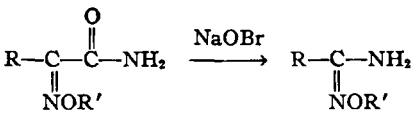
Preparation of *O*-Alkylamidoximes from α-Alkyloximinocarboxamides by the Hofmann Hypobromite Reaction

By DOMINICK A. COVIELLO

O-Alkylamidoximes were prepared by treatment of α-alkyloximinocarboxamides with sodium hypobromite. Of the five prepared, two have not been previously reported and one was reported as being an unstable oil. Structures were proven by NMR and nitrogen analysis.

Amidoximes yield *O*-alkyl ethers when treated with an alkyl halide or alkyl sulfate in the presence of base. Amidoxime hydrobromides or hydrochlorides have been treated with excess sodium ethoxide followed by an alkyl halide (1), or by shaking a sodium hydroxide solution of the amidoxime with methyl sulfate (2). Another investigator utilized alkyl halides in hydroalcoholic solutions of potassium hydroxide to *O*-alkylate amidoximes (3). Although a few aliphatic derivatives have been prepared in like manner, a recent review (4) points out that the conversion is not always successful. Attempts at *O*-alkylation of the sodium salt of ethanamidoxime with alkyl halides, for example, resulted in the formation of oils which could not be distilled without decomposition even at reduced pressure (5). On the other hand, α-oximinopropanamidoxime or α-methyloximinopropanamidoxime were alkylated with methyl sulfate in the presence of 20% sodium hydroxide solution (6) as well as hexanamidoxime which was alkylated with ethyl iodide in sodium ethoxide (7).

If one considers the conversion of a carboxamide to an amine with sodium hypobromite as a decarbonylation, it would immediately be obvious that *O*-alkylamidoximes might result from the treatment of α-alkyloximinocarboxamides with the reagent as follows:



Since *O*-alkylamidoximes have been reported as stable to hot base (8) one could expect to isolate the expected products if they were stable in base for at least 20 minutes at 70° assuming the reaction proceeded in the usual way with the amides in question.

Treatment of the *O*-benzyl ethers of five α-alkyloximinocarboxamides with sodium hypobromite produced the corresponding *O*-alkylamidoxime. Of those prepared, *O*-benzylbenzamidoxime and *O*-benzyl-2-phenethanamidoxime are known; *O*-benzylethanamidoxime has been reported as an unstable oil (5), and the *O*-benzyl ethers of propanamidoxime and hexanamidoxime are new compounds. The known compounds were characterized by comparison of melting points and NMR data, the unknown by nitrogen analysis and NMR data as summarized in Table I.

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It has been pointed out in a review (9) that as the molecular weight of the amide increases the yield of amine usually decreases in the Hofmann reaction. The results of this work are in keeping with that observation. It is felt that in the case of the reactions which produce solid *O*-alkylamidoximes, yields might be improved by a chromatographic separation.

EXPERIMENTAL

α-Alkyloximinocarboxamide intermediates have been reported previously (10).

***O*-Benzylbenzamidoxime.**—A 9.4-Gm. quantity of sodium hydroxide was dissolved in 80 ml. of water. The solution was cooled to 0° and 2.4 ml. of bromine was added. To the ice-cold solution was added 10.16 Gm. (0.04 mole) of α-benzyloximinophenylacetamide. The solution was stirred until most of the amide was in solution when heating was started with continued vigorous stirring. The reaction was accompanied by effervescence when the temperature approached 70°. Heating and stirring were continued for 20 minutes while the temperature went to 80°. The resulting oil became viscous on cooling, and standing overnight caused the oil to solidify. Two crystallizations from ethanol yielded 1 Gm. (11%) of white crystals which melted at 86 to 88.5° as compared with the reported m.p. of 90.5° (8).

***O*-Benzylphenylethanamidoxime.**—By the above procedure, 10.76 Gm. (0.04 mole) of α-benzyloximino-β-phenylpropionamide was treated with sodium hypobromite. An oil was produced which crystallized after cooling and standing overnight. Crystallization of the product from alcohol-water four times yielded 0.5 Gm. (5.2%) of buff-colored crystals melting at 52.5 to 54°; reported m.p. was 55° (11). Treatment with Norit-A yielded a white product but did not change the melting point.

***O*-Benzylethanamidoxime.**—A sodium hypobromite solution was prepared in the manner described above and 7.6 Gm. (0.04 mole) of α-benzyloximinopropionamide was added to the ice-cold solution with stirring. When solution was effected the solution was heated slowly to 75° with vigorous stirring and held at that temperature for 20 minutes, allowed to cool, and stand for 1 hour. The mixture was extracted with ether and dried over $MgSO_4$ for 24 hours. The products from three separate experiments were combined, the ether removed by distillation, and the product distilled at reduced pressure. The resulting clear oil distilled at 88–90°/0.19 mm. and weighed 8.37 Gm. (36.2%).

Anal.—Calcd. for $C_9H_{12}N_2O$; N, 17.07. Found, N, 17.00.

***O*-Benzylpropanamidoxime.**—In the manner described, 14.42 Gm. (0.07 mole) of α-benzyliminobutyramide was treated with sodium hypobromite.

TABLE I.—NMR ANALYSIS OF *O*-ALKYLAMIDOXIMES

$$R-C(=NOR')-NH_2$$

R	R'	Peak in CPS TMS Standard	Description	No. of Protons	Assignment
Methyl	Benzyl	106	Sharp singlet	3	CH_3
		275	Broad band	2	NH_2
		297	Sharp singlet	3	CH_2 (benzyl)
		438	Sharp singlet	5	Phenyl
Ethyl	Benzyl	64	Triplet	3	CH_3
		121	Quartet	2	CH_2 (ethyl)
		270	Broad band	2	NH_2
		296	Sharp singlet	2	CH_2 (benzyl)
		437	Sharp singlet	5	Phenyl
Pentyl	Benzyl	42–162	Series of three broad bands	11	Pentyl
		269	Broad band	2	NH_2
		299	Broad-sharp singlet	2	CH_2 (benzyl)
		441	Sharp singlet	5	Phenyl
Phenyl	Benzyl	276	Broad band	2	NH_2
		299	Sharp singlet	2	CH_2 (benzyl)
		440	Multiple sharp bands	10	Phenyl (2)
Benzyl	Benzyl	285	Sharp singlet	2	CH_2 (benzyl attached to carbon)
		256	Broad-sharp singlet	2	NH_2
		290	Sharp singlet	2	CH_2 (benzyl in ether linkage)
		422, 430	Two sharp singlets with some overlapping	10	Phenyl (2)

During the reaction time of 20 minutes the temperature went briefly to 92°. The mixture was cooled, allowed to stand overnight, extracted with ether: dried over $MgSO_4$, and distilled. A clear oil, 5.7 Gm. (45.7%), distilled at 81–82°/0.08 mm.

Anal.—Calcd. for $C_{10}H_{14}N_2O$; N, 15.73. Found N, 15.70.

***O*-Benzylhexanamidoxime.**—α-Benzyloximinoheptanoamide (9.2 Gm.) was reacted as described above with an appropriate amount of NaOBr. The resulting dark-red oil was distilled four times to obtain 0.5 Gm. (6%) of a yellowish oil boiling at 125–130°/0.3 mm.

Anal.—Calcd. for $C_{13}H_{20}N_2O$; N, 12.72. Found N, 12.74.

Nitrogen analyses were carried out on the Coleman nitrogen analyzer except for *O*-benzylhexanamidoxime which was analyzed by Micro-Tech Laboratories, Skokie, Ill. NMR spectra were run on the Varian A-60.

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α-Alkyloximinonitriles by Pyrolysis of α-Alkyloximinocarboxamides with Phosphorus Pentoxide

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A preparation of α-alkyloximinonitriles is described in which the corresponding α-alkyloximinocarboxamides are heated with phosphorus pentoxide *in vacuo*. Structures were proven by infrared analysis and basic hydrolysis of the nitriles to the corresponding acids.

IN A PREVIOUS COMMUNICATION (1), it was reported that attempts to cyclize β-phenethyl amides of α-alkyloximino acids to the corresponding 3,4-dihydroisoquinolines were fruitless. It was pointed out that experimental evidence indicated that the work-up of the reaction mixture apparently resulted in the hydrolysis of the amide to yield the amine moiety which could be isolated. There was no indication of the fate of the acid portion of the molecule, but it was assumed that under the conditions of the reaction, the oxime moiety decomposed thus accounting for the failure of the cyclization reaction.

In reconsidering the reaction, it was thought that it would be worthwhile to determine the fate of the acid portion of the molecule under similar conditions

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