buffer and at approximately pH 8 in the veronal system) in relation to the Michaelis constants of the enzyme, the equilibrium concentrations of the substrates and the dissociation of the inhibitors may all be factors.

It is of interest to compare the values for sulfanilamide and thiophene-2-sulfonamide with those given in the literature. Thus, Davenport,[7] using a manometric method, obtained values of 7×10^{-7} *M* and 1.6×10^{-7} *M*, respectively, for the 50% inhibitory end-point of these two sulfonamides, and Krebs[3b] reported 9×10^{-7} *M* and 3×10^{-7} *M*, respectively, by use of a similar method. These data agree reasonably well with the results obtained in the veronal buffer system. The values obtained by means of the Philpot method are generally considerably higher for 50% inhibition. From the standpoint of relative values in comparison with sulfanilamide, of course, these differences are less important.

TABLE IV

RELATIVE INHIBITORY EFFECT OF VARIOUS AROMATIC SULFONAMIDES ON CARBONIC ANHYDRASE

Compound	Inhibitory activity (HCO_3^-) 50%	~100%
Sulfanilamide	1	1
o-Toluenesulfonamide[a]	1.8	
Metanilamide	2.5	
Benzenesulfonamide[a]	4.0	
p-Toluenesulfonamide[a]	8.5	
p-Chlorobenzenesulfonamide	18	
p-Nitrobenzenesulfonamide	23	
p-Benzenedisulfonamide	40	170
3,4-Dichlorobenzenesulfonamide	56	160
Prontosil	50	<56 (?)
Neoprontosil	200	<85 (?)

[a] The corresponding values calculated from Krebs[3b] report are 1.4, 2 and 9, respectively.

Aromatic Sulfonamides.—In addition to the heterocyclic sulfonamides, a number of aromatic derivatives were studied. The results obtained with a few of the most active of these are given in Table IV, in terms of their relative activity compared with sulfanilamide on a molar basis in the bicarbonate system. The high activity of Prontosil (4′-sulfamyl-2,4-diaminoazobenzene hydrochloride) and Neoprontosil[17] (disodium 2-(4′-sulfamylphenylazo)-7-acetamido-1-hydroxynaphthalene-3,6-disulfonate) reported by Krebs[3b] was confirmed. While reproducible values for ~100% inhibition were not obtained because of the interfering color of these substances, their high activity did not appear to be maintained at this level. From the standpoint of *in vivo* studies, these compounds would also suffer from the disadvantage that they are rather readily converted to the much less active sulfanilamide.[18]

Summary

The inhibition of carbonic anhydrase by a series of heterocyclic and aromatic sulfonamides has been investigated. Some of the heterocyclic unsubstituted sulfonamides have been found to be about 100–2000 times as active as sulfanilamide. The relationship between acid dissociation constants and inhibitory activity has also been studied.

[17] We are greatly indebted to Dr. C. M. Suter, Sterling-Winthrop Research Institute, Rensselaer, New York, for a supply of these materials.

[18] Fuller, *Lancet*, **I**, 191 (1937); Litchfield, White and Marshall, *J. Pharmacol.*, **72**, 291 (1941).

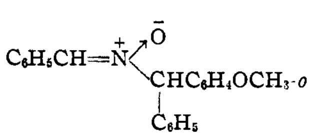
STAMFORD, CONN. RECEIVED MARCH 21, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Rearrangement of Oxime N-Ethers

BY ARTHUR C. COPE AND ALFRED C. HAVEN, JR.[1]

Allyl- and benzyldialkylamine oxides have been found to undergo thermal rearrangement with migration of the allyl or benzyl group from nitrogen to oxygen, forming trialkylhydroxylamines.[2] The N-ethers of oximes possess a semi-polar nitrogen–oxygen bond such as is present in amine oxides, and it therefore seemed possible that N-allyl and N-benzyl oxime ethers would undergo thermal rearrangement to the isomeric O-ethers. Such rearrangements have been observed to occur during acid hydrolysis of certain N-benzyl and N-benzhydryl oxime ethers. Martinoff[3] has reported that heating N-*o*-methoxybenzhydrylbenzaldoxime (I) with 12% hydrochloric acid resulted in formation of the isomeric O-ether together with its hydrolysis products, di-(*o*-methoxybenzhydryl) ether, benzaldehyde and hydroxylamine hydrochloride. Hydrolysis of N-*m*-methoxybenzhydrylbenzaldoxime and N-*p*-methoxybenzhydrylbenzaldoxime with dilute hydrochloric acid also was found to form the products expected from the isomeric O-ethers, which accordingly were probably formed as intermediates. Grammaticakis[4] observed that N-α-(*p*-methoxyphenyl)-propylbenzaldoxime (II) on treatment with concentrated hydrochloric acid formed benzaldehyde, hydroxylamine hydrochloride and anethole. He postulated rearrangement of II to the isomeric O-ether prior to hydrolysis, and formation of anethole by dehydration of α-ethyl-*p*-methoxybenzyl alcohol formed by hydrolysis of the O-ether. An alternate path which would explain the formation of anethole would be decomposition of the N-ether II in a reaction similar to the thermal decomposition of N,N-



$$C_6H_5CH{=}\overset{+}{N}{<}^{\bar{O}}_{CH(C_6H_5)C_6H_4OCH_3\text{-}o}$$

I

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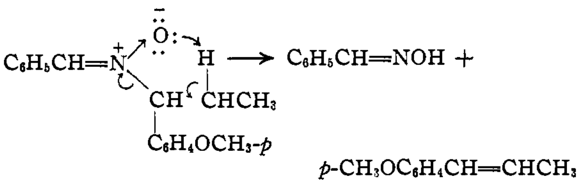
[1] Arthur D. Little Predoctoral Fellow, 1949–1950.

[2] (a) Meisenheimer, *Ber.*, **52**, 1667 (1919); (b) Kleinschmidt and Cope, THIS JOURNAL, **66**, 1929 (1944); (c) Cope and Towle, *ibid.*, **71**, 3423 (1949).

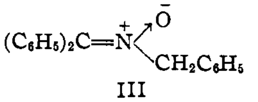
[3] Martinoff, *Ann. chim.*, [11] **7**, 424 (1937).

[4] Grammaticakis, *Compt. rend.*, **205**, 60 (1937).

dimethyl-(α-phenylethyl)-amine oxide into N,N-dimethylhydroxylamine and styrene[5]


II

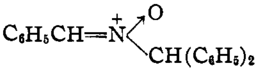
We have investigated the benzyl, benzhydryl and triphenylmethyl ethers of benzophenone oxime in order to determine whether N-benzyl-type oxime ethers are susceptible to a purely thermal rearrangement to the isomeric O-ethers. Benzophenone N-benzyloxime (III) and O-benzyloxime (IV) have been obtained as a mixture in which the O-ether predominates by the alkylation of benzophenone oxime with benzyl iodide[6] or benzyl chloride[7] in the presence of sodium ethoxide. A small amount of N-benzhydrylbenzaldoxime (V) also was formed, which is the product of a base-catalyzed rearrangement of III, a type of rearrangement which was first noted by Behrend.[7,8] Under a variety of conditions this alkylation reaction was found to yield 62–70% of the O-ether IV and 7–12% of the N-ether III, and accordingly was not a useful preparative method for III. The N-ether III was prepared in satisfactory yield (65%) by the condensation of benzhydrylideneimine (liberated from the hydrochloride with ammonia) with N-benzylhydroxylamine[7] in ligroin. The same reactants formed N-benzhydrylbenzaldoximine (V) when sodium ethoxide in ethanol was used as the base rather than ammonia, evidently by the Behrend rearrangement of III.


$(C_6H_5)_2C=\overset{+}{N}(\rightarrow\overset{-}{O})CH_2C_6H_5$

III

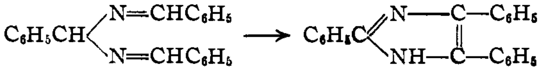
$(C_6H_5)_2C=N—O—CH_2C_6H_5$

IV

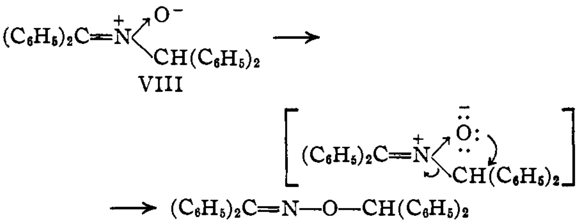

$C_6H_5CH=\overset{+}{N}(\rightarrow\overset{-}{O})CH(C_6H_5)_2$

V

Attempts to effect the thermal rearrangement of III to IV were unsuccessful. Samples of III which were heated at temperatures of 150 to 200° for five minutes to twenty-eight hours either were unchanged or decomposed to a brown oil from which IV could not be isolated. Similar results were obtained in the presence of zinc chloride and boron trifluoride. Examination of the mixture formed when III was heated at 200° for five hours showed the presence of relatively large amounts of ammonia and benzophenone and smaller quantities of benzoic acid and 2,4,5-triphenylimidazole (VII). The formation of VII probably results from the cyclization and dehydrogenation[9] of hydrobenzamide (VI), which is formed readily from benzaldehyde and ammonia. The probable course of the decomposition is thermal cleavage of III into benzaldehyde and benzhydrylideneimine, followed by hydrolysis of the latter compound with trace amounts of water to benzaldehyde and ammonia. Recombination of the benzaldehyde and ammonia would form hydrobenzamide, liberating water which would permit repetition of the hydrolysis. The formation of benzoic acid from benzaldehyde under these conditions could result from the Cannizzaro reaction.


VI VII

Alkylation of the potassium salt of benzophenone oxime with benzhydryl bromide in benzene formed the N-benzhydryl ether (VIII) in 31% yield and the O-benzhydryl ether (IX) in 54% yield. The reaction was heterogeneous and required two days for completion; in a mixture of *t*-butanol and benzene the reaction was complete in one and one-half hours, but the yields of VIII and IX were reduced to 16 and 49%, respectively. VIII has been prepared previously by the oxidation of N,N-dibenzhydrylhydroxylamine, obtained from the reaction of phenylmagnesium bromide with N-benzhydrylbenzaldoxime.[10] Evidence reported supporting the structure assigned to VIII was its reduction with aluminum amalgam to dibenzhydrylamine.[10] Further proof of the structure of VIII has been obtained by catalytic hydrogenation in the presence of a Raney nickel catalyst, which removed the oxygen and yielded N-benzhydrylidenebenzhydrylamine, and by comparison of its ultraviolet absorption spectrum (Fig. 1) with the ultraviolet spectrum reported for III.[7] The hydrolysis of VIII with concentrated hydrochloric acid, which had been reported to give inconclusive results,[10] was shown to yield benzophenone and hydroxylamine hydrochloride. Formation of these products can be explained by postulating rearrangement of VIII to IX prior to hydrolysis.


VIII IX

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[5] Cope, Foster and Towle, THIS JOURNAL, 71, 3929 (1949).

[6] Alessandri, *Atti accad. Lincei*, 23, II, 217 (1914); *C. A.*, 9, 1045 (1915).

[7] Ramart-Lucas and Hoch, *Bull. soc. chim.*, [5] 5, 987 (1938).

[8] Behrend, *Ann.*, 265, 238 (1891); Neubauer, *ibid.*, 298, 187 (1897).

[9] Radziszewski, *Ber.*, 10, 70 (1877).

[10] Alessandri, *Gazz. chim. ital.*, 51, I, 75 (1921).

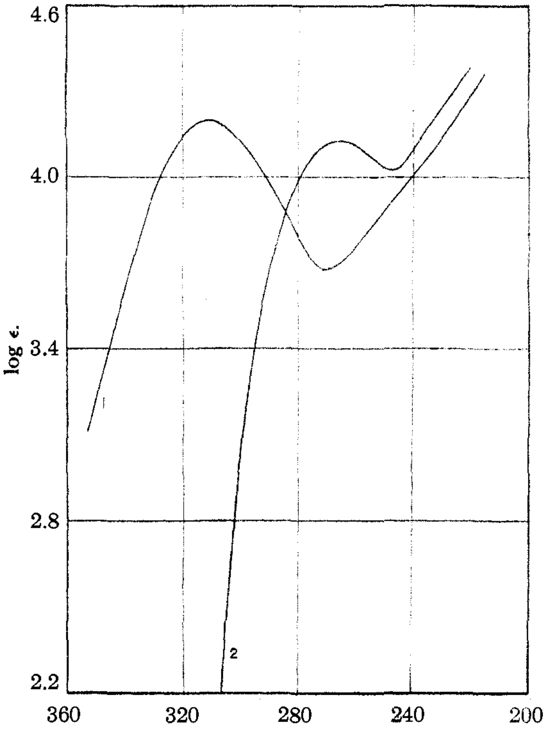

Fig. 1.—Ultraviolet absorption spectra: Curve 1, benzophenone N-benzhydryloxime (VIII); $\lambda_{max.}$ 311 mμ (log $\epsilon_{max.}$ 4.20); Curve 2, benzophenone O-benzhydryloxime (IX); $\lambda_{max.}$ 266 mμ (log $\epsilon_{max.}$ 4.13) (both in methylcyclohexane solution).

Benzophenone O-benzhydryloxime (IX), which has not been described previously, was separated from the less soluble N-ether formed in the alkylation of benzophenone oxime with benzhydryl bromide and purified by recrystallization. Evidence for the structure of IX was obtained from its ultraviolet absorption spectrum (Fig. 1), which proved to be very similar to the spectrum reported for IV.[7] Further evidence was obtained by reduction of IX with zinc and acetic acid, which yielded benzhydrylamine and benzhydrol. Hydrolysis of IX with concentrated hydrochloric acid yielded benzophenone and hydroxylamine hydrochloride. Under conditions which resulted in complete hydrolysis of VIII to these products 59% of IX was recovered, possibly because IX, during or immediately after its formation from VIII, may be more labile to hydrolysis by hydrochloric acid. The hydrolyses of both VIII and IX are heterogeneous, and therefore their rates may have little significance.

The N-ether VIII was found to undergo thermal rearrangement to the O-ether IX; at 200° the reaction was complete in one-half hour and the yield was essentially quantitative. It was possible to conduct the rearrangement of VIII to IX in solution in diethylcarbitol, and to follow the kinetics of the reaction by determining the decrease in absorption at 310 mμ in the ultraviolet spectrum due to the N-ether VIII. The rearrangement followed first order kinetics; the rates at four temperatures are shown in Fig. 2, and typical data for the rearrangement at 449° K. in Table I. The activation energy for the rearrangement of VIII to IX was determined from the dependence of the first order rate constants on temperature (Fig. 3). The observed value of ΔE^*, 40 kcal. per mole, was rather large; calculation of the entropy of activation (ΔS^*) (Table II) showed that it was unusually large for a first order reaction (13.6 entropy units) and positive. The large positive entropy of activation can be explained in two ways.[11] The first and preferred explanation is that the N-ether VIII is more highly solvated than the less polar activated complex, in which the combined solvent

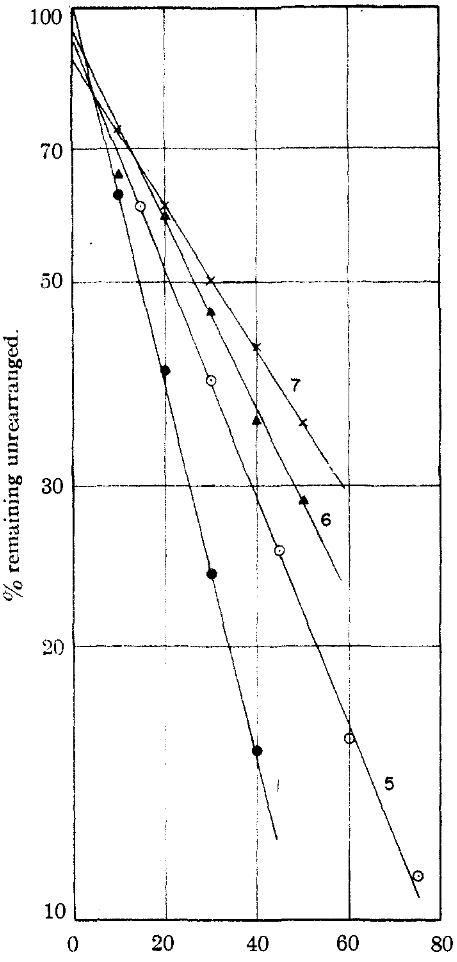

Fig. 2.—Rate of rearrangement of benzophenone N-benzhydryloxime (VIII) to benzophenone O-benzhydryloxime (IX). Curve numbers correspond to the numbers of the rate runs in Table II, in which the temperatures are specified.

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(11) We are indebted to I. Amdur, John D. Roberts and C. Gardner Swain for discussions of these interpretations.

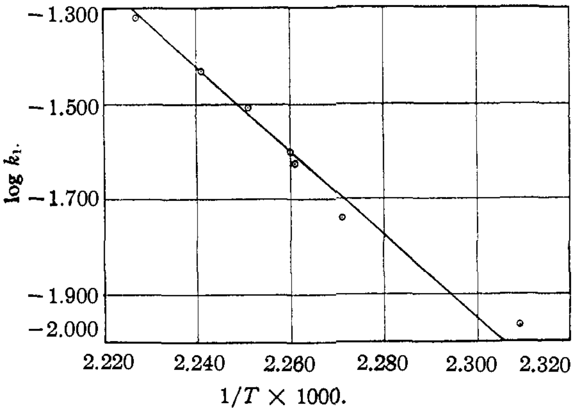
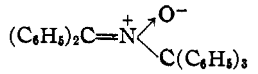


Fig. 3.—Dependence of the first-order rate constant k_1 on temperature for the rearrangement of VIII to IX.

molecules have been lost at least in part, resulting in a less rigid structure for the activated complex (compared to the solvated reactant). A second and less probable interpretation is detachment of the benzhydryl group (presumably as a carbonium ion) in the activated complex, which would cause an increase in the degrees of freedom of the activated complex that could result in a positive entropy of activation. The latter explanation is unlikely, because the related rearrangement of benzylmethylaniline oxide to O-benzyl-N-methyl-N-phenylhydroxylamine can be conducted in the presence of aqueous sodium hydroxide without the formation of benzyl alcohol, which would be expected to form if the migrating group became detached as an ion during the rearrangement.[2]

The fact that the rearrangement of VIII to IX follows first order kinetics provides evidence that the reaction is intramolecular, involving what is essentially a transitory three-membered cyclic intermediate in which the benzhydryl group becomes attached to oxygen at virtually the same time that it is detached from nitrogen. Similar evidence had been obtained previously for a transitory six-membered cyclic intermediate in the rearrangement of allyl groups in three-carbon systems,[12] but in dyad systems the only previous evidence for an intramolecular mechanism was the occurrence of inversion in the rearrangement of crotylmethylaniline oxide.[2b]

The alkylation of benzophenone oxime with triphenylmethyl chloride in the presence of potassium *t*-butoxide yielded only the O-triphenylmethyl ether, XI. The O-ether structure XI



$$(C_6H_5)_2C{=}\overset{+}{N}\begin{matrix}\nearrow O^- \\ \searrow C(C_6H_5)_3\end{matrix}$$

X

$(C_6H_5)_2C{=}N{-}O{-}C(C_6H_5)_3$

XI

was assigned to the product on the basis of the ultraviolet absorption spectrum (Fig. 4), which provides a useful general method for distinguishing between oxime O- and N-ethers.[7] Another possible route for the synthesis of the N-ether X which was investigated was the condensation of benzhydrylideneimine with N-triphenylmethylhydroxylamine, a reaction analogous to the one used for the synthesis of the N-benzyl ether III. N-Triphenylmethylhydroxylamine was prepared in 73% yield by the alkylation of hydroxylamine with triphenylmethyl chloride by a procedure described by Stieglitz and Leech.[13] The structure of the product was confirmed by reduction with zinc dust and acetic acid to triphenylmethylamine. Attempts to condense benz-

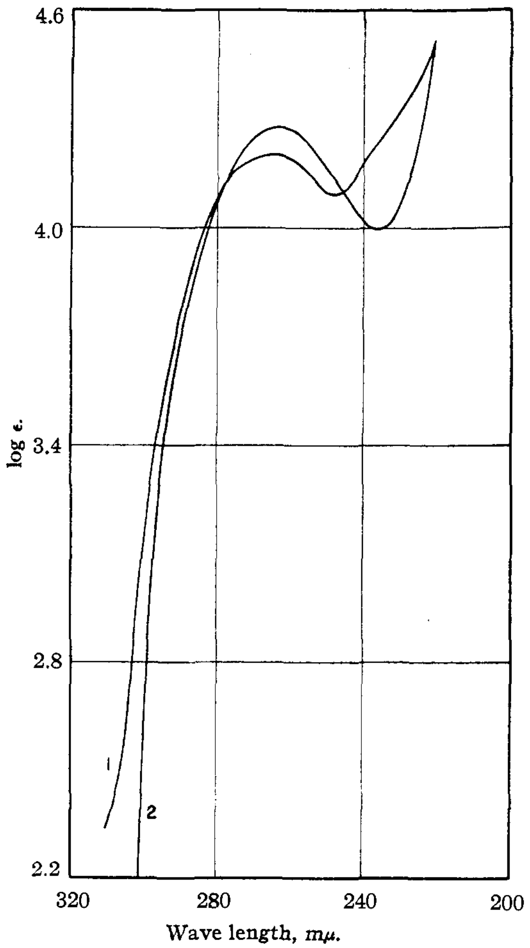


Fig. 4.—Ultraviolet absorption spectra: Curve 1, benzophenone O-triphenylmethyloxime (XI), $\lambda_{max.}$ 266 mμ (log $\epsilon_{max.}$ 4.21); Curve 2, O-triphenylmethylbenzaldoxime (XIV), $\lambda_{max.}$ 261.5 mμ (log $\epsilon_{max.}$ 4.28) (both in methylcyclohexane solution).

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[12] (a) Cope, Hoyle and Heyl, THIS JOURNAL, **63**, 1843 (1941); (b) Cope, Hofmann and Hardy, *ibid.*, **63**, 1852 (1941); (c) Foster, Cope and Daniels, *ibid.*, **69**, 1893 (1947). In ref. 12c, page 1895, column 1, there is a typographical error in the expression for k, based on the theory of absolute reaction rates, in which the experimental activation energy E appears. The relation should read

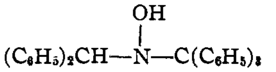
$$k = ek'Te^{\Delta S^{\ddagger}/R}e^{-E/RT}/h$$

Correspondingly, the sentence defining s should read "set s equal to $(ek'T/h)e^{\Delta S^{\ddagger}/R}$," and the equation for $\Delta S^{\ddagger}$ should read $\Delta S^{\ddagger} = R \ln s - R \ln (k'T/h) - R$. The values of $\Delta S^{\ddagger}$ which appear in Table II on page 1895 are correct.

[13] Stieglitz and Leech, THIS JOURNAL, **36**, 272 (1914).

hydrylideneimine with N-triphenylmethylhydroxylamine in ligroin under conditions similar to those used in the synthesis of the N-benzyl ether III were unsuccessful. When the reactants were heated together at 120° without a solvent, a small yield of benzophenone O-triphenylmethyloxime (XI) was obtained. It is believed that the N-ether X was formed, but rearranged to the O-ether XI at the temperature of the condensation reaction.

Another possible route for the preparation of benzophenone N-triphenylmethyloxime (X) would consist of the preparation and oxidation of N-benzhydryl-N-triphenylmethylhydroxylamine (XII). Several attempts to prepare XII were unsuccessful. The product obtained from the reaction of phenylmagnesium bromide with benzophenone N-benzhydryloxime was an oil which could not be crystallized or oxidized to X with mercuric oxide. The direct alkylation of N-triphenylmethylhydroxylamine with benzhydryl bromide was unsuccessful. N-Benzhydrylhydroxylamine was prepared by the method of Plattner and Behrend[14] and alkylated with triphenylmethyl chloride in benzene solution. Analysis of the product indicated that it was isomeric with XII, but the compound could not be oxidized with mercuric oxide or hydrogen peroxide, indicating that it was probably N-benzhydryl-O-triphenylmethylhydroxylamine (XIII).



$$(C_6H_5)_2CH{-}\overset{\displaystyle OH}{\overset{|}{N}}{-}C(C_6H_5)_3$$

XII

$(C_6H_5)_2CHNHOC(C_6H_5)_3$

XIII

The condensation of benzaldehyde with N-triphenylmethylhydroxylamine at 120–140° has been reported by Stieglitz and Leech[13] to form triphenylcarbinol and a product melting at 114° which analyzed correctly for the expected N-triphenylmethylbenzaldoxime. Repetition of their preparation yielded 39% of a compound, m. p. 119.5–120.5°, which was identified as O-triphenylmethylbenzaldoxime (XIV) by analysis, comparison of its ultraviolet absorption spectrum (Fig. 4) with the spectra of other oxime O- and N-ethers, and reduction with zinc and acetic acid to triphenylcarbinol and benzylamine. It is believed that in this case also the N-ether was the initial product, and that rearrangement under the conditions of the condensation formed the O-ether.

$$C_6H_5CH{=}N{-}O{-}C(C_6H_5)_3$$

XIV

Experimental[15]

Alkylation of Benzophenone Oxime with Benzyl Iodide.—Potassium ethoxide was prepared from potassium (1.96 g.) and 50 ml. of absolute ethanol and benzophenone oxime (9.86 g.) was dissolved in the solution with warming. The solution was cooled to 10° in an ice-bath and 10.9 g. of benzyl iodide was added; a precipitate of potassium iodide formed rapidly. The mixture was allowed to stand overnight at room temperature and the potassium iodide was separated by filtration and washed with a small amount of absolute ethanol. The combined filtrate and washings, which were neutral, were concentrated under reduced pressure and poured into cold water. The oil which precipitated crystallized on standing overnight at 5°, and after drying amounted to 13.5 g. The solid was triturated three times with a total of 200 ml. of petroleum ether. Concentration of the petroleum ether solution yielded a small amount of the N-benzyl ether (III), which was combined with the residue from the petroleum ether extraction and crystallized from ethanol. The yield of crude III which separated as cubes with m. p. 105–117° was 1.76 g. (12.2%). Recrystallization from cyclohexane and from ethanol raised the m. p. to 119.5–120°. Further concentration of the petroleum ether solution yielded an oil which was crystallized from ethanol and yielded 8.9 g. (62%) of the crude O-benzyl ether IV, m. p. 45–52°. Recrystallization from aqueous ethanol raised the m. p. to 57–57.5°. The melting points of III and IV agreed with those reported by Alessandri.[6] A similar alkylation in which sodium ethoxide in absolute ethanol was substituted for potassium ethoxide gave 7 and 67% yields of III and IV, respectively. An alkylation conducted with sodium ethoxide as the base in benzene at the reflux temperature yielded 70% of IV and no N-ether could be isolated.

Benzophenone N-Benzyloxime (III).—N,N-Dibenzylhydroxylamine was prepared by the method of Jones and Sneed,[16] except that the inorganic salts formed in the alkylation were not removed by filtration. The suspension was treated with ice-water and filtered to separate N,N-dibenzylhydroxylamine, which was immediately recrystallized from ethanol and obtained in 71.5% yield as white needles, m. p. 121–124°.

N,N-Dibenzylhydroxylamine (17.6 g.) was stirred with 36.8 g. of yellow mercuric oxide in 100 ml. of ether. The heat of reaction caused the ether to reflux for one hour, and after three hours the suspension was filtered and the filtrate was concentrated. The crude product (16.8 g.) was recrystallized from a mixture of acetone and ligroin, and yielded 15.7 g. (90%) of N-benzylbenzaldoxime,[16,17] m. p. 81.5–83.5°. Air had been used previously for this oxidation.[16]

N-Benzylhydroxylamine was prepared by hydrolysis of N-benzylbenzaldoxime[16] and purified by recrystallization from a mixture of benzene and petroleum ether; yield 88%, m. p. 56–58.5°.

N-Benzylhydroxylamine (7.0 g.) and benzhydrylideneimine hydrochloride[18] (13.2 g.) were suspended in 100 ml. of dry ligroin (b. p. 90–100°) in a flask equipped with a reflux condenser, Hershberg stirrer and a gas inlet tube. The suspension was stirred and warmed slowly while dry ammonia was passed over the surface. After one hour at the reflux temperature the fine white precipitate was separated by filtration and the yellow filtrate was concentrated under reduced pressure. The residual oil was recrystallized from a mixture of benzene and petroleum ether and yielded 8.5 g. of the N-benzyl ether III, m. p. 119–120°. The total yield including material from a second crop of crystals, 2.2 g., was 65%.

Thermal Decomposition of Benzophenone N-Benzyloxime (III).—A 4.89-g. sample of III was sealed in an evacuated tube and heated for five hours at 200°. The products were a brown oil, ammonia and 0.11 g. of crystalline ammonium benzoate, which was separated by dissolving the oil in benzene and identified by conversion to benzoic acid. Concentration of the benzene solution yielded 0.14 g. of a solid which was crystallized to a constant m. p. of 275.5–276° from a mixture of benzene and petroleum ether and identified as 2,4,5-triphenylimidazole by analysis,

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[14] Plattner and Behrend, *Ann.*, **278**, 364 (1893).

[15] Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy and his associates for analyses.

[16] Jones and Sneed, THIS JOURNAL, **39**, 677 (1917).

[17] Beckmann, *Ber.*, **22**, 435 (1889).

[18] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 234.

m. p. and mixed m. p. with a known sample.[9] Distillation under reduced pressure of the residue obtained by concentrating the mother liquor yielded 1.7 g. of benzophenone. The residue could not be crystallized from *n*-propyl alcohol, in which the O-ether IV is relatively insoluble. After a short-path distillation of the residue at 0.3 mm., the only solid which could be isolated from the distillate by crystallization was a small additional amount of 2,4,5-triphenylimidazole.

Alkylation of Benzophenone Oxime with Benzhydryl Bromide.—Potassium *t*-butoxide was prepared from 1.96 g. of potassium and 100 ml. of dry *t*-butanol, and most of the *t*-butanol was removed by distillation at atmospheric pressure. Dry benzene was added and the distillation was continued with stirring until the vapor temperature reached 78°. A solution of benzophenone oxime (9.86 g.) in dry benzene was added and distillation was continued until the vapor temperature became constant at 80°. A solution of 12.35 g. of benzhydryl bromide in dry benzene was added making the total volume approximately 150 ml., and the mixture was stirred and heated at the reflux temperature for forty-five hours. The reaction mixture was still slightly basic at the end of that period, but the yellow salt of the oxime apparently had been entirely replaced by a fine white precipitate of potassium bromide. The hot suspension was filtered and the potassium bromide was washed with acetone. The combined filtrate and washings were concentrated, diluted with petroleum ether and seeded with the N-ether VIII. VIII crystallized in a crude yield of 5.58 g. (30.7%), and was recrystallized from ethanol with little loss; m. p. 162–166°. The compound does not have a narrow melting point range even after repeated recrystallization from ethanol, probably because it rearranges to IX slowly as it melts. The pure compound melted at 165–167° when introduced into a melting point bath at 155° and heated at a rate of three degrees per minute. Alessandri reports m. p. 163–164° for VIII prepared by another route.[10]

An oil was obtained on concentration of the mother liquors from the crystallization of VIII, which on crystallization from ethanol yielded 9.85 g. (54%) of crude benzophenone O-benzhydryloxime (IX), m. p. 90–94°. An analytical sample crystallized to constant melting point from ethanol or methanol was obtained as a white, microcrystalline powder, m. p. 101.5–102°.

Anal. Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.83; N, 3.85. Found: C, 85.60; H, 6.08; N, 4.08.

A similar alkylation mixture in which the *t*-butanol was not removed by distillation and which contained the same amounts of the reactants in 100 ml. of *t*-butanol and 50 ml. of benzene became neutral after heating at the reflux temperature for one and one-half hours. The yield of VIII was 2.97 g. (16.4%), and the yield of IX was 8.86 g. 49%.

Structure of Benzophenone N-Benzhydryloxime (VIII).—A 1-g. sample of VIII was heated under reflux with 50 ml. of concentrated hydrochloric acid for one-half hour. The cooled suspension was extracted with benzene and the residual oil obtained on concentrating the extract was treated with 2,4-dinitrophenylhydrazine.[19] Benzophenone 2,4-dinitrophenylhydrazone was isolated in a yield of 0.96 g. (96%) and identified by m. p. (240–241°) and mixed m. p. with a known sample. Concentration of the aqueous phase from the benzene extraction yielded 0.20 g. of crude hydroxylamine hydrochloride, which after recrystallization amounted to 0.16 g. (83%) and had m. p. and mixed m. p. with a known sample of 153–158° (dec.). The other expected hydrolysis products, benzhydrol or its transformation products formed by reaction with hydrochloric acid, were not isolated.

Hydrogenation of 0.396 g. of VIII in 25 ml. of absolute ethanol at atmospheric pressure in the presence of a small amount of W-7 Raney nickel[20] became very slow after nine hours and the absorption of 102% of two molar equivalents of hydrogen. The mixture was heterogeneous throughout the course of the reduction. The catalyst was separated and washed with benzene. Concentration of the extracts yielded 0.21 g. of a compound, m. p. 143–147°, which after three recrystallizations from ethanol had m. p. 151–152° and was identified as N-benzhydrylidenebenzhydrylamine[21] by mixed m. p. with a known sample.

Structure of Benzophenone O-Benzhydryloxime (IX).—IX (1.95 g.) was heated under reflux for two hours with a mixture of 25 ml. of concentrated hydrochloric acid and 25 ml. of ethanol which had been saturated with hydrogen chloride. The resulting oil was extracted with ether and the extracts were concentrated to an oil which was treated with dilute sodium hydroxide to hydrolyze any benzhydryl chloride present. Subsequent treatment with 2,4-dinitrophenylhydrazine yielded 0.26 g. (13%) of benzophenone 2,4-dinitrophenylhydrazone. The aqueous phase from the ether extraction yielded 0.25 g. (67%) of hydroxylamine hydrochloride. Hydrolysis of 1 g. of IX with 40 ml. of concentrated hydrochloric acid for one hour at the reflux temperature yielded 0.59 g. (59%) of recovered IX, which was isolated by crystallization. Treatment of an oil obtained by concentration of the mother liquor with 2,4-dinitrophenylhydrazine[19] yielded 0.34 g. of benzophenone 2,4-dinitrophenylhydrazone (83% based on the amount of IX which had hydrolyzed).

IX (2.0 g.) in 100 ml. of glacial acetic acid was heated to 100° and 1.44 g. of zinc dust was added with vigorous stirring. The mixture was stirred and heated for forty minutes and concentrated under reduced pressure to a volume of 30 ml. The concentrate was poured into 500 ml. of ice-water and extracted with benzene. The benzene extracts were concentrated and the residual oil was crystallized from methylcyclohexane, yielding 0.57 g. (56%) of benzhydrol, m. p. 63.5–66°. The aqueous phase from the benzene extraction was concentrated under reduced pressure, made strongly alkaline with sodium hydroxide and re-extracted with benzene. The extracts were concentrated to 25 ml. and treated with a solution of 1.26 g. of picric acid in 10 ml. of benzene. Benzhydrylamine picrate,[22] m. p. 203.5–205° (dec.), was obtained in a yield of 1.63 g. (72%) and identified by m. p. and mixed m. p. with a known sample.

Rearrangement of Benzophenone N-Benzhydryloxime (VIII) to Benzophenone O-Benzhydryloxime (IX).—A 0.23-g. sample of the N-benzhydryl ether (VIII) was sealed in an evacuated tube and heated at 200° for one-half hour. The resulting oil was crystallized from 10 ml. of ethanol and yielded 0.22 g. (96%) of the O-benzhydryl ether (IX), m. p. 100.5–101.5°.

The following procedure was used in determining the kinetics of the rearrangement of VIII to IX. A solution was prepared containing approximately 1% by weight of VIII in diethylcarbitol (dried over sodium and redistilled). Portions of this solution were sealed in ampoules made from 6-mm. Pyrex tubing, which were placed in a large thermostat containing oil at a constant temperature. At definite time intervals tubes were removed and immediately cooled in ice-water. The tubes were then opened and the solutions were diluted by weighing small samples into volumetric flasks and diluting them with purified methylcyclohexane. The optical densities of these solutions at 310 mμ were then determined with a Beckman quartz ultraviolet spectrophotometer. The concentrations of the N-benzhydryl ether VIII could be calculated from the optical densities. The contributions to the absorption at 310 mμ of diethylcarbitol ($\epsilon_{310m\mu} = 0.0133$) and of the O-benzhydryl ether IX ($\epsilon_{310m\mu} = 87.4$) were shown to be negligible compared to the N-benzhydryl ether VIII ($\epsilon_{310m\mu} = 16{,}000 \pm 200$). The per cent. rearrangement was determined by comparing the concentrations of VIII

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(19) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 3rd Edition, John Wiley and Sons, Inc., New York, N. Y., p. 171.

(20) Adkins and Billica, THIS JOURNAL, **70**, 695 (1948).

(21) Cantarel, *Compt. rend.*, **210**, 403 (1940).

(22) Alessandri, ref. 6, p. 258, reports m. p. 202° (dec.). Biltz and Seydel, *Ber.*, **44**, 413 (1911), report m. p. 205–206° (dec.).

determined by this analytical method with the concentrations calculated for the solutions assuming that no rearrangement had occurred. The analytical method was shown to be accurate to within less than 2%. Temperature control was maintained within 0.1°, and the thermometers employed were calibrated against one certified by the Bureau of Standards. The data for a typical run are presented in Table I. In this run, the diethylcarbitol solution contained 1.075% by weight of VIII, and the weighed samples of the solution after heating were diluted with purified methylcyclohexane to a volume of 10.0 ml. for optical density measurements.

TABLE I

REARRANGEMENT OF VIII TO IX IN DIETHYL CARBITOL AT 449.0°K.

Time, minutes	Sample, mg.	Optical density	Initial concn. of VIII, m./l. $\times 10^5$	Final concn. of VIII, m./l. $\times 10^5$	% unrear.
0.0	15.2	0.710	4.51	4.51	100.0
10.0	15.5	.451	4.60	.286	62.2
20.0	13.2	.247	3.91	1.57	40.2
30.0	15.3	.171	4.54	1.085	24.0
40.0	13.5	.097	4.01	0.616	15.4
50.0	12.3	.053	3.65	0.336	9.3

The first order rate constants for the rearrangement of VIII to IX at several temperatures are listed in Table II, and the rates at four temperatures are shown graphically in Fig. 2. The activation energy was determined to be 40 kcal. per mole from a plot of log k_1 against $1/T$ (Fig. 3), using the equation $\Delta E^* = -4.58\ (\Delta \log k_1/\Delta 1/T)$ (or $\Delta E^* = -4.58 \times$ slope). The entropies of activation were calculated from the equation $\Delta S^* = R \ln s - R \ln k'T/h - R$, where R = 1.987 cal./°K.; s = frequency factor = $k_1 e^{\Delta E^*/RT}$; k' = Boltzmann constant = 1.3805×10^{-16} erg/°K.; h = Planck constant = 6.624×10^{-27} erg sec. (see ref. 12c).

TABLE II

FIRST ORDER RATE CONSTANTS AND ENTROPIES OF ACTIVATION FOR THE REARRANGEMENT OF VIII TO IX

Rate run no.	Temp., °K.	First order rate constant $k_1 \times 10^4$ (sec.$^{-1}$)	$s \times 10^{-16}$	ΔS^*, entropy units
1	449.0	7.97	2.4	13.6
2	433.0	1.82	2.8	14.0
3	442.3	4.20	2.4	13.6
4	446.2	6.18	2.4	13.6
5	444.2	5.18	2.4	13.6
6	442.2	3.95	2.3	13.5
7	440.2	3.03	2.5	13.5

The product was isolated from one rearrangement of VIII under the conditions of the kinetic runs to make sure that the reaction formed IX in the presence of diethylcarbitol as a solvent. A solution of 0.2296 g. of VIII in dry diethylcarbitol (5.481 g.) was placed in a tube, which was sealed and heated for one hundred and sixty minutes at 449°K. The tube was cooled and its contents were poured into water. The partially crystalline oil which separated was extracted with benzene and recrystallized from ethanol. The yield of IX obtained as two crops was 0.181 g. (78.7%), which after recrystallization from ethanol melted at 99–101° and did not depress the m. p. of an authentic sample of IX.

Alkylation of Benzophenone Oxime with Triphenylmethyl Chloride.—Potassium *t*-butoxide was prepared from 1.17 g. of potassium and 150 ml. of dry *t*-butanol, and benzophenone oxime (5.91 g.) was added. The resulting yellow suspension was stirred under reflux for ten minutes, after which a solution of 8.38 g. of triphenylmethyl chloride in 50 ml. of dry benzene was added during a period of one-half hour at the reflux temperature. After an additional period of reflux of one-half hour the mixture was cooled and diluted with water. The non-aqueous phase was separated, concentrated and the benzene solution was diluted with petroleum ether. A product crystallized in crude yield of 12.5 g. (95%), which after recrystallization from ethanol or a mixture of benzene and petroleum ether melted at 154.6–155.8°. The ultraviolet absorption spectrum of this compound (Fig. 4) establishes its structure as benzophenone O-triphenylmethyloxime (XI).

Anal. Calcd. for $C_{32}H_{25}NO$: C, 87.44; H, 5.73; N, 3.19. Found: C, 87.21; H, 5.95; N, 3.32.

N-Triphenylmethylhydroxylamine.—This compound was prepared by the alkylation of hydroxylamine with triphenylmethyl chloride according to the procedure of Stieglitz and Leech[13] in 73% yield. It had the broad melting point range of 130–137° when introduced into a melting point bath at 125° and heated at a rate of 3° per minute. Its structure was confirmed by reduction of a 0.5-g. sample by stirring with 0.5 g. of zinc dust and 20 ml. of glacial acetic acid for three hours at room temperature. The solids were separated and washed with hot alcohol and the filtrate and washings were concentrated under reduced pressure. The residual oil was treated with sodium hydroxide, extracted with ether, and triturated with petroleum ether. The crude triphenylmethylamine obtained amounted to 0.33 g. (70%), m. p. 97–99.5°, and after recrystallization from ethanol had m. p. and mixed m. p. with a known sample of 100.5–101.5°.

Condensation of N-Triphenylmethylhydroxylamine with Benzhydrylideneimine.—A mixture of benzhydrylideneimine (0.04–0.07 mole) and benzophenone was prepared by distillation of the residue obtained by thermal decomposition of benzophenone oxime.[18] N-Triphenylmethylhydroxylamine (7.99 g.) was added and the mixture was heated at 120° for six hours. The yellow oil was dissolved in 25 ml. of benzene and the solution was diluted with 150 ml. of petroleum ether. A very small amount of a white precipitate was separated. Crystals could not be obtained from the solution and it was concentrated and allowed to stand at room temperature. After seven weeks a crystalline product which had formed was separated by decantation and washed with ether and petroleum ether. It amounted to 1.0 g. (7.8%), m. p. 145–155°. Recrystallization from a mixture of benzene and petroleum ether resulted in little loss and showed that the product was benzophenone O-triphenylmethyloxime, m. p. and mixed m. p. with a known sample prepared by alkylating benzophenone oxime with triphenylmethyl chloride, 153–155°.

Alkylation of N-Benzhydrylhydroxylamine with Triphenylmethyl Chloride.—N-Benzhydrylhydroxylamine was prepared by the procedure of Plattner and Behrend[14] from acetoxime and benzhydryl bromide in aqueous acetic acid. The yield of the recrystallized product, m. p. 76–77°, was 46%. N-Benzhydrylhydroxylamine (5.96 g.) and triphenylmethyl chloride (5.00 g.) were dissolved in 50 ml. of dry benzene and heated under reflux for twenty minutes. The white solid N-benzhydrylhydroxylamine hydrochloride which separated was washed with hot benzene; it amounted to 2.93 g. (82.5%), m. p. 176–177° (dec.). The combined benzene filtrate and washings were concentrated to a volume of 20 ml. and diluted with petroleum ether. A crude product crystallized in a yield of 6.78 g., m. p. 105–120°, which was readily soluble in benzene and acetone, slightly soluble in hot ethanol, and insoluble in ether and petroleum ether. It was recrystallized from a mixture of benzene and ethanol and yielded 4.77 g., m. p. 118–125° (slight dec.). Recrystallization raised the m. p. to 124.5–129° (slight dec., placed in a melting point bath at 120° and heated at a rate of 3° per minute).

Anal. Calcd. for $C_{32}H_{27}NO$: C, 87.04; H, 6.17; N, 3.17. Found: C, 86.82; H, 6.17; N, 3.13.

Condensation of Benzaldehyde with N-Triphenylmethylhydroxylamine.—Benzaldehyde (13.3 g.) and N-triphenylmethylhydroxylamine (7.02 g.) were heated in a nitrogen atmosphere at 130° for two and one-half hours. The resulting yellow oil was seeded with triphenylcarbinol and filtered after partial crystallization had occurred. Recrystallization of the solid from a mixture of benzene and petroleum ether yielded 0.93 g. (14%) of triphenylcarbinol. The residue obtained from the mother liquors from this crystallization and the original filtrate from which triphenylcarbinol had been separated was crystallized from ethanol and yielded 3.59 g. (39%) of a condensation product, m. p. 112.5-115°. Recrystallization from ethanol raised the m. p. to a constant value of 119.5-120.5°. Stieglitz and Leech[13] report m. p. 114°. The ultraviolet absorption spectrum of this compound (Fig. 4) indicates that it is O-triphenylmethylbenzaldoxime (XIV).

Anal. Calcd. for $C_{26}H_{21}NO$: C, 85.92; H, 5.83; N, 3.85. Found: C, 85.93; H, 5.87; N, 4.14.

Evidence confirming the structure of XIV was obtained by reduction. A 2-g. sample of XIV was dissolved in 100 ml. of hot glacial acetic acid and reduced by addition of 1.44 g. of zinc dust, with stirring. The mixture was stirred for forty-five minutes at 100° and then concentrated under reduced pressure to a volume of 30 ml. One hundred milliliters of 1 *N* hydrochloric acid and benzene were added, and the benzene layer was separated. The benzene solution was concentrated and diluted with petroleum ether, yielding 0.99 g. (69%) of triphenylcarbinol. The aqueous phase was concentrated under reduced pressure to a volume of 15 ml. and made strongly basic with concentrated sodium hydroxide solution. The alkaline solution was extracted with four 25-ml. portions of benzene, and the benzene extracts were concentrated and treated with 5.5 millimoles of picric acid in benzene. Benzylamine picrate was obtained in a yield of 0.99 g., m. p. 191-193° (dec.) (53.6%) and after recrystallization from ethanol was identified by m. p. (197-199° dec.) and mixed m. p. with a known sample.

Oxidation of N-Benzhydrylhydroxylamine.—In an attempt to reduce N-benzhydrylhydroxylamine with zinc and sodium hydroxide, the product isolated was an oxidation product, benzophenone oxime. The following similar experiment in which the zinc was omitted showed that the compound is easily oxidized by air in alkaline solution. N-Benzhydrylhydroxylamine (0.50 g.) was stirred with a solution of 0.50 g. of sodium hydroxide in 20 ml. of 95% ethanol for three hours at room temperature. The solution was poured into 100 ml. of water and extracted with three 25-ml. portions of ether. The extracts were concentrated, and the residual oil was crystallized from a mixture of benzene and petroleum ether. Benzophenone oxime was obtained in a yield of 0.47 g. (95%) and identified by its m. p. (142.5-143.5°) and mixed m. p. with an authentic sample.

Absorption Spectra.—The ultraviolet absorption spectra shown in Figs. 1 and 4 were determined with a Beckman model DU quartz spectrophotometer. The methylcyclohexane used as a solvent was purified by redistillation (b. p. 100-101°) and passed through a column of activated silica gel. The same solvent and instrument were used in determining the concentration of VIII in mixtures of VIII and IX from the optical density at 310 mμ in kinetic runs.

Summary

Benzophenone N-benzhydryloxime (VIII) has been found to rearrange quantitatively to benzophenone O-benzhydryloxime (IX) on heating at temperatures of 160 to 200°. The rate of the rearrangement in diethylcarbitol solution was determined by an analytical method depending upon differences in the ultraviolet absorption spectra of VIII and IX, and was found to follow first-order kinetics. This information indicates that the mechanism of rearrangement involves an intramolecular process, probably occurring through a transitory three-membered cyclic intermediate in which the benzhydryl group becomes attached to oxygen as it is detached from nitrogen.

Benzophenone N-benzyloxime (III) did not rearrange to benzophenone O-benzyloxime (IV) on heating, but decomposed into products which can be explained by initial thermal decomposition of III into benzaldehyde and benzhydrylideneimine. Attempts to prepare benzophenone N-triphenylmethoxime (X) and N-triphenylmethylbenzaldoxime led to benzophenone O-triphenylmethyloxime (XI) and O-triphenylmethylbenzaldoxime (XIV), respectively, instead, indicating that the triphenylmethyl group rearranged from nitrogen to oxygen under the conditions of the reactions employed with the object of preparing the N-substituted compounds.

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Some Compounds of Interest in Cancer Chemotherapy[1]

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The inhibition of tumor growth, under special conditions, by hydrocarbon carcinogens[3] requires further investigation in view of the current interest in the chemotherapy of cancer. Effective use of this inhibitory power depends upon the preparation of hydrocarbon derivatives which possess enhanced ability to inhibit tumor growth and no carcinogenicity.

One possibility considered was a modification of the terminal ring of several polynuclear hydrocarbons to contain what was at the time thought to be the hydroxymethylene ketone structure of ring C of colchicine, one of the most effective agents against animal tumors. Recent work[4]

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(3) Haddow and Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 277 (1939).

(4) (a) Dewar, *Nature*, **155**, 141, 479 (1945); (b) Tarbell, *et al.*, THIS JOURNAL, **71**, 244 (1949); **72**, 240-244 (1950); (c) Santavy, *Collection Czechoslovak. Chem. Commun.*, **14**, 145 (1949).