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Studies on the Organic Fluorine Compounds. IX.[1] Reactions of (Trifluoromethyl)quinolines with Metal Hydrides[2]

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Reduction of (trifluoromethyl)quinolines by nucleophilic attack of hydride was studied. Sodium borohydride reduced only 3-(trifluoromethyl)quinoline to methyl derivative, while lithium aluminum hydride reduced other isomers to methylquinolines and 3-(trifluoromethyl)quinoline to 3-(difluoromethyl)-1,2-dihydroquinoline. The mechanisms were proposed.

In the studies of (trifluoromethyl)pyridines and (trifluoromethyl)quinolines, we reported the effect of trifluoromethyl group on the reactivity of heterocyclic N-oxide[4] and, further, the effect of a nitrogen atom in the heterocycle on the nucleophilic substitution reaction of the trifluoromethyl group.[1,5] In this paper we report the investigation of the reaction of metal hydrides with (trifluoromethyl)quinolines, considering it to be an example of nucleophilic reaction at the carbon atom of a trifluoromethyl group.

2-, 3-, 4-, and 6-(trifluoromethyl)quinoline (I, II, III, and IV) were respectively treated with sodium borohydride and with lithium aluminum hydride in absolute ether. In the cases of both reagents, the reactivity of 3-(trifluoromethyl)quinoline (II) was quite different from those of other isomers, as shown in the case of alcoholysis of (trifluoromethyl)quinoline.[1] These results suggest that the reduction of 3-(trifluoromethyl)quinoline proceeds by a special mechanism. To describe in more detail, on conducting a prolonged reflux of each (trifluoromethyl)quinoline with sodium borohydride in absolute ether, I, III, and IV, respectively, were almost completely recovered, while II was reduced to 3-methylquinoline (VI) in 36% yield. On the other hand, I, III, and IV were reduced with lithium alumnum hydride in the same condition to the corresponding methylquinolines (V, VII, and VIII) in the yields of 28%, 10%, and 66%, respectively, while II was reduced to 3-(difluoromethyl)-1,2-dihydroquinoline (IX) in the yield of 71%. II was reduced to IX with lithium aluminum hydride even at 0—5°. These results are shown in Table I. The structures of methylquinolines (V, VI, VII, and VIII) were determined by the comparison of infrared (IR) spectra and admixture of their picrates with the authentic samples. IX was a quite unstable liquid and showed a mother peak at *m/e* 181 and fragment peaks at 130 (M-51) and 51 (CHF_2) in mass spectrum. IR spectrum of IX showed ν_{NH} at 3400 cm^{-1}. IX was dehydrogenated with chloranil, followed by hydrolysis, to give quinoline-3-aldehyde, which was identified with the authentic sample obtained by the oxidation of 3-methylquinoline with selenium oxide. These facts suggest that IX was 3-(difluoromethyl)dihydroquinoline, but whether IX was 1,2-dihydro- or 1,4-dihydroquinoline could not be determined. To make this point clear, we examined the reduction of II with diisobutyl aluminum hydride, which reduces quinoline rings selectively

1) Part VIII: Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **19**, 624 (1971).
2) Presented at the 90th Annual Meeting of the Pharmaceutical Society of Japan, Sapporo, July 1970.
3) Location: *Kitashinjuku 3-chome, Shinjuku-ku, Tokyo.*
4) *a*) Y. Kobayashi and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **17**, 510 (1969); *b*) Y. Kobayashi, I. Kumadaki, and S. Taguchi, *Chem. Pharm. Bull.* (Tokyo), **17**, 2335 (1969).
5) Y. Kobayashi, I. Kumadaki, S. Taguchi, and Y. Hanzawa, *Tetrahedron Letters*, **1970**, 3901.

Table I. Products and Yields of Reduction Reactions

Reagent / Starting material	$NaBH_4$ product (%)	$LiAlH_4$ product (%)
2-(Trifluoromethyl)-quinoline	—	quinaldine (28.4)
3-(Trifluoromethyl)-quinoline	3-methylquinoline (36)	3-(difluoromethyl)1,2-dihydroquinoline (71.2)
4-(Trifluoromethyl)-quinoline	—	lepidine (10.6)
6-(Trifluoromethyl)-quinoline	—	6-methylquinoline (65.5)

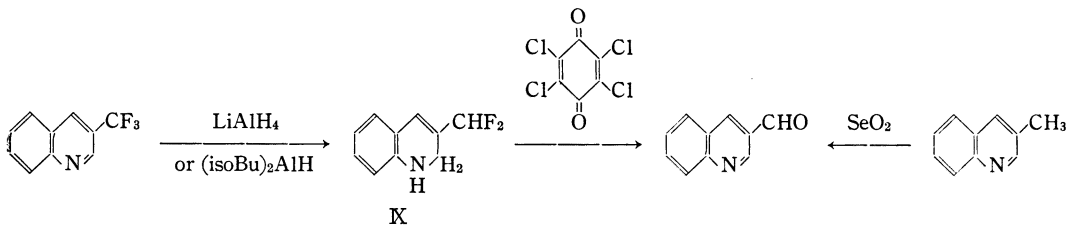

Chart 1

to 1,2-dihydroquinoline.[6] The oil obtained from this reduction was identified with IX by the comparison of IR spectra and nuclear magnetic resonance (NMR). Thus the structure of IX was proved to be 3-(difluoromethyl)-1,2-dihydroquinoline. The above results are summarized in Chart 1. On the other hand, benzotrifluoride was completely recovered in the above conditions. This fact shows that quinoline rings played an important role in these reactions.

As regards the reaction mechanism, the following observations were made and a schema shown in Chart 2 would be proposed. In the reduction by sodium borohydride, only the 3-isomer (II), which had been expected to be least sensitive to nucleophilic reagent, was reduced to 3-methylquinoline. This fact may reasonably be explained by the presence of 1,4-dihydroquinoline intermediate, which had been proposed in the case of alcoholysis of II.[1] I, III, and IV are not reactive enough to be reduced by sodium borohydride in direct hydride exchange reaction. In contrast with sodium borohydride, lithium aluminum hydride could directly reduce the trifluoromethyl group activated by quinoline rings, as shown in the results of I, III, and IV. But in the case of II, lithium aluminum hydride attacked 2-position of the quinoline ring, possibly influenced by the formation of N-Al bond. In the reaction of II with lithium aluminum hydride, reduction occurred at 2-position of the quinoline ring, which seems to be due to the intra-molecular hydride shift of the intermediate (X) formed by coordination between the vacant d-orbital of the aluminum atom and nitrogen atom. On the other hand, in the case of II and sodium borohydride, as BH_4^- has no d-orbital unlike AlH_4^-, it cannot form an intermediate like the above one with the nitrogen atom of the quinoline ring.[7] Consequently, intermolecular attack at 4-position predominates. Moreover, in the 1,2-dihydro compound, the lone pair on the nitrogen atom could not activate C–F bond as strongly as in the case of 1,4-dihydro compound; in the former, the trifluoromethyl group is present in the δ-position of the dienamine system, while in the latter, in the β-position of the enamine system. Therefore, the single fluorine atom was replaced by a hydrogen atom in the case of the intermediates (X–XIII) with lithium aluminum hydride (Chart 2.)

6) W.P. Newmann, *Liebig's Ann. Chem.*, **618**, 90 (1958).
7) J. Kuthan, J. Prochazkova, and E. Janeckova, *Coll. Czech. Chem. Comm.*, **33**, 3558 (1968).

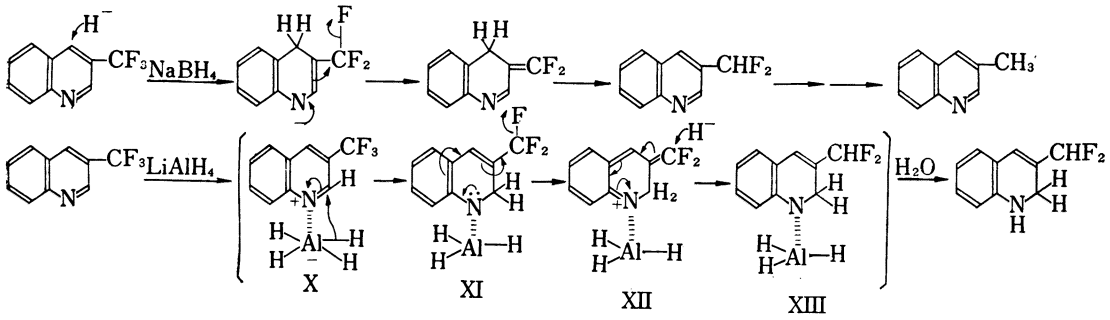

Chart 2

Experimental

Reaction of 3-(Trifluoromethyl)quinoline with $NaBH_4$——To a solution of II (500 mg) in abs. ether (30 ml), $NaBH_4$ (300 mg) was added and the mixture was refluxed for 10 hr with stirring. After the reaction mixture was cooled to room temperature, ether saturated with water was dropped into it; the precipitate was filtered off, the filtrate was washed with water, and the ether layer was dried over Na_2SO_4. Evaporation of ether gave yellow residue, the CH_2Cl_2 solution of which was submitted to chromatography over Al_2O_3. The first effluent with CH_2Cl_2 gave II (242 mg) and the second elution gave yellow liquid. Yield, 158 mg (36.4%). This compound was identified with the authentic sample of 3-methylquinoline, synthesized by Skraup method from aniline and metacroleine, by comparing IR spectra and mixture melting point of their picrates (mp 187°).

Reaction of (Trifluoromethyl)quinolines with $LiAlH_4$——i) To a solution of I (500 mg) in abs. ether (30 ml), $LiAlH_4$ (300 mg) was added and the mixture was refluxed for 10 hr. After the reaction mixture was worked up in the same manner as above, yellow liquid was obtained after the removal of ether. This oil was submitted to chromatography over Al_2O_3. From the first effluent with CH_2Cl_2, the starting material (220 mg) was recovered. The second effluent gave yellow liquid (103.2 mg), which was identified with quinaldine by comparing IR spectra and mixture melting point of their picrates (mp 190—191°).

ii) To a solution of III (300 mg) in abs. ether (30 ml), $LiAlH_4$ (200 mg) was added and the mixture was refluxed for 10 hr. After the reaction mixture was worked up as above, the yellow liquid, which was obtained after the removal of ether, was submitted to chromatography in the same manner as above. The first effluent gave the starting material (213 mg). The second effluent gave yellow liquid. Yield, 23 mg (10.6%). This substance was identified with lepidine by comparing IR spectra and mixture melting point of their picrates (mp 165—167°).

iii) To a solution of IV (282 mg) in abs. ether (30 ml), $LiAlH_4$ (200 mg) was added and the mixture was refluxed for 10 hr. After the reaction mixture was worked up as above, the yellow liquid obtained was submitted to chromatography over Al_2O_3. The first effluent with CH_2Cl_2 gave the starting material (61.2 mg). The second effluent gave yellow liquid, which was identified with 6-methylquinoline by comparing IR spectra and mixture melting point of their picrates (mp 227—228°). Yield, 132.7 mg (65.5%). NMR τ: 7.48 (CH_3); no olefinic H was detected. *Anal.* Calcd. for $C_{16}H_{12}O_7N_4$ (picrate): C, 51.62; H, 3.25; N, 15.05. Found: C, 51.56; H, 3.84; N, 14.57.

iv) To a solution of II (234 mg) in abs. ether (20 ml), $LiAlH_4$ (100 mg) was added and the mixture was refluxed for 10 hr. The reaction mixture was worked up as above. After the evaporation of the solvent *in vacuo* in nitrogen atmosphere, the residue obtained was submitted to vacuum distillation in nitrogen atmosphere to give yellow oil (bp 115°/25 mmHg). Yield, 153 mg (71.2%). IR cm^{-1}: ν_{NH} 3400 ($CHCl_3$). Mass Spectrum *m/e*: 181 (M^+), 130 ($M-CHF_2$), 51 (CHF_2).

3-(Difluoromethyl)-1,2-dihydroquinoline (IX)——To a solution of II (200 mg) in abs. benzene (10 ml) in nitrogen atmosphere, (iso-$C_4H_9)_2$-AlH (1 ml) was added and the mixture was stirred at room temperature for 2 hr and, further, at 40° for 1 hr. To the reaction mixture, a mixture of dioxane (2 ml) and H_2O (0.5 ml) was added gradually.

The precipitate was filtered and the filtrate was dried over Na_2SO_4. After the solvent was removed, the residue was submitted to chromatography over SiO_2. Effluent with CH_2Cl_2 afforded yellow oil (30 ml) of 3-(difluoromethyl)-1,2-dihydroquinoline, which was identified with the oil obtained in iv) above by comparing IR spectra.

Dehydrogenation of 3-(Difluoromethyl)-1,2-dihydroquinoline——To a solution of II (550 mg) in abs. ether (20 ml), $LiAlH_4$ (100 mg) was added, the mixture was refluxed for 10 hr, and the reaction mixture was worked up as above. After the removal of the solvent, the residue was dissolved in benzene. To the

solution chloranil (400 mg) was added and the mixture was refluxed for 4 hr. The crystals precipitated by cooling were filtered off and the benzene layer was shaken with aq. solution of Na_2CO_3 and dried over Na_2SO_4. After the removal of benzene, CH_2Cl_2 was added to give dark purple residue and the solution was submitted to chromatography over SiO_2. The effluent gave green oil (161 mg), which crystallized when kept standing for 2 days. mp, 188—190°. IR cm^{-1}: $\nu_{C=O}$ 1690 (KBr); ν_{NH} was not detected. Mass Spectrum *m/e*: 157 (M^+). This compound was identified with 3-quinolinealdehyde, which was obtained by oxidation of 3-methylquinoline with selenium dioxide, by comparing IR spectra and mixture melting point.

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