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The Rearrangement of Isoflavanone Oximes with Lithium Aluminum Hydride

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The reaction of isoflavanone oxime (III), 7-methoxyisoflavanone oxime (IV), and 4′,7-dimethoxyisoflavanone oxime (V) with lithium aluminum hydyride in ether for 20 hr under refluxing gave 3-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepine derivatives (XVII, XVIII and XIX) but not the expected 4-aminoisoflavans. When a similar reaction was carried out using flavanone oxime and 7-methoxyflavanone oxime, only 4-aminoflavans were obtained, and the rearrangement reaction observed in isoflavanone oximes did not occur. Therefore, it may be considered that, in the reaction of chromanone oximes and lithium aluminum hydride, the position (C_2 or C_3) and the size of the substituent exerts a remarkable influence on the rearrangement reaction, while the methoxyl group at the 7-position (*para* position to the oximino group) has little effect.

By the catalytic hydrogenation of flavanone oxime (I), Bognár and his co-workers[1] obtained 4-aminoflavan (II), which is an intermediate in the course of the synthesis of one of the stereoisomers of flavan-4-ol. They also reported that, in the reduction of I using diborane or lithium aluminum hydride or aluminum amalgam, II was always obtained. In the preceding paper[2] it was reported that the catalytic hydrogenation of isoflavanone oximes in the presence of palladium on carbon gave 4-aminoisoflavans, which are intermediates for the synthesis of *trans*-isoflavan-4-ols. In order to obtain 4-aminoisoflavans, an ether solution of isoflavanone oximes was reduced with lithium aluminum hydride. However, the expected 4-aminoisoflavans were not obtained; a different kind of compouds was isolated. This paper will describe the results of these reactions.

When an ether solution of isoflavanone oxime (III), 7-methoxyisoflavanone oxime (IV), and 4′,7-dimethoxyisoflavanone oxime (V) was refluxed with lithium aluminum hydride for 20 hr and then treated with 6 $_N$ hydrochloric acid, hydrochlorides of unknown basic compounds, were obtained, IX mp 220°C, X mp 247°C, and XI mp 186°C respectively. These compounds (IX, X, and XI) are different from the hydrochlorides[2] of 4-aminoisoflavans (XII, XIII, and XIV), which are the catalytic hydrogenation products of III, IV, and V respectively. The IX, X, and XI compounds, show a broad ν_{N^+-H} band between 2800—2300 cm^{-1} in their infrared spectra, and may be assumed to be hydrochlorides of secondary amines in view of the infrared spectra[2] of XII, XIII, and XIV. In the infrared spectra of *N*-acetyl derivatives of the amines, no band corresponding to the N–H stretching vibration is observed, but one assigned to the carbonyl group of $N-COCH_3$ appears at 1640 cm^{-1}. The above data also support the idea that IX, X, and XI are secondary amine hydrochlorides. From the reactions of IX and X with nitrous acid, the nitroso compounds XV and XVI, possessing the characteristic absorption ($\nu_{N=O}$) of N–N=O at 1450 cm^{-1}, are obtained. These compounds are converted to the original amine hydrochlorides (IX and X), after catalytic hydrogenation with Raney Ni and subsequent treatment with hydrochloric acid. Therefore, it is clear that the reaction with nitrous acid and the successive catalytic hydrogenation does not change the skeletons of these compounds.

The molecular weights of the amines (XVIII and XIX) were determined to be 255 and 285 respectively by mass spectrometry; these values accord with those of 4-amino-7-methoxyisoflavan (VII) and 4-amino-4′,7-dimethoxyisoflavan (VIII). The elemental analyses of XVIII and XIX agree with $C_{16}H_{17}ON$ and $C_{17}H_{19}O_3N$ respectively, which correspond to the molecular formulae of VII and VIII. In the mass spectra of 4-aminoisoflavans, the peaks of $M-NH_3$ and $M-NH_3-H$ are observed, while, in those of XVIII and XIX, no corresponding peaks are observed*1 (Fig. 2).

On the basis of these data, it may reasonably be concluded that the unknown compounds, IX, X, and XI, obtained by the lithium aluminum hydride reduction of isoflavanone oximes are secondary amine hydrochlorides isomeric with 4-aminoisoflavan hydrochlorides.

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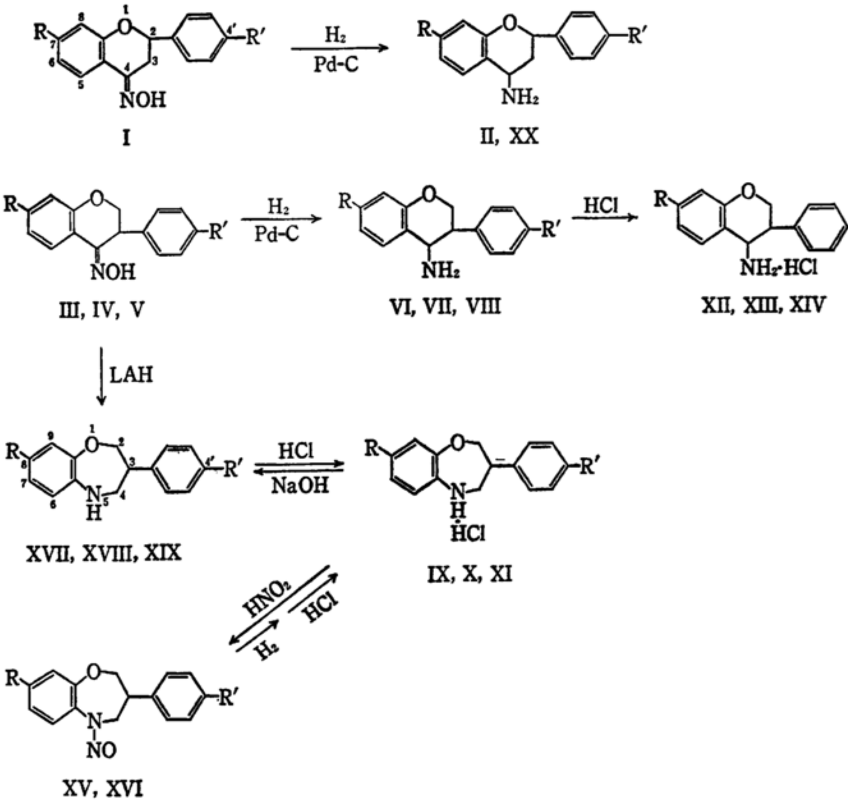
[1] R. Bognár, M. Rakosi, H. Fletcher, D. Kohoe, E. M. Philibin and T. S. Wheeler, *Tetrahedron*, **18**, 135 (1962).

[2] S. Yamaguchi, S. Ito, I. Suzuki and N. Inoue, This Bulletin, **41**, 2073 (1968).

*1 The details will be reported elsewhere.



I, II, III, VI, IX, XII, XV, XVII: R=R′=H
IV, VII, X, XIII, XVI, XVIII, XX: R=OCH_3, R′=H
V, VIII, XI, XIV, XIX: R=R′=OCH_3

Fig. 1

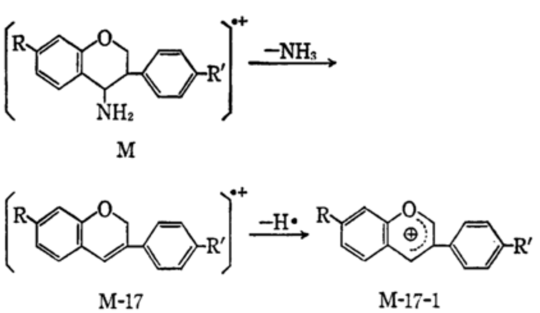


Fig 2.

Recently, a few examples of secondary amines being produced by rearrangement in the reduction of oximes with lithium aluminum hydride have been found. Smith and his co-workers[3] have reported that, in the reduction of oximes of aldehydes or ketones, the rearrangement products were obtained together with the corresponding normal reduction products. For example, the reduction of oximes of acetophenone and propiophenone afforded phenylethylamine (16%) and phenylpropylamine (14%), together with α-aminoethylbenzene and α-aminopropylbenzene, respectively.

Harfenist and Magniens[4] have reported that, in the lithium aluminum hydride reduction of oximes of six-membered ring ketones fused to phenothiazine, seven-membered cyclic amines (Table 1) were formed by ring enlargement. Graham and Williams[5] mentioned that, in the lithium aluminum

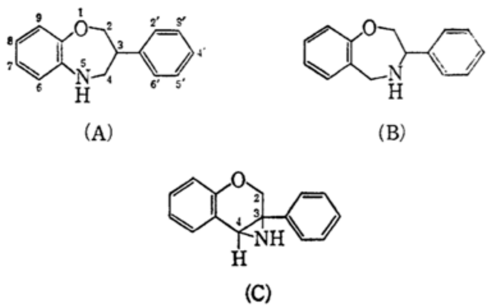

(A) (B) (C)

Fig. 3

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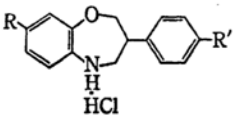
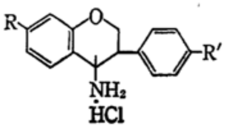
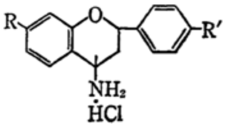
[3] D. R. Smith, M. Maienthal and J. Tiptor, *J. Org. Chem.*, **17**, 294 (1952).

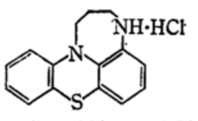
[4] M. Harfenist and E. Magniens, *J. Am. Chem. Soc.*, **80**, 6080 (1965).

[5] S. H. Graham and A. J. S. Williams, *Tetrahedron*, **21**, 3263 (1965).

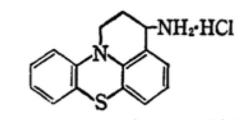
TABLE 1. $\mathrm{p}K_a$ VALUES OF AMINE HYDROCHLORIDES

						
	$\mathrm{p}K_a$*		$\mathrm{p}K_a$[2]		$\mathrm{p}K_a$	
R=R′=H	IX	4.05	XII	7.25	II	7.40
R=OCH_3, R′=H	X	4.60	XIII	7.45	XX	7.95
R=R′=OCH_3	XI	4.65	XIV	7.50		

* measured in 15% aq. EtOH.

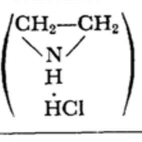


3.75 (in 50% Me_2SO)[4]



8.11 (in 50% Me_2SO)[4]

Aziridine 7.98[7]



$$\left(\begin{array}{c} CH_2\text{—}CH_2 \\ N \\ H \\ \dot{H}Cl \end{array}\right)$$

hydride reduction of phenyl alkyl ketone oximes, bulky alkyl group increase the yields of secondary amines produced by rearrangement. On the other hand, Kitahonoki *et al.*[6] found that the reduction of ketoximes and aldoximes with lithium aluminum hydride in tetrahydrofuran causes a rearrangement affording azirizines.

The number of *aliphatic hydrocarbon protons* (4.67—3.08 ppm)[*2] indicated by the NMR spectra of IX, X and XI is five,[*3] this fact also supports the idea that these compounds are not azirizine derivatives (Fig. 3 (C).).

The $\mathrm{p}K_a$ values of azirizines are reported to be around 7.9[7]. However, as will be described later, those of IX, X, and XI are 4.05, 4.60, and 4.65 respectively (Table 1). In addition, azirizine compounds cause ring opening during catalytic reduction, affording primary amines. Since the *N*-nitroso derivatives of the compounds obtained in this experiment, as has been mentioned, gave the original secondary amines upon high-pressure hydrogenation, the formation of azirizine derivatives is also obviated.

Accordingly, it may be considered that the IX, X, and XI compounds possess the A- or B-type structure, as shown in Fig. 3, structures which are derived by the enlargement of the chromane ring, involving the rearrangment of the benzenoid carbon adjacent to the C_4 of isoflavanone oximes to the nitrogen atom of the oximino group.

Since A is a monoalkyl aniline derivative and B is a benzylamine derivative, there must be remarkable difference between their $\mathrm{p}K_a$ values. The $\mathrm{p}K_a$ values of IX, X, and XI were measured by the ultraviolet absorption method[8] using a Britton-Robinson buffer solution. These values were then compared with those of 4-aminoisoflavans reported in the preceding paper,[2] and with *those*[4] of the rearrangement products of oximes of phenothiazine derivatives (Table 1). From the data shown in Table 1, it may reasonably be concluded that the amines (XVII, XVIII, and XIX) obtained by the lithium aluminum hydride reduction of isoflavanone oximes possess the A-type structure.

Lyle and Troscianec[9] indicated that, in the lithium aluminum hydride reduction of oximes of acetophenone derivatives, the electron-releasing group at the *para* position gave more rearrangement products, and the electron-attracting group gave less. Different from Lyle's results, in this experiment the rearrangement product was obtained in a good yield (70—90%), irrespective of the presence or absence of the methoxyl group at the 7-position of isoflavanone oximes. It has been reported[1] that the reduction of flavanone oxime afforded only the normal reduction product even though lithium aluminum hydride was used. The present authors reinvestigated the reduction of flavanone oximes following the method of Bognár and found that the *product was only 4-aminoflavan (II), identical with* the product obtained by the catalytic hydrogenation of flavanone oxime. When a similar experiment was carried out using 7-methoxyflavanone oxime, only 4-amino-7-methoxyflavan (XX) was obtained, and the rearrangment product was not isolated. The $\mathrm{p}K_a$ values of hydrochlorides of II and XX are

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6) K. Kitahonoki, K. Kodera, Y. Matsukawa, S. Miyazaki, T. Okuda, H. Takahashi and Y. Takano, *Tetrahedron Letters*, **1965**, 1059.

*2 The NMR spectra were determined with a Varian A-60 spectrometer, at 60 Mc, using deuterochloroform as the solvent and tetramethylsilane as the internal reference.

*3 If the secondary amines obtained in this experiment are aziridine derivatives, they must have three aliphatic hydrocarbon protons.

7) G. J. Buistand and H. Lucas, *J. Am. Chem. Soc.*, **79**, 6157 (1957).

8) K. Nakanishi, "Yukikagaku no Shinpo," Vol. XII, ed. by M. Murakami, Kyoritsu Shuppan, Tokyo (1947), p. 19.

9) R. E. Lyle and H. J. Troscianec, *J. Org. Chem.*, **20**, 1757 (1955).

7.40 and 7.95 respectively; these values are close to those of 4-aminoisoflavans. Therefore, it may be considered that, in the reaction of chromanone oximes with lithium aluminum hydride, the position (C_2 or C_3) and the size of the substituent exerts a remarkable influence on the rearrangement reaction, but that the methoxyl group at the 7-position (the *para* position to the oximino group) has little effect. From a similar reaction using chromanone oximes substituted with various groups at the C_2 or C_3 position, the following conclusions were drawn: first, chromanone oximes without a C_2 substituent gave only the rearrangement products; second, chromanone oximes with a C_2 substituent gave a mixture of the normal reduction products (primary amines) and the rearrangement products (secondary amines); third, the more bulky substituents at C_2 gave the more normal reduction products and the fewer rearrangement products. This problem will be reported on later in more detail.

The mechanism concerning the rearrangement reaction of chromanone oxime with lithium aluminum hydride will be reported on by Kitahara and the present authors in the near future.

Experimental[*4]

Reduction of Isoflavanone Oxime (III) with $LiAlH_4$. To a swirling suspension of 1 g of $LiAlH_4$ in 80 m*l* of ether, there was added, drop by drop, a solution of 1 g of III in 70 m*l* of ether at room temperature. After having been allowed to reflux for 20 hr, the reaction mixture was decomposed with water under cooling with ice. The ether layer was washed with 1 N sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After the removal of the ether, 6 N hydrochloric acid was added, giving 0.8 g (80% yield) of crude crystals. Recrystallization from ethanol gave 0.6 g of 3-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin hydrochloride (IX), mp 218—220°C. $\nu_{\text{N}^+\text{-H}}$ 2800—2300 cm^{-1}.

Found: C, 68.53; H, 6.02; N, 5.21%. Calcd for $C_{15}H_{16}ONCl$: C, 68.83; H, 6.16; N, 5.35%.

By the usual method, 200 mg of the hydrochloride (IX) was acetylated with pryidine-acetic anhydride, giving 150 mg of acetate, mp 190—191°C (from ethanol). ν_{COCH_3} 1653 cm^{-1}.

Found: C, 76.17; H, 6.49; N, 5.02%. Calcd for $C_{17}H_{17}O_2N$: C, 76.38; H, 6.41; N, 5.24%.

A solution of 100 mg of the acetate in 5 m*l* of ethanol and 0.5 m*l* of concentrated hydrochloric acid was refluxed for 10 hr. The crystals obtained after the removal of the ethanol were recrystallized from ethanol to give the hydrochloride (IX). The neutralization of 100 mg of IX with 1 N sodium hydroxide gave an oily substance, which was extracted with ether and dried over anhydrous sodium sulfate; the solvent was then removed, but did not give crystals.

Reduction of 7-Methoxyisoflavanone Oxime (IV) with $LiAlH_4$. A solution of 2 g of IV in 120 m*l* of ether was added, drop by drop, to a swirling suspension of 2 g of $LiAlH_4$ in 80 m*l* of ether at room temperature. After it had been refluxed for 20 hr, the reaction mixture was decomposed with water under cooling with ice. The ether layer was washed with 1 N sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After the removal of the ether, 6 N hydrochloric acid was added to effect crystallization (1.8 g, 90% yield). Recrystallization from acetic acid gave 1.5 g of 3-phenyl-8-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine hydrochloride (X), mp 240—243°C. $\nu_{\text{N}^+\text{-H}}$ 2800—2300 cm^{-1}.

Found: C, 66.06; H, 6.18; N, 4.61%. Calcd for $C_{16}H_{18}O_2NCl$: C, 65.86; H, 6.22; N, 4.83%.

By the usual method, 200 mg of X was acetylated with pyridine - acetic anhydride, thus affording 170 mg of acetate, mp 142—143°C. ν_{CO} 1651 cm^{-1}.

Found: C, 73.09; H, 6.65; N, 4.64%. Calcd for $C_{18}H_{19}O_3N$: C, 72.70; H, 6.44; N, 4.71%.

The crystals obtained by the neutralization of 200 mg of X with 1 N sodium hydroxide were recrystallized from methanol, giving 100 mg of free amine (XVIII), mp 81—82°C. ν_{NH} 3350 cm^{-1}.

Found: C, 75.39; H, 6.64; N, 5.24%. Calcd for $C_{16}H_{17}O_2N$: C, 75.27; H, 6.71; N, 5.49%.

Reduction of 4′,7-Dimethoxyisoflavanone Oxime (V) with $LiAlH_4$. A solution of 1.3 g of V in 60 m*l* of tetrahydrofuran was added, drop by drop, to a swirling suspension of 1.3 g of $LiAlH_4$ in 50 m*l* of ether at room temperature. 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 1 N sodium hydroxide and water, and then dried over anhydrous sodium sulfate. After the removal of the solvent, 6 N hydrochloric acid was added to give a solid, (0.97 g). Recrystallization from ethanol gave 0.5 g of 3-(4′-methoxyphenyl)-8-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine hydrochloride (XI), mp 185—186°C. $\nu_{\text{N}^+\text{-H}}$ 2800—2300 cm^{-1}.

Found: C, 63.65; H, 6.14; N, 4.56%. Calcd for $C_{17}H_{20}O_3NCl$: C, 63.41; H, 6.23; N, 4.35%.

The acetylation of 100 mg of XI with pyridine-acetic anhydride by the general method gave 90 mg of acetate, mp 158—159°C. ν_{COCH_3} 1651 cm^{-1}.

Found: C, 69.52; H, 6.34; N, 4.07%. Calcd for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28%.

The crystals obtained by the neutralization of 200 mg of XI with 1 N sodium hydroxide were recrystallized from ethanol, giving free amine (XIX), mp 83—84°C. ν_{NH} 3355 cm^{-1}.

Found: C, 71.31; H, 6.78; N, 4.97%. Calcd for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91%.

Reaction of 3-Phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepine Hydrochloride (IX) and Nitrous Acid. To a swirling solution of 700 mg of IX in 30 m*l* of 50% acetic acid, there was added, drop by drop, a solution of 600 mg of sodium nitrite in 30 m*l* of water under cooling with ice. After the solution had been stirred for 1 hr, the crystals produced were filtered and washed with water; 500 mg of crude crystals (mp 78—80°C) were thus obtained. Recrystallization from diluted methanol gave a *N*-nitroso compound (XV), mp 56—58°C. $\nu_{\text{N=O}}$ 1450 cm^{-1}.

Found: C, 71.02; H, 5.42; N, 10.92%. Calcd for $C_{15}H_{14}O_2N_2$: C, 70.85; H, 5.55; N, 11.02%.

Reaction of 3-Phenyl-8-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine Hydrochloride (X) and Nitrous Acid. A solution of 0.8 g of sodium nitrite in

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[*4] All melting points are uncorrected. The ether used in these experiments was dried over $LiAlH_4$.

70 m*l* of water was added, drop by drop, to a swirling solution of 1.2 g of X in 250 m*l* of 50% acetic acid under cooling with ice. After the solution had been stirred for 1 hr, the crystals produced were filtered and washed with water; 1.1 g of crude crystals, mp 86—88°C, were thus obtained. Recrystallization from ethanol gave a *N*-nitroso compound (XVI), mp 64—66°C. $\nu_{N=O}$ 1450 cm^{-1}.

Found: C, 67.42; H, 5.34; N, 9.55%. Calcd for $C_{16}H_{16}O_3N_2$: C, 67.59; H, 5.67; N, 9.85%.

Catalytic Reduction of the 3-Phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepine-*N*-nitroso Compound (XV) by Raney-Ni. A mixture of 100 mg of XV and 100 mg of Raney-Ni (W-4) in 30 m*l* of ethanol was submitted to hydrogenation in an autoclave (hydrogen pressure: 62 atm) at 65°C for one and a half hr. After the removal of the solvent, 6 N hydrochloric acid was added to crystallize the residue. Recrystallization from ethanol gave crystals, mp 218—219°C, whose mixed melting point with IX was undepressed.

Catalytic Reduction of the 3-Phenyl-8-methoxy-2,3,4,5-tetrahydro-1,5-benzoxazepine-*N*-nitroso Compound (XVI) by Raney-Ni. A mixture of 100 mg of XVI and 100 mg of Raney-Ni (W-4) in 50 m*l* of ethanol was submitted to hydrogenation in an autoclave (hydrogen pressure: 62 atm) at 60°C for 1.5 hr. After the removal of the solvent, 6 N hydrochloric acid was added to afford crystals. Recrystallization from acetic acid gave crystals of a mp of 240—242°C, which was undepressed on admixture with X.

Reduction of Flavanone Oxime (I) by $LiAlH_4$. A solution of 1 g of I in 70 m*l* of ether was added, drop by drop, to a swirling suspension of 1 g of $LiAlH_4$ in 80 m*l* of ether at room temperature. The mixture was refluxed for 20 hr, and then decomposed with water under cooling with ice and worked up as has been described above for III. The crystals obtained, 0.78 g, were recrystallized from ethanol, affording 4-aminoflavan hydrochloride, mp 267—270°C, which did not show any depression of melting point on admixture with the compound obtained by the catalytic reduction of I using palladium on carbon as a catalyst.

Reduction of 7-Methoxyflavanone Oxime by $LiAlH_4$. To a swirling suspension of 1 g of $LiAlH_4$ in 80 m*l* of ether, there was added, drop by drop, a solution of 1 g of 7-methoxyflavanone oxime in 100 m*l* of ether at room temperature. The mixture was then refluxed for 20 hr. By working up in the usual manner, 910 mg of crystals were obtained. Recrystallization from ethyl acetate gave 4-amino-7-methoxyflavan, mp 220°C (undepressed on admixture with the compound[10] obtained by the catalytic reduction of 7-methoxyflavanone oxime using palladium on carbon as a catalyst).

The authors wish to express their thanks to Mr. Hideji Abe for his measurement of the mass spectra.

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[10] N. Inoue, S. Yamaguchi and S. Fujiwara, This Bulletin, **37**, 588 (1964).