STUDIES IN PYRAN, ITS ANALOGS, AND RELATED COMPOUNDS

XXXVIII. Reduction of O-Derivatives of Oximes with Lithium Aluminum Hydride*

V. A. Zagorevskii, N. V. Dudykina, and L. M. Meshcheryakova

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The lithium aluminum hydride reduction of the ethers and tosylates of chroman-4-one oxime and related compounds has been studied. It has been found that the ethers of the oximes, like the oximes, do not undergo a normal, but rather an anomalous, reduction. The tosylates of the oximes exhibit a higher tendency to undergo anomalous reduction than the corresponding oximes. During the synthesis of the ethers of the oximes it was established that the use of dimethylformamide as the medium for alkylation of the oxime salts helps to suppress the side reaction forming nitrones.

In preceding papers [1–3] it was shown that the lithium aluminum hydride reduction of chroman-4-one oximes and related compounds can form not only the products of the normal reaction, i.e., the corresponding primary amines, but also (in a number of cases, predominantly) secondary amines, as the result of reductive rearrangement. Thus, the experimental material given previously shows that the lithium aluminum hydride reduction of the oximes has a definite preparative value in the synthesis of both primary amines and the products of the anomalous reduction.

Continuing our investigations in this direction, we have studied the action of lithium aluminum hydride on ethers of the oximes (Table 1). According to the literature [4], the reduction of ethers of oximes (for example, benzyl ethers of benzophenone and acetophenone oximes) takes place normally, without rearrangement. However, the reduction of the methyl ether of chroman-4-one oxime (I) gave us an unexpected result: in addition to 57% primary amine (4-amino-chroman) we obtained 22% of a secondary amine (2,3,4,5-tetrahydro-1,5-benzoxazepine), i.e., the product of the reductive cleavage of the ring. The reduction of the methyl ether of thiochroman-4-one took place similarly. A check of these observations on the methyl ether of benzophenone oxime showed that in this case, also, reductive rearrangement took place. This induced us to determine the direction of reduction in benzyl ethers of some oximes (the oximes of benzophenone, acetophenone, and chroman-4-one). In all experiments the formation of secondary amines was found, although in considerably smaller amounts than in the reduction of the methyl ethers, or the oximes themselves (according to the literature [11], benzophenone oxime forms a mixture of benzylaniline and benzhydrylamine in a ratio of 1.4 : 1).

It is probable, that esters of oximes of aliphatic, aromatic and aromatic ketones will behave with respect to lithium aluminum hydride in a manner similar to that of the corresponding oximes [3, 12]. It is assumed that the reaction with esters of oximes will take place through the formation of oximes by reductive deacylation [12].

There is no information on the reduction of oxime O-sulfonates. We have found that the tosylates of chroman-4-one and thiochroman-4-one oxime have a considerably greater tendency than the corresponding oximes to undergo anomalous reduction. While the action of lithium aluminum hydride on the oximes of these ketones gave 43% 2,3,4,5-tetrahydro-1,5-benzoxazepine and 61% 2,3,4,5-tetrahydro-1,5-benzothiazepine [1], the tosylates of these oximes were converted into the corresponding secondary amines to the extent of 54 and 81%, the yields of primary amines falling considerably. An additional confirmation of this phenomenon was obtained by comparative experiments on the reduction of acetophenone oxime and its tosylate under absolutely identical conditions: the tosylate gave no less than 71% N-ethylaniline, and the oxime gave 17% of this amine and 50% α-phenylethylamine (11% of the initial oxime being recovered).

It appeared to us that the results obtained here on the reduction of ethers and tosylates of oximes must be borne in mind in any discussion of the possible mechanism of the anomalous behavior of the oximes. In any case, the

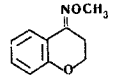
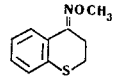
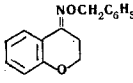
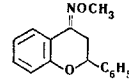
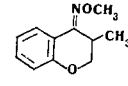
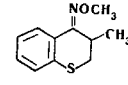
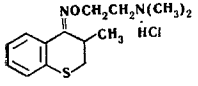
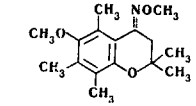
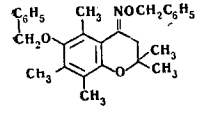
*For part XXXVII, see [23].

Table 1. Results of the Reduction of O-Derivatives of Oximes with Lithium Aluminum Hydride

Experiment no.	Initial oxime derivative	Conditions of reduction			Reaction products: primary secondary amines	Yield of hydrochlorides, %	
		solvent	amount of $LiAlH_4$, moles	Time of boiling, hr		of the individual amine (mp, °C)	of the unseparated amine mixture
1	Methyl ether of chroman-4-one oxime	Ether	3	3,5	4-Aminochroman 2,3,4,5-Tetrahydro-1,5-benzoxazepine	57 (229—231[5]) 22 (202—203[1])	5
2	Benzyl ether of chroman-4-one oxime	Ether	3	4,5	4-Aminochroman 2,3,4,5-Tetrahydro-1,5-benzoxazepine [a]	60 (228—229) 18 (200—201[1])	7
3	Methyl ether of thiochroman-4-one oxime	Ether	3	6,0	4-Aminothiochroman 2,3,4,5-Tetrahydro-1,5-benzothiazepine [b]	58 (228—229[6]) 11 (205—206,5[1])	10
4	Methyl ether of benzophenone oxime	Tetrahydrofuran	6	15	Benzhydrylamine N-Benzylaniline [d]	14 [c] 86 [c]	—
5	Methyl ether of benzophenone oxime	Tetrahydrofuran	6	15	Benzhydrylamine N-Benzylaniline	51 [c] 49 [c]	—
6	Benzyl ether of benzophenone oxime	Tetrahydrofuran	4	3,5	Benzhydrylamine N-Benzylaniline [e]	62 (269—270[8]) 8 (yield of the base)	17
7	Benzyl ether of benzophenone oxime	Tetrahydrofuran	1	7,0	Benzhydrylamine N-Benzylaniline	69 10	—
8	Benzyl ether of acetophenone oxime	Ether	3	7,0	α-Phenylethylamine N-Ethylaniline	42 (156—156,5[9]) [e]	20 (with the regeneration of 23% of the inital ether)
9	Tosylate of chroman-4-one oxime	Ether	2	4,0	2,3,4,5-Tetrahydro-1,5-benzoxazepine [a]	54 (200—201,5[1])	22
10	Tosylate of thiochroman-4-one oxime	Ether	4	5,0	2,3,4,5-Tetrahydro-1,5-benzothiazepine	81 (203—205[1])	6
11	Tosylate of acetophenone oxime	Ether	3	3,5	N-Ethylaniline [g]	71 (175,5—176,5[10])	20

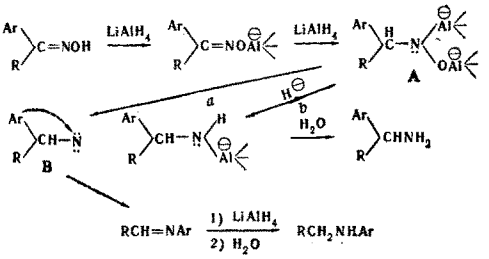
[a] Base, mp 53-54° C [1]. [b] N-Tosyl derivative, mp 137-138° C [1]. [c] Relative yield of base from the results of gas-liquid chromatography (check with the authentic substance), at a total yield of the mixture of hydrochlorides of ~70%. [d] Base, mp 35.5-36.5° C [7]. [e] Base, mp 37° C [7]. [f] Could not be isolated in the pure state. Its presence was established by thin-layer chromatography of the base and the tosylation product. [g] N-Tosyl derivative, mp 84.5-85° C [10].

Table 2. Ethers of Oximes

Ether	Method of preparation	Amount of starting materials and solvent, and reaction conditions	Bp, °C (mm) and n_D or mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
$(C_6H_5)_2C{=}NOCH_3$	A	0.03 mole oxime in 20 ml of DMF; 0.035 mole dimethyl sulfate, and 0.09 mole NaH in 30 ml DMF; 2 hr, 50-60° C	60,5—61,5[19] (methanol)	$C_{14}H_{13}NO$							90
$(C_6H_5)_2C{=}NOCH_2C_6H_5$	A	1 hr, 65-75° C	57—58[20, 21] (methanol)	$C_{20}H_{17}NO$							83
$(C_6H_5)_2C{=}NOCH_2C_6H_5$	C	0.05 mole ketone and 0.06 mole $C_6H_5CN_2ONH_2$ (in toluene)	55—56,5 (methanol)	$C_{20}H_{17}NO$							94
$(C_6H_5)(CH_3)C{=}NOCH_3$	A	0.04 mole oxime in 20 ml DMF, 0.06 mole dimethyl sulfate, and 0.12 mole NaH in 30 ml DMF, 45 min 80-95° C	76—79(5)[22]; 1,5408(22,5)	$C_9H_{11}NO$	72.33 72.05	7.59 7.62	9.29 9.46	72.45	7.42	9.38	65
$(C_6H_5)(CH_3)C{=}NOCH_2C_6H_5$	C	0.04 mole acetophenone and 0.045 mole $C_6H_5CH_2ONH_2$ (in xylene)	161—162(5); 1,5820(22,5)	$C_{15}H_{15}NO$	80.23 80.39	6.80 6.76	6.31 6.39	79.96	6.71	6.21	73
	B	0.033 mole chromanone, 0.09 mole $CH_3ONH_2 \cdot HCl$, 0.05 mole Na_2CO_3, and 40 ml methanol; 20-30 min, 50°C	mp 22-23° [4] 113—114(4,5); 1,5760(23,5)	$C_{10}H_{11}NO_2$	67.93 67.75	6.17 6.24	7.90 8.03	67.78	6.25	7.90	85
	B	0.021 mole thiochromanone, 0.06 mole $CH_3ONH_2 \cdot HCl$, 0.031 mole Na_2CO_3, and 30 ml methanol, 30 min, 50° C	143—144(5,5); 1,6240(22,5)	$C_{10}H_{11}NOS$[a]	62.14 62.32	5.74 5.82	7.43 7.36	62.14	5.69	7.24	94
	B	0.04 mole chromanone and 0.05 mole of $C_6H_5CH_2ONH_2$ (in toluene)	137—138(0,08); 1,6070(23,5)	$C_{16}H_{15}NO_2$	75.40 75.41	6.18 6.20	5.82	75.86	5.96	5.53	92
	B	0.02 mole of flavanone, 0.049 mole of $CH_3ONH_2 \cdot HCl$, 0.024 mole of Na_2CO_3, and 65 ml of methanol	95—96 (methanol)	$C_{16}H_{15}NO_2$	76.04 75.84	6.24 6.06	5.87 5.84	75.86	5.96	5.53	28
	A	0.01 mole oxime in 10 ml DMF, 0.015 mole dimethyl sulfate in 3 ml DMF, and 0.03 ml NaH in 10 ml of DMF; 2 hr, 75-80° C	107—108(3); 1,5635(22)	$C_{11}H_{13}NO_2$	68.65 68.70	6.82 7.04	7.30 7.39	69.08	6.85	7.32	55
	A	Similarly (16 hr, 20° C)	144—145(4—5)	$C_{11}H_{13}NOS$	64.09 64.12	6.36 6.43	6.70 6.86	63.73	6.32	6.75	48
	A	Similarly (1 hr, 50° C[b])	129—130 (ethyl acetate)	$C_{14}H_{20}N_2OS \cdot HCl$[c]	55.71 55.67	7.26 7.34	5.12 5.15	55.90	7.03		57
	A	0.024 mole NaH in 10 ml, 0.004 mole 6-hydroxy-2,2,5,7,8-pentamethyl-chroman-4-one oxime in 5 ml DMF, and 0.015 mole dimethyl sulfate; 1.5 hr, 50° C	114—115 (absolute ethanol)	$C_{16}H_{23}NO_3$	69.18 68.97	8.49 8.70		69.27	8.36	5.05	24
	A	0.028 mole NaH in 20 ml DMF, 0.005 mole 6-hydroxy-2,2,5,7,8-pentamethyl chromanone in 5 ml of DMF and 0.014 mole benzyl chloride; 1.5 hr, 60° C	104,5—105,5 (ethanol-acetone)	$C_{28}H_{31}NO_3$[d]	78.17 78.27	7.56 7.31	3.41 3.48	78.27	7.26	3.25	55

[a] Found, %: S 16.58, 16.39. Calculated, %: S 16.59. [b] After the reaction mixture had been poured into ice water it was extracted with ether, the ethereal layer was separated (it contained 34% of the initial oxime), and the aqueous layer was made alkaline with sodium carbonate and extracted with ether, the ethereal extract was dried with potassium carbonate, and the designated hydrochloride was precipitated with hydrogen chloride. [c] Found, %: Cl 11.66, 11.60; S 10.42, 10.26. Calculated, %: Cl 11.75; S 10.66. The IR spectrum (in oil) lacked the strong band in the 1520-1540-cm^{-1} region that is characteristic for nitrones [16]. [d] The IR spectrum (in oil) did not agree with the nitrone form.

reduced capacity of the benzyl ethers of the oxime as compared with the oximes themselves and, in turn, the lower tendency of the latter, compared with their tosylates, to undergo anomalous reduction are arguments against the reduction mechanism according to which, as assumed in one published paper [13], the anomalous and normal reductive processes take place through the same intermediate stage, which is structurally independent of the oxygen-containing part of the oxime. Thus, the mechanism of reduction of the oximes [13] must be refined by assuming competing transformations of an intermediate compound of type A by routes *a* and b, and therefore postulating that the intermediate intermediate compound B considered in this paper [13] is responsible only for the anomalous reduction process. Compounds of type A figuring in this scheme are in fact N-substituted hydroxylamines (their metal derivative) and the capacity of the latter for undergoing anomalous reduction, like the corresponding oximes, has been shown previously [11]. Application of this scheme of transformations to oxime ethers and esters permits us to take into account the influence of the group which is substituted for the hydrogen atom of the hydroxyl in the oxime. It is possible that their capacity for coordination with aluminum hydride affects the direction of the transformation of the type A compound (by route *a* or b). We may also note that the mechanism of the anomalous reduction of oximes, including an intermediate rearrangement (of the Beckmann type) of the oxime into an amide, as proposed previously [14] is not in harmony with a whole series of facts (see [1, 11]).



In this paper we also describe the synthesis of a number of ethers of heterocyclic ketoximes (Table 2) with the aim of testing them for pharmacological activity, bearing in mind the fact that among ethers and esters of the oximes there are substances with various types of biological activity. The synthesis of the oxime ethers was carried out by two known methods: by alkylating the oximes, and by the reaction of O-substituted hydroxylamines with the corresponding ketones. Alkali metal salts of the oximes, on alkylation with alkyl sulfates or alkyl halides, may give not only the ethers of the oximes but also the products of N-alkylation, i.e., nitrones, sometimes in predominating amounts [15, 16]. We assumed that the use of dimethylformamide (DMF) as the solvent would promote a more selective O-alkylation of the oximes, since the anions are poorly solvated by aprotic polar solvents. In actual fact, taking as examples the reaction of dimethyl sulfate with acetophenone and benzophenone oximes, and that of benzyl chloride with benzophenone oxime, the assumption has been confirmed. Ethers of the oximes were obtained with yields of 91, 65, and 83%, respectively, and the formation of nitrones was suppressed almost completely. For comparison, the methylation of benzophenone oxime with dimethyl sulfate in aqueous alkali [15] gave 23% ether and 45% nitrone.

Some other ethers of chromanone oximes were obtained by the same method (information on the ethers and esters of the oximes is given in Table 2).

EXPERIMENTAL

The tosylates of chroman-4-one, thiochroman-4-one, and acetophenone oximes were obtained by published methods [17, 18]. The ethers of the oximes were synthesized from the corresponding ketones and hydroxylamine ethers, with the exception of the methyl ether of benzophenone oxime, which was obtained by methylating the oxime (for purification it was treated with hydrogen chloride in petroleum ether). The purity of the oxime ethers was checked by chromatography in a thin layer of Al_2O_3 in comparison with the corresponding ketones and/or oximes and by the chromatography of ethers of acetophenone and benzophenone oximes with the corresponding nitrones.

Lithium aluminum hydride containing less than 1% (by weight) Cl ion was used for reducing the oxime ethers and esters, with the exception of experiment 4 (Table 1) in which the lithium aluminum hydride was prepared by the reaction in ether of $AlBr_3$ with an excess of LiH (the excess of LiH was eliminated after the reaction had gone to completion) with subsequent replacement of the ether by tetrahydrofuran. The separation of the reaction products (primary aliphatic-aromatic amines and secondary amines of the aniline series) was based on the differences in their ionization constants [1, 2]. In all cases a chromatographic check was carried out in a thin layer of Al_2O_3 (activity grade VI, benzene) in comparison with authentic samples of the bases.

Oxime ethers and esters. A) Anhydrous DMF and then, with water cooling, a solution of the appropriate oxime in DMF were added to 60% NaH. After the evolution of hydrogen had ceased (several minutes) the alkylating agent (dimethyl sulfate, benzyl chloride, or β-dimethylaminoethyl chloride) was gradually added. The reaction mixture was stirred, poured into ice water, and extracted with ether or benzene. The organic solution was evaporated, the residue was dried by the addition and evaporation of benzene, and it was distilled in vacuo or recrystallized and, except for the esters of acetophenone and benzophenone oximes and the dimethylaminoethyl ether of 3-methylthiochromanone oxime, the substances were additionally purified by precipitating the contaminating initial oximes and nitrones in the form of their hydrochlorides (by adding to a solution of the reaction products in petroleum ether an ethereal solution of hydrogen chloride).

B) A solution of $NH_2OCH_3 \cdot HCl$ in methanol was added to a solution of the corresponding ketone in methanol and then, with stirring and cold water cooling, finely ground anhydrous sodium carbonate was added in small portions. The reaction mixture was heated, the methanol was distilled off in vacuo, the residue was treated with $MgSO_4$, the ether was distilled off, and the residue was distilled in vacuo or recrystallized.

C) A solution of the appropriate ketone and O-ether of hydroxylamine in 20 ml of absolute toluene or xylene was boiled for 3 hr 30 min with the water being taken off in a Dean and Stark trap containing barium oxide, the solvent was evaporated off, and the residue was distilled in vacuo or recrystallized.

Reduction of acetophenone oxime. A solution of 2.7 g (0.019 mole) of acetophenone oxime in 30 ml of ether was added to a solution of 3.04 g (0.08 mole) of lithium aluminum hydride (from $AlBr_3$ and an excess of LiH) in 64 ml of ether. The mixture was boiled for 5 hr, decomposed with 30 ml of moist ether and 50 ml of 10% NaOH, and extracted with ether (3 × 40 ml). The combined ethereal solutions were extracted with 10% HCl (2 × 20 ml); 11% of the initial oxime remained in the ether. The acid solution was evaporated to dryness, and the residue [a mixture of primary and secondary amine hydrochlorides (2.82 g, i.e., 90%)] was separated into the free amines by a method described previously [1, 2]. The amines in ethereal solution were converted into the hydrochlorides in the usual way. The yield of N-ethylaniline hydrochloride was 0.55 g (17%), mp 172–173.5° C. There was melting point depression when mixed with an authentic sample having mp 174.5–175° C [10]. The yield of α-phenylethylamine hydrochloride was 1.57 g (50%), mp 157.5–158° C. There was no melting point depression in admixture with an authentic sample having mp 157.5–158° C [9]. N-Benzoyl derivative, mp 119° C (mixed melting point test with an authentic sample [9]).

The reduction of the tosylate of acetophenone oxime and the treatment of the reaction mixture were carried out under completely similar conditions (Table 1, experiment 11).

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Institute of Pharmacology and Chemotherapy, AMS USSR,
Moscow