) (a) Ramart-Lucas and J. Hoch, *Bull. Soc. Chim.*, **5**, 987 (1938); (b) F. Nerdel and I. Huldschinsky, *Chem. Ber.*, **86**, 1005 (1953).

(23) H. Goldschmidt, *Z. Elektrochem.*, **14**, 581 (1908).

(24) A similar preference for the *anti*-aldoxime is reported from the dehydration of aldoximes to nitriles (*trans* elimination).[25]

(25) C. R. Hauser, J. W. LeMaistre, and A. E. Rainsford, *J. Am. Chem. Soc.*, **57**, 1056 (1935).

(26) W. Swietoslawski and M. Popow, *Bull. Soc. Chim. France*, **35**, 137 (1924).

(27) (a) D. Y. Curtin, E. J. Grubbs, and C. G. McCarty, *J. Am. Chem. Soc.*, **88**, 2775 (1966); (b) O. L. Brady and L. Klein, *J. Chem. Soc.*, 874 (1927).

(28) A referee has suggested that " . . . in the silver oxide process the coordination of the silver ion with the nitrogen of the oxime is responsible for facilitating rotation about the C=N bond."

(29) A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Longmans, London, p 719.

(30) Reactions with methyl iodide were stirred at room temperature for *ca.* 24 hr.

(31) In case of methylation a solid remains, from which the nitrone VIa can be separated by addition of 100 ml of petroleum ether (bp 30–60°) and 10 ml of ether.

(32) Larger quantities of *anti*-benzaldoxime could not be obtained by simple scaling-up of the usual procedure.[29] A modified method, avoiding any prolonged contact with acid, was devised: A. Sele and E. Buehler, submitted for publication.

TABLE IV

O-ALKYL BENZALDOXIMES (*syn*-V AND *anti*-IX) AND N-ALKYL-α-PHENYLNITRONES (VI)

Alkyl	Mp or bp, °C (mm)	$n^{20}D$	C, %	H, %	N, %
O-Methyl Va[a]	95 (20)	1.4578	70.93	6.73	10.28 found
IXa[b]	86 (10)	1.5469	70.93	6.68	10.20 found
N-Methyl VIa[c]	82–83	...	70.37	6.68	10.15 found
			71.09	6.71	10.36 calcd
O-Ethyl Vb[d]	98 (8)	1.5369	72.35	7.53	9.39 found
IXb[e]	98 (8)	1.5351	72.33	7.52	9.60 found
N-Ethyl VIb	116 (0.8)	1.6065	72.70	7.60	9.22 found
			72.46	7.43	9.39 calcd
O-Isopropyl Vc	104 (8)	1.5298	73.47	7.98	8.77 found
IXd[f]	107 (10)	1.5244	73.59	8.20	8.80 found
N-Isopropyl VIc	164 (8)	1.5868	73.54	8.17	8.82 found
			73.59	8.03	8.58 calcd
O-Benzyl Vd[d,g]	123 (0.5)	1.5927	79.75	6.38	6.74 found
N-Benzyl VId[h]	80–81	...	79.29	6.23	6.42 found
			79.59	6.20	6.63 calcd

[a] J. Petraczek, *Chem. Ber.*, **16**, 826 (1883); J. Traube, *ibid.*, **53**, 1486 (1920). [b] Contains *ca.* 7% of the *syn* isomer. K. Auwers and B. Ottens, *Chem. Ber.*, **57**, 456 (1924). [c] H. Goldschmidt, *ibid.*, **23**, 2177 (1890); E. Beckmann, *Ann.*, **365**, 205 (1909). [d] E. Beckmann, *Chem. Ber.*, **22**, 1536 (1889). [e] Contains *ca.* 11% of the *syn* isomer. [f] Contains *ca.* 12% of the *syn* isomer. [g] P. Grammaticakis, *Compt. Rend.*, **224**, 1568 (1947). [h] E. Beckmann, *Chem. Ber.*, **22**, 435, 438 (1889).

ether (bp 30–60°) or fractional distillation under vacuum of the oils furnished the pure nitrones VIa–d in yields of about 50–80% (Table IV).

Alkylation of *anti*-Benzaldoxime VIII in the Presence of Silver Oxide.—To 5 g of *anti*-benzaldoxime[32] and 10 g of silver oxide, 40–45 ml of alkyl iodide was added with stirring. After the initial exothermic reaction subsided, the mixture was refluxed and stirred for an additional hour. The hot reaction mixture was filtered, the solid was washed with chloroform, and the combined filtrates were evaporated. The remaining oils were distilled under vacuum to give colorless liquids which contained predominantly the O-alkyl *anti*-benzaldoximes (IXa–c, Table IV).

Product Analysis by Nmr.—Reactions for product analysis (O/N ratio in Table I) were carried out on a 0.01 *M* basis (alkyl halide in 5–10% excess) in 20–25 ml of absolute ethanol. After completion of the alkylation, the solution was evaporated at room temperature[33] and the remaining product was freed of inorganic material as previously described. An aliquot of the solvent-free residue was dissolved in enough DMSO-d_6 to make *ca.* a 20% solution. The regions used for ratio determinations by nmr have been fivefold expanded (H_B in Table II and $H_{B'}$ in Table III; in some cases, *e.g.*, methylation and benzylation, the H_D or $H_{D'}$ protons can also be utilized).

α-Phenyl-N-triphenylmethylnitrone (VIe).—A solution was prepared from 1.21 g (0.01 mole) of *anti*-benzaldoxime[32] in 20 ml of absolute ethanol containing 0.23 g (0.01 mole) of sodium. To the stirred solution 2.78 g (0.01 mole) of triphenylmethyl chloride was added. A slightly exothermic reaction took place and a precipitate formed. The mixture was stirred for 10 min and cooled overnight. Filtration yielded 3 g of a crude white product with mp 132–134°. Recrystallization from 80% ethanol gave 2.7 g of pure product, mp 143–144° (λ_{max}^{EtOH} 252 mμ (log ε 4.23); nmr showed two complex patterns centering around τ = 1.86 and 2.51 ppm).

Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.50; H, 5.79; N, 3.89.

O-Triphenylmethyl Benzaldoxime (Ve). A. *syn*-Benzaldoxime was treated the same way previously described for the formation of VIe. Filtration of the cooled reaction mixture yielded 3 g of crude white product with mp 114–117°. Recrystallization from 90% ethanol gave 2.5 g of pure product, mp 118° (lit.[11] mp 119.5–120.5° cor), λ_{max}^{EtOH} 260 mμ (log ε 4.27); nmr showed a singlet at τ = 1.46 ppm due to CH=N and a complex pattern centering around τ = 2.62 ppm due to the C_6H_5 groups (hydrogen ratio 1/20, respectively).

Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.36; H, 5.80; N, 3.77.

B. Thermal Isomerization of VIe to Ve.—An evacuated, sealed glass tube containing 0.36 g of VIe was kept in a metal bath at 200° for 30 min. When cool, the oily product became a glassy solid. Recrystallization from ethanol–water yielded 0.34 g of Ve, mp 116–118°. A mixture melting point with Ve (obtained from procedure A) showed no depression, and the nmr and ultraviolet spectra were identical with those of Ve.

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(33) Because of the volatile nature of the O-alkyl benzaldoximes Va–c, particular care should be taken in preparation of the samples, especially during solvent removal.

A General Synthesis of N-Hydroxyamino Acids[1a]

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A general synthesis for nitrones and N-substituted hydroxylamines has been applied to the synthesis of a series of N-hydroxyamino acids.

Several N-hydroxyamino acids have been identified in recent years as components of various antibiotics isolated from microbial fermentations. The N-hydroxyamino acids characterized from naturally occurring peptides are N-hydroxyglycine (from hadacidin),[2] N-hydroxyleucine (from pulcherrimin),[3] N-hydroxyisoleucine (from aspergillic acid),[4] N-hydroxytyrosine and -alanine (from mycelianamide),[5] as well as δ-N-hydroxyornithine (from ferrichromes[6] and albomycin)[7] and ε-N-hydroxylysine (from mysobactin).[8]

Since many of these N-hydroxy peptides have antibiotic and antitumor activities[2,9] or represent potent microbial growth factors,[10] several synthetic methods

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