Chem. Pharm. Bull. 29(11)3130—3133(1981)

Reaction of 1,2,3,4-Tetrahydroquinazolin-4-ones with Acid Anhydride. IV[1)]

Jiroh Horiuchi, Yasuo Takeuchi, and Masatoshi Yamato*

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700, Japan

(Received April 20, 1981)

The reaction of 2-substituted 1-methyl-1,2,3,4-tetrahydroquinazolin-4-ones (THQ) with acetic anhydride afforded two types of products depending on the number of C_2-substituents. The reaction of 2-monosubstituted 1-methyl-THQ (**6**) gave the corresponding N_3-acetyl-THQ derivatives (**7**), while the reaction of 2,2-disubstituted 1-methyl-THQ (**8**) afforded rearranged products, 2,3-disubstituted 1-methyl-1,4-dihydroquinolin-4-ones (**9**). A mechanism is proposed for the reaction of **8** to give **9**.

Keywords——1,2,3,4-tetrahydroquinazolin-4-ones; acetic anhydride; 1,4-dihydroquinolin-4-ones; acetylation; rearrangement

We recently found that the reaction of 1-benzyl-1′-methylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**1**) with acetic anhydride and pyridine gives 2-benzyl-5-methyl-1,2,3,4,5,10-hexahydrobenzo[*b*]-[1,6]-naphthyridin-10-one (**2**), while a similar reaction of 1-benzylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinazolin)]-4′-one (**3**) gives another type of product, 1-(1-benzyl-1,2,5,6-tetrahydro-4-pyridyl)-2-methyl-1,4-dihydroquinazolin-4-one (**4**).[3)]

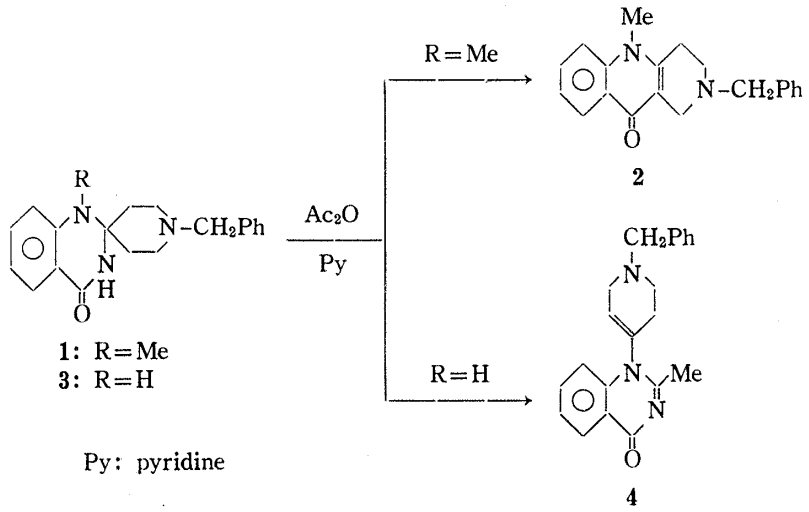


Chart 1

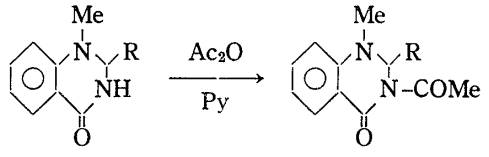
In a subsequent study on the reaction of 1,2,3,4-tetrahydroquinazolin-4-one (THQ) derivatives with acetic anhydride, it was found that various types of products were obtained depending on the presence or absence of the N_1-substituent and the kind and number (one or two) of the C_2-substituents of THQ derivatives. We previously reported the reaction of 1-unsubstituted THQ derivatives.[1)]

In the present work, we examined the reaction of 1,2-disubstituted or 1,2,2-trisubstituted THQ derivatives and found that the corresponding N_3-acetyl-THQ derivatives or the rearranged products, 1,4-dihydroquinolin-4-ones, were obtained depending on the number (one or two) of C_2-substituents.

NII-Electronic Library Service

2-Substituted 1-methyl-THQ derivatives were prepared by stirring of a mixture of 2-methylaminobenzamide (**5**)[4] with various aldehydes or ketones according to the method of Böhme and Böing.[5] The preparation of **5** was successfully carried out by sodium borohydride reduction of 2-aminobenzamide in the presence of formaldehyde.

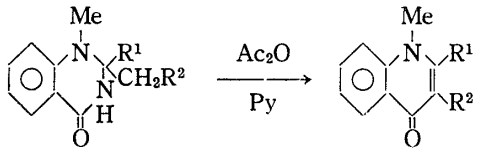
The formation of N_3-acetyl-THQ derivatives was observed in the reaction of 2-monosubstituted 1-methyl-THQ derivatives. For example, heating of 1-methyl-2-phenyl-THQ (**6a**)[6] with acetic anhydride and pyridine at 100°C for 2 h afforded 3-acetyl-1-methyl-2-phenyl-THQ (**7a**)[2] in 85% yield. Similarly, 1-methyl-2-phenethyl-THQ (**6b**)[7] afforded 3-acetyl-1-methyl-2-phenethyl-THQ (**7b**) in 65% yield, and 1,2-dimethyl-THQ (**6c**)[8] gave 3-acetyl-1,2-dimethyl-THQ (**7c**)[2] in 97% yield (Chart 2).



6 **7**

a: R=Ph
b: R=CH_2CH_2Ph
c: R=Me

Chart 2



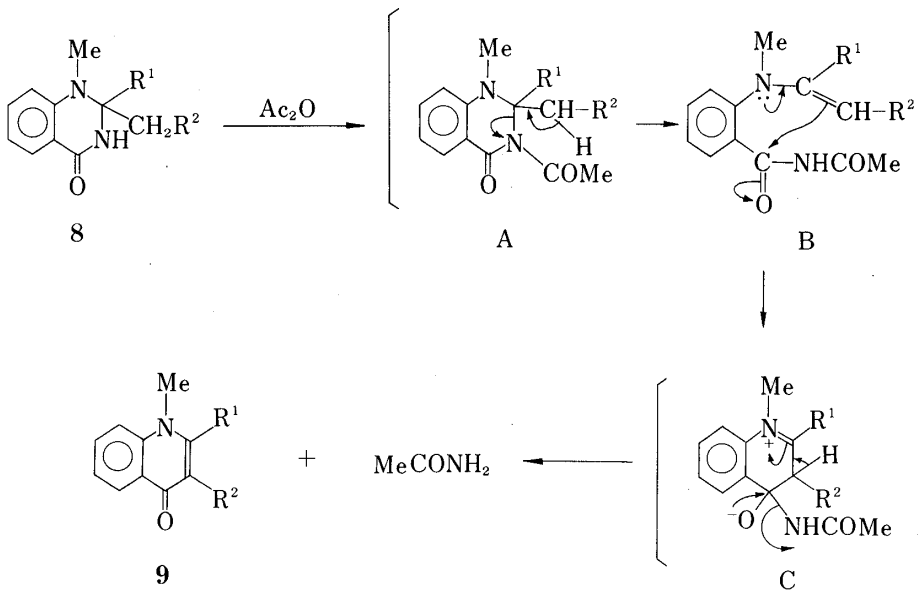
8 **9**

a: R^1=CH_2Ph, R^2=Ph
b: R^1=Et, R^2=Ph
c: R^1=Me, R^2=CH_2Ph

Chart 3

These results are similar to those of the reaction of 2-monosubstituted THQ derivatives, which gave the corresponding N_1,N_3-diacetyl-THQ derivatives.[1] These 2-monosubstituted N-acetyl-THQ derivatives are stable since the steric repulsion by the C_2-substituents might be relatively small.

The reaction of 2,2-disubstituted 1-methyl-THQ derivatives (**8**) gave rearranged products, 1,4-dihydroquinolin-4-ones (**9**). For example, heating of 2,2-dibenzyl-1-methyl-THQ (**8a**) with acetic anhydride and pyridine at 100°C for 4 h afforded 2-benzyl-1-met 1,4-dihydroquinolin-4-one (**9a**) in 51% yield. Similarly, 2-ber yl-1 (**8b**) gave 2-ethyl-1-methyl-3-phenyl-1,4-dihydroquinolin-4-one (**9b** yi dimethyl-2-phenethyl-THQ (**8c**) gave 3-benzyl-1,2-dimethyl-1,4-d inolin-4-one (**9c**) in 38% yield (Chart 3).



8 A B **9** C

Chart 4

NII-Electronic Library Service

The formation of **9** from **8** might occur by a path similar to that of **2** from **1**, and the mechanism is proposed to be as shown in Chart 4.

An enamine intermediate (B) might be initially formed by N_3-acetylation and successive ring cleavage, and might then be further converted into **9** by cyclization and subsequent elimination of acetamide. The results of reaction of **8a**—**c** suggested that the nature of the C_2-substituents might contribute to the stability of the intermediate (B), since the reaction of **8a,b** (having a C_2-benzyl group) gave a higher yield of **9a,b** than that of **8c** (having a C_2-phenethyl group).

An analogous reaction has been reported: the reaction of 1-unsubstituted 2,2-disubstituted THQ, in which one of the substituents is a carbamoylmethyl group, gave 3-carbamoyl-1,4-dihydroquinolin-4-ones. For example, 2-methyl-2-(N-phenyl)carbamoylmethyl-THQ gave 2-methyl-3-(N-phenyl)carbamoyl-1,4-dihydroquinolin-4-one.[1] The reaction mechanism might be similar to those of 2,2-disubstituted 1-methyl-THQ derivatives (**8**) as regards the formation of an enamine as an intermediate in view of the lability of the protons of the C_2-substituents.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken with a Hitachi R-24 spectrometer at 60 MHz, with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 spectrometer, and infrared absorption (IR) spectra on a Nipponbunko A-102 spectrometer.

2-Methylaminobenzamide (**5**)——2-Aminobenzamide powder (5 g) was added to a solution of 37% formaldehyde (9 ml) in EtOH (300 ml) in small portions, and the mixture was stirred at room temperature for 5 h. After excess formaldehyde had been removed *in vacuo*, $NaBH_4$ (3 g) was added to the residual solution. The solution was stirred at room temperature for 0.5 h and acidified with 10% HCl, then made basic with 10% NaOH to give a precipitate of **5** (5 g, 91%), which was recrystallized from MeOH, mp 160—161°C (162°C).[3] Compound **5** was identified by comparison of its NMR and IR spectra with those of an authentic sample.

3-Acetyl-1-methyl-2-phenethyl-1,2,3,4-tetrahydroquinazolin-4-one (**7b**)——A mixture of **6b**[6] (1 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 100°C for 12 h. Most of the acetic anhydride and pyridine was evaporated off *in vacuo*, and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 10% NaOH and H_2O, dried over $MgSO_4$, and concentrated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel with CH_2Cl_2 gave 0.75 g (65%) of **7b** as a colorless oil. *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.12; H, 6.52; N, 9.13. IR ν_{max}^{Nujol} cm^{-1}: 1690, 1610. NMR ($CDCl_3$) δ: 1.83—2.35 (2H, m, $C\underline{H}_2CH_2Ph$), 2.61 (3H, s, $COCH_3$), 2.43—2.81 (2H, m, $C\underline{H}_2Ph$), 3.04 (3H, s, NCH_3), 5.93 (1H, t, $J=7$ Hz, C_2–H). MS *m/e*: 308 (M^+).

2,2-Dibenzyl-1-methyl-1,2,3,4-tetrahydroquinazolin-4-one (**8a**)——A mixture of **5** (5 g) and dibenzyl ketone (7 g) was heated at 180°C for 15 h. The resulting product was chromatogrophed on a column of silica gel with CH_2Cl_2 to give 1.4 g (12%) of **8a**, mp 197—200°C. *Anal.* Calcd for $C_{23}H_{22}N_2O$: C, 80.67; H, 6.48; N, 8.18. Found: C, 80.47; H, 6.48; N, 7.91. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1655. NMR ($CDCl_3$) δ: 2.95 (3H, s, NCH_3), 3.22 (4H, d, $J=6$ Hz, $C\underline{H}_2Ph$), 7.92—8.12 (1H, broad s, NH). MS *m/e*: 342 (M^+).

2-Benzyl-2-ethyl-1-methyl-1,2,3,4-tetrahydroquinazolin-4-one (**8b**)——A mixture of **5** (3 g), methyl phenethyl ketone (3 g), and *p*-TsOH (catalytic amount) was heated at 140°C for 6 h. The resulting product was chromatographed on a column of silica gel with CH_2Cl_2 to give 2.8 g (50%) of **8b**, mp 174—176°C. *Anal.* Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.98; H, 7.17; N, 10.15. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1660. NMR (DMSO-d_6) δ: 0.89 (3H, t, $J=7$ Hz, $CH_2C\underline{H}_3$), 1.24—2.37 (2H, m, $C\underline{H}_2CH_3$), 2.86 (3H, s, NCH_3), 2.97 (2H, d, $J=7$ Hz, $C\underline{H}_2Ph$), 8.04 (1H, broad s, NH). MS *m/e*: 280 (M^+).

1,2-Dimethyl-2-phenethyl-1,2,3,4-tetrahydroquinazolin-4-one (**8c**)——A mixture of **5** (5 g) and benzylacetone (5 g) was heated at 180°C for 15 h. The resulting product was chromatographed on a column of silica gel with benzene to give 2.2 g (24%) of **8c**, mp 117—118°C. *Anal.* Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.05; H, 7.26; N, 10.07. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1655. NMR (DMSO-d_6) δ: 1.38 (3H, s, C_2–CH_3), 1.75—2.30 (2H, m, $C\underline{H}_2CH_2Ph$), 2.55—2.73 (2H, m, $C\underline{H}_2Ph$), 2.80 (3H, s, NCH_3), 8.21—8.39 (1H, broad s, NH). MS *m/e*: 280 (M^+).

2-Benzyl-1-methyl-3-phenyl-1,4-dihydrquinolin-4-one (**9a**)——A mixture of **8a** (0.5 g), acetic anhydride (5 ml), and dry pyridine (0.5 ml) was heated at 100°C for 3 h. After removal of the acetic anhydride *in vacuo*, the residue was recrystallized from a mixture of benzene and cyclohexane to give 0.24 g (51%) of **9a**, mp 203—206°C. *Anal.* Calcd for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.63; H, 5.77; N, 4.13. IR ν_{max}^{Nujol} cm^{-1}: 1620. NMR ($CDCl_3$) δ: 3.56 (3H, s, NCH_3), 4.20 (2H, s, $C\underline{H}_2Ph$). MS *m/e*: 325 (M^+).

NII-Electronic Library Service

2-Ethyl-1-methyl-3-phenyl-1,4-dihydroquinolin-4-one (**9b**)——A mixture of **8b** (1 g), acetic anhydride (10 ml), and dry pyridine (1 ml) was heated at 100°C for 4 h. After removal of the acetic anhydride and pyridine *in vacuo*, the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 10% NaOH and H_2O and concentrated *in vacuo* to give 0.52 g (55%) of **9b**, mp 203—205°C. *Anal.* Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.80; H, 6.18; N, 5.16. IR ν_{max}^{Nujol} cm^{-1}: 1615. NMR ($CDCl_3$) δ: 1.09 (3H, t, $J=8$ Hz, $CH_2\underline{CH_3}$), 2.64 (2H, q, $J=8$ Hz, $\underline{CH_2}CH_3$), 3.71 (3H, s, NCH_3). MS *m/e* 263 (M^+).

3-Benzyl-1,2-dimethyl-1,4-dihydroquinolin-4-one (**9c**)——A mixture of **8c** (0.28 g), acetic anhydride (5 ml), and dry pyridine (1 ml) was heated at 120°C for 5 h. After removal of the acetic anhydride and pyridine *in vacuo*, the residue was recrystallized from a mixture of benzene and cyclohexane to give 0.09 g (38%) of **9c**, mp 215—216°C. *Anal.* Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.52; N, 5.32. Found: C, 82.05; H, 6.38; N, 5.27. IR ν_{max}^{Nujol} cm^{-1}: 1615. NMR ($CDCl_3$) δ: 2.34 (3H, s, C_2–CH_3), 3.60 (3H, s, NCH_3), 4.07 (2H, s, $\underline{CH_2}Ph$). MS *m/e* 263 (M^+).

References and Notes

1) Part III: M. Yamato, J. Horiuchi, and Y. Takeuchi, *Chem. Pharm. Bull.*, **29**, 3124 (1981).
2) M. Yamato, J. Horiuchi, and Y. Takeuchi, *Chem. Pharm. Bull.*, **29**, 3055 (1981).
3) M. Yamato, J. Horiuchi, and Y. Takeuchi, *Chem. Pharm. Bull.*, **28**, 2623 (1980).
4) I.M. Heilbron, F.N. Kitchen, E.B. Parkes, and G.D. Sutton, *J. Chem. Soc.*, **127**, 2167 (1925).
5) H. Böhme and H. Böing, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **293**, 1011 (1960).
6) M. Hans and S.M. Christian, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **309**, 572 (1976).
7) M. Hans and S.M. Christian, *ibid*, **309**, 503 (1976).
8) D. Chakravarti, R.N. Chakravarti, L.A. Cohen, B. Dasgupta, S. Datta, and H.K. Miller, *Tetrahedron*, **16**, 224 (1961).

NII-Electronic Library Service