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The Rearrangement of Chromanone Oximes with Lithium Aluminum Hydride

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The lithium aluminum hydride reduction of 7-methoxychromanone oxime (I) and 7-methoxy-3-methylchromamone oxime (II) gave only the rearrangement product (the 2,3,4,5-tetrahydro-1,5-benzoxazepine derivative). 7-Methoxy-2-methylchromanone oxime (III) and 7-methoxy-2-isopropylchromanone oxime (IV) gave a mixture of the rearrangement product (secondary amine) and the normal reduction product (primary amine). 7-Methoxy-2-*t*-butylchromanone oxime (V) gave only the normal reduction product. The main conclusions to be drawn from these results are as follows: (1) The chromanone oximes without a C_2 substituent give only the rearrangement product. (2) The chromanone oximes with a C_2 substituent give a mixture of the normal reduction product and the rearrangement product. (3) The more bulky substituent at C_2 gives the more normal reduction product and the smaller quantity of the rearrangement product.

The reduction of ketoximes and aldoximes with lithium aluminum hydride has been reported, in numerous instances, to give the corresponding primary amine.[2] However, in the reduction of certain arylketoximes[3] and aldoximes[4], the pri-

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2) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers Inc., New York (1956), p. 751.

3) a) D. R. Smith, M. Maienthal and J. Tipton, *J. Org. Chem.*, **17**, 294(1952); b) R. E. Lyle and H. J. Troscianiec, *ibid.*, **20**, 1757(1955); c) M. N. Rerick, C. H. Trottier, R. A. Daignault and J. D. DeFoe, *Tetrahedron Lett.*, **1963**, 629; b) S. H. Graham and A. J. S. Williams, *Tetrahedron*, **21**, 3263(1965).

4) A. E. Petrarca and E. M. Emery, *Tetrahedron Lett.*, **1963**, 635.

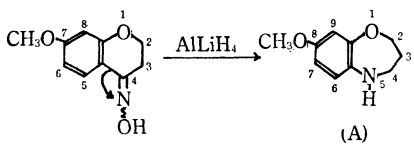
mary amine was accompanied by an isomeric secondary amine which was produced by the migration of the aryl group. It has also been reported that the addition of aluminum chloride to lithium aluminum hydride increased the yield of the secondary amine.[3]

In most of the systems investigated, the secondary amine has been a minor product of the reduction, but in special cases of highly-substituted arylketoximes where the aryl group is part of the phenoxazine ring system, the exclusive product has been the secondary amine.[5]

In the reduction of tetramethylbenzocyclobutenone oxime with lithium aluminum hydride, the sole product is the secondary amine, and the primary amine has not been detected.[6] The lithium aluminum hydride reduction of tetramethylcyclobutenone oxime gave only the rearrangement product,[7] while the same reaction of cyclopentanone oxime gave the primary amine accompanied by the secondary amine.[3] Recently it has been reported that the reduction of benzylketoximes with lithium aluminum hydride in refluxing tetrahydrofuran gave the aziridine derivatives, together with primary amine.[8]

Inoue and his co-workers reported the rearrangement in the reduction of isoflavanone oximes with lithium aluminum hydride.[9] The reduction of isoflavanone oxime, 7-methoxyisoflavanone oxime, and 7,4′-dimethoxyisoflavanone oxime with lithium aluminum hydride in refluxing ether afforded the corresponding tetrahydro-1,5-benzoxazepine derivatives. The same reaction of flavanone oximes gave no rearrangement product, but only the normal reduction product (4-aminoflavan).

From these results it was considered that the position (C_2 or C_3) and the size of a substituent in the chromanone oxime may exert a remarkable influence on the reaction between the chromanone oximes, with or without a C_2 or C_3 alkyl substituent, and lithium aluminum hydride.



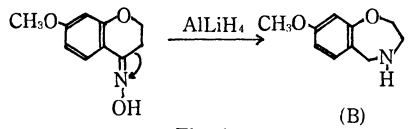


Fig. 1

The reaction of 7-methoxychromanone oxime (I) and 7-methoxy-3-methylchromanone oxime (II) with lithium aluminum hydride in refluxing ether and subsequent treatment with hydrochloric acid gave the amine hydrochlorides, X (mp 208—209°C) and XI (mp 182—183°C) respectively.

In both cases no by-product was found, and the X and XI were not identical with the 7-methoxy-4-aminochroman hydrochloride VI (mp 206—207°C) and the 7-methoxy-3-methyl-4-aminochroman hydrochloride VII (mp 205—206°C) which were obtained by the catalytic hydrogenation of I and II respectively.

The same reaction of 7-methoxy-2-methylchromanone oxime (III) gave two amine hydrochlorides, XII (mp 214—215°C) and VIII (mp 204—205°C). 7-Methoxy-2-isopropyl chromanone oxime (IV) also gave two amine hydrochlorides, XIII (mp 161—163°C) and IX (mp 196—197°C), by the same reaction. The VIII and IX were found to be identical with the 7-methoxy-2-methyl-4-aminochroman hydrochloride which were obtained by the catalytic hydrogenation of III and IV respectively.

The lithium aluminum hydride reduction of 7-methoxy-2-*t*-butylchromanone oxime (V) and subsequent treatment with hydrochloric acid gave only amine hydrochloride with a mp of 230—231°C (XIV); this was identical with the hydrochloride of the catalytic hydrogenation product of V.

The infrared spectra of X,XI, XII, and XIII all show a broad band at 3000—2400 cm^{-1} which is a characteristic absorption of secondary amine hydrochloride (ν^{+}_{NH}). On the other hand, the infrared spectra of VI, VII, VIII, IX, and XIV all show a broad band of $\nu^{+}_{NH_2}$ (primary amine salt) at 3200—2700 cm^{-1}.

The treatment of X, XI, XII, and XIII with acetic anhydride and pyridine gave acetamido derivatives, XV (mp 98—100°C), XVI (bp 160°C/2mmHg), XVII (mp 106—107°C), and XVIII (mp 95—96°C) respectively. The infrared spectra of XV, XVI, XVII, and XVIII all showed a characteristic band at 1660 cm^{-1} (ν_{CO} of CH_3CON) and no band of ν_{NH}.

The same treatment of the 4-aminochroman hydrochlorides, VI, VII, VIII, IX, and XIV, gave acetamido derivatives, XIX (mp 170—171°C), XX (mp 150—151°C), XXI (mp 184—185°C), XXII (mp 151—152°C), and XXIII (mp 177—178°C) respectively. The infrared spectra of XIX, XX, XXI, XXII, and XXIII all showed absorption bands of 3260 cm^{-1} (ν_{NH}) and 1640 cm^{-1} (ν_{CO}).

A comparison of the infrared spectra of these two series of acetamido derivatives shows that X, XI, XII, and XIII are secondary amine hydrochlorides.

The molecular weights of XV, XVI, XVII, and

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7) F. Lautenshlaeyer and G. F. Wright, *Can. J. Chem.*, **41**, 863 (1963).

8) a) K. Kitahonoki, K. Kotera, Y. Matsukawa, S. Miyazaki, T. Okada, H. Takahashi and Y. Takano, *Tetrahedron Lett.*, **1965**, 1059. b) K. Kotera, T. Okada and S. Miyazaki, *ibid.*, **1967**, 841.

9) N. Inoue, S. Yamaguchi and S. Ito, This Bulletin, **41**, 2078 (1968).

Table 1. pK_a values of tetrahydrobenzoxazepines and 4-aminochromans

Compound (a)	pK_a	Compound (b)	pK_a
VI	8.62	X	5.05
VII	8.60	XI	5.05
VIII	8.65	XII	5.10
IX	8.60	XIII	5.35
XIV	8.55		

(a) Determined by UV method using Britton-Robinson's buffer solution.[12]
(b) Determined by titration using 1/100 N NaOH solution.

XVIII, as observed by mass spectrometry, were the same as those of XIX, XX, XXI, and XXII respectively.[10]

Accordingly, it may be considered that the X, XI, XII, and XIII compounds possess an A- or B-type structure which is derived by the ring enlargement of the chroman ring involving the migration of the phenyl group (A) or C_3 (B) to the nitrogen atom of the oximino group. (Fig. 1)

Since A is a monoalkylaniline derivative and B is a benzylamine derivative, there must be a remarkable difference between their pK_a values. The pK_a values of X, XI, XII, and XIII are shown in Table 1, along with those of the 4-aminochroman hydrochlorides, VI, VII, VIII, IX, and XIV.

From the data shown in Table 2 it may reasonably be concluded that the free amines of X, XI, XII, and XIII possess the A-type structure, which is a derivative of tetrahydrobenzoxazepine.

The summarized results of the lithium aluminum hydride reduction of the chromanone oximes are shown in Table 2. The reduction of flavanone oximes (2-phenylchromanone oximes) with lithium aluminum hydride gave only the corresponding 4-aminoflavans, not the rearrangement product (the secondary amine). On the other hand, the same reaction of isoflavanone oximes (3-phenylchromanone oximes) gave the rerrangement products, exclusively, not the corresponding 4-aminoisoflavan.[9]

As is shown in Table 1, 7-methoxychromanone oxime (I) and 7-methoxy-3-methylchromanone oxime (II) give the rearrangement products exclusively.

It is clear that the substituent on C_2 or C_3 exerts a remarkable influence on the yield of the rearrangement product in this reaction.

7-Methoxy-2-methylchromanone oxime (III) gives the rearrangement product in a 50% yield and the 4-amino compound in a 10% yield. 7-Methoxy-2-isopropylchromanone oxime (IV) gives the rerrangement product in a 35% yield and the 4-amino compound in a 50% yield. 7-Methoxy-2-*t*-butylchromanone oxime (V) does not give the rearrangement product, but only the corresponding 4-amino compound.

Thus, it is evident that the more bulky substituent at C_2 gives the more normal reduction product (4-aminochroman) and the smaller quantity of the rearrangement product. The chromanone oxime with a substituent at C_3 and the unsubstituted chromanone oxime give only the rearrangement product and no 4-aminochroman derivative.

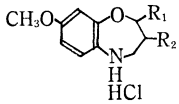
The mechanism involved in the rearrangement reaction of chromanone oxime with lithium aluminum hydride will be reported by Kitahara and his co-workers in the near future.

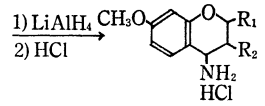
Experimental

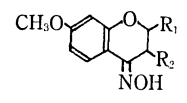
All the melting points are uncorrected. The infrared spectra were recorded with a Hitachi EPI-510 infrared spectrophotometer.

7-Methoxychromanone Oxime (I), 7-Methoxy-3-methylchromanone Oxime (II), 7-Methoxy-2-methylchromanone Oxime (III), 7-Methoxy-2-isopropylchromanone Oxime (IV), and 7-Methoxy-2-*t*-butylchromanone Oxime (V). *General Procedure.* The chromanone (1 g)[11] was refluxed for 10 hr with hydroxylamine hydrochloride (1 g), anhydrous ethanol (10 ml), and pyridine (10 ml). After cooling, the reaction mixture was poured into water; the precipitate was then recrystallized from dilute ethanol to give the

Table 2. Reduction of chromanone oximes







		(yield, %)	(yield, %)	(total yield, %)
$R_1=R_2=H$;	I	VI (0)	X (70)	(70)
$R_1=H$, $R_2=CH_3$;	II	VII (0)	XI (85)	(85)
$R_1=CH_3$, $R_2=H$;	III	VIII (10)	XII (50)	(60)
$R_1=CH(CH_3)_2$, $R_2=H$;	IV	IX (50)	XIII (35)	(85)
$R_1=C(CH_3)_3$, $R_2=H$;	V	XIV (80)	(0)	(80)

10) The details will be reported elsewhere.
11) The synthesis of these chromanones will be reported elsewhere by N. Inoue and his co-workers.
12) H. T. S. Britton and R. A. Robinson, *J. Chem. Soc.*, **1931**, 1456.

oxime almost quantitatively. The analytical data of chromanone oximes and their melting points are reported in Table 3.

Table 3. Chromanone oximes

Chromanone oxime	Mp (°C)	Formula	Analysis % Found N	Calcd N
I	135—136	$C_{10}H_{11}O_3N$	7.42	7.25
II	115—116	$C_{11}H_{13}O_3N$	6.67	6.76
III	161—163	$C_{11}H_{13}O_3N$	6.72	6.76
IV	94—95	$C_{13}H_{17}O_3N$	5.89	5.95
V	158—159	$C_{14}H_{19}O_3N$	5.72	5.62

7-Methoxy-4-aminochroman Hydrochloride (VI), 7-Methoxy-3-methyl-4-aminochroman Hydrochloride (VII), 7-Methoxy-2-methyl-4-aminochroman Hydrochloride (VIII), 7-Methoxy-2-isopropyl-4-aminochroman Hydrochloride (IX), and 7-Methoxy-2-*t*-butyl-4-aminochroman Hydrochloride (XIV). *General Procedure.* The oxime (1 g) in acetic acid (50 m*l*) containing 0.5 m*l* of 70% perchloric acid was hydrogenated by the usual manner at ordinary pressure and temperature in the presence of 1 g of 5% palladium on carbon.[13] The catalyst was then filtered off, and the acetic acid solution was concentrated under reduced pressure. To the residue, 6N hydrochloric acid was added to give crystals, which were then recrystallized from a suitable solvent. All the experimental results are summarized in Table 4.

By the usual method, the hydrochloride was acetylated with acetic anhydride in the presence of pyridine. The analytical data of these acetamido derivatives and their melting points are reported in Table 5.

Reduction of 7-Methoxychromanone Oxime (I) with Lithium Aluminum Hydride. To a swirling suspension of 1.9 g of lithium aluminum hydride in 100 m*l* of ether, there was added, drop by drop and at room temperature, a solution of 1.9 g of I in 150 m*l* of ether. After it had been refluxed for 24 hr, the reaction mixture was decomposed with water under cooling with ice. The ether layer was washed with 1N sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After the removal of the solvent, 6N hydrochloric acid was added to give 1.4 g of crude crystals (90% yield). Recrystallization from ethanol gave 0.9 g of 8-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine hydrochloride (X); mp 208—210°C. ν_{NH}^{+} 3000—2400 cm^{-1}.

Found: C, 55.43; H, 6.28; N, 6.38%. Calcd for $C_{10}H_{14}O_2NCl$: C, 55.60; H, 6.55; N, 6.49%.

By the usual method, the hydrochloride (X) was acetylated with pyridine-acetic anhydride to give a viscous liquid; bp 160—180°C/2 mmHg. On standing at room temperature the liquid gradually deposited crystals of an amide; mp 98—100°C. ν_{COCH_3} 1660 cm^{-1}.

Found: C, 64.63; H, 6.51; N, 5.93%. Calcd for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.83; N, 6.33%.

Table 5. 4-Acetamidochromans

Compound	Mp (°C)	Formula	Analysis % Found (Calcd) C	H	N
XIX	170—171	$C_{12}H_{15}O_3N$	65.28 (65.14)	6.71 (6.83)	6.25 (6.33)
XX	150—151	$C_{13}H_{17}O_3N$	66.27 (66.36)	7.04 (7.28)	5.96 (5.95)
XXI	184—185	$C_{13}H_{17}O_3N$	66.62 (66.36)	7.13 (7.28)	5.96 (5.95)
XXII	151—152	$C_{15}H_{21}O_3N$	68.12 (68.41)	7.98 (8.04)	5.36 (5.32)
XXIII	177—178	$C_{16}H_{23}O_3N$	69.32 (69.28)	8.24 (8.36)	5.12 (5.05)

Reduction of 7-Methoxy-3-methylchromanone Oxime (II) with Lithium Aluminum Hydride. A solution of 1 g of II in 100 m*l* of ether was added, drop by drop and at room temperature, to a swirling suspension of lithium aluminum hydride in 80 m*l* of ether. After it had been allowed to reflux for 24 hr, the reaction mixture was decomposed with water under cooling with ice. The layer was washed with 1N sodium

Table 4. 4-Aminochroman hydrochlorides

Compound	Yield %	Mp (°C)	Recryst. solvent	Formula	Analysis % Found (Cacld) C	H	N
VI	70	206—207	Ethanol	$C_{10}H_{14}O_2NCl$	55.41 (55.60)	6.32 (6.55)	6.43 (6.49)
VII	85	205—206	Ethanol	$C_{11}H_{16}O_2NCl$	57.62 (57.45)	7.18 (7.04)	6.07 (6.09)
VIII	80	204—205	Ethanol	$C_{11}H_{16}O_2NCl$	57.21 (57.45)	7.02 (7.04)	6.08 (6.09)
IX	72	195—196	Ethyl acetate	$C_{13}H_{20}O_2NCl$	60.48 (60.57)	7.65 (7.82)	5.28 (5.44)
XIV	70	230—231	Ethyl acetate	$C_{14}H_{22}O_2NCl$	61.66 (61.86)	8.07 (8.16)	5.13 (5.15)

13) Five percent palladium on carbon, obtained from the Kawakami Research Institute, was used in the experimental.

hydroxide and water, and then dried over sodium sulfate. After the removal of the ether, 6N hydrochloric acid was added to give a solid (870 mg, 85% yield). Recrystallization from chloroform-benzene gave 500 mg of 8-methoxy-3-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepine hydrochloride (XI); mp 182—183°C. ν^{+}_{NH} 3000—2400 cm^{-1}.

Found: C, 57.67; H, 7.01; N, 6.10%. Calcd for $C_{11}H_{16}O_2NCl$: C, 57.45; H, 7.04; N, 6.09%.

By the usual method, the hydrochloride (XI) was acetylated with pyridine-acetic anhydride to give a liquid; bp 160—180°C/2 mmHg. ν_{COCH_3} 1660 cm^{-1}.

Found: C, 66.02; H, 6.95; N, 5.65%. Calcd for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95%.

Reduction of 7-Methoxy-2-methylchromanone Oxime (III) with Lithium Aluminum Hydride. A solution of III in 130 m*l* of ether was added, drop by drop and at room temperature, to a swirling suspension of 1 g of lithium aluminum hydride in 130 m*l* of ether. After it had been refluxed for 24 hr, the reaction mixture was decomposed with water under cooling with ice. The ether layer was washed with 1N sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After the removal of the solvent, 6N hydrochloric acid was added; it was then allowed to stand overnight at room temperature, and the solid which separated (530 mg, 50%) was recrystallized from ethanol to give 400 mg of 8-methoxy-2-methyl-2,3,4,5-tetrahydro-1,5-benzoxazepine hydrochloride (XII); mp 214—215°C, ν^{+}_{NH} 3000—2400 cm^{-1}.

Found: C, 57.20; H, 7.25; N, 6.05%. Calcd for $C_{11}H_{16}O_3NCl$: C, 57.45; H, 7.04; N, 6.09%.

The filtrate was allowed to stand overnight under cooling with ice; the solid which thus separated (110 mg, 10%) was identical with 7-methoxy-2-methyl-4-aminochroman hydrochloride (VIII).

By the usual method, the hydrochloride (XII) was acetylated with pyridine-acetic anhydride; this gave crystals which were then recrystallized from benzene-petroleum ether to give an amide; mp 106—107°C, ν_{COCH_3} 1660 cm^{-1}.

Found: C, 66.58; H, 7.21; N, 5.72%. Calcd for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95%.

Reduction of 7-Methoxy-2-isopropylchromanone Oxime (IV) with Lithium Aluminum Hydride. To a swirling suspension of 2 g of lithium aluminum hydride in 100 m*l* of ether, there was added, drop by drop at room temperature, a solution of 2 g of IV in 150 m*l* of ether. The reaction mixture was then treated as above. After the removal of the solvent, 6N hydrochloric acid was added; the solution was subsequently allowed to stand overnight at room temperature. The solid which separated (1.03 g, 50%) was filtered and recrystallized from chloroform to give colorless crystals which were identical with 7-methoxy-2-isopropyl-4-aminochroman hydrochloride (IX). After filtrate had been allowed to stand overnight under cooling with ice, the solid which separated (720 mg, 35%) was filtered and recrystallized from ethyl acetate to give 8-methoxy-2-isopropyl-2,3,4,5-tetrahydro-1,5-benzoxazepine hydrochloride (XIII); mp 161—163°C, ν^{+}_{NH} 3000—2400 cm^{-1}.

Found: C, 61.65; H, 8.02; N, 5.05%. Calcd for $C_{14}H_{22}O_2NCl$: C, 61.86; H, 8.16; N, 5.32%.

By the usual manner, the hydrochloride (XIII) was acetylated with pyridine-acetic anhydride. Recrystallization from dilute methanol then gave an amide; mp 95—96°C, ν_{COCH_3} 1660 cm^{-1}.

Found: C, 68.12; H, 7.98; N, 5.35%. Calcd for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32%.

Reduction of 7-Methoxy-2-*t*-butylchromanone Oxime (V) with Lithium Aluminum Hydride. To a swirling suspension of 1.5 g of lithium aluminum hydride in 100 m*l* of ether, there was added, drop by drop and at room temperature, a solution of 1.5 g of V in 100 m*l* of ether. The solid (1.32 g, 80%) obtained by the usual treatment was recrystallized from ethyl acetate to give colorless crystals which were identical with 7-methoxy-2-*t*-butyl-4-aminochroman hydrochloride (XIV).

Methods of the pK_a Determination of Amines. *(A) Determination by the Titration Method.* The values of pK_a in Table 1 (Compounds VI, VII, VIII, IX, and XIV) were taken as the values of the amines at the mid-points of the titration curves, plotting the volume of 1/100 N aqueous sodium hydroxide against pH.

(B) Determination by the UV Method. The ultraviolet spectra were recorded with a Hitachi EPI-032 ultraviolet spectrophotometer. The values of pK_a in Table 1 (Compounds X, XI, XII, and XIII) were taken as the pH values of the amines in the Britton-Robinson buffer solution at the mid-points of the titration curves, plotting the absorbance at λ_{max} of the free amines against pH. The concentrations and the λ_{max} values of these amines are shown in Table 6.

Table 6.

Amine	Concentration (mol/*l*)	λ_{max} (mμ)
X	2.71×10^{-4}	292.5
XI	2.43×10^{-4}	292
XII	2.71×10^{-4}	292.5
XIII	2.89×10^{-4}	293.5

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