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Transformation of Quinazoline into 2(1*H*)-Quinolinones with Alkanoic Anhydrides

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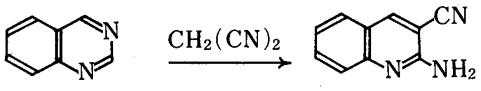
Quinazoline (**1**) was transformed into 3-substituted 2(1*H*)-quinolinones (**4**) by reaction with alkanoic anhydrides (**3**). Similar transformation was also found to occur with 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium iodide (**9**), giving 5-substituted 1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-6-yl alkanoates (**10**).

Keywords——quinazoline; quinolinone; alkanoic anhydride; ring transformation; pyrazolopyrimidinium salt; pyrazolopyridine

In the previous paper,[1] we reported that quinazoline (**1**), on treatment with active methylene compounds in the absence of a base catalyst, was transformed into quinolines. For example, **1** reacted with malononitrile to give 2-amino-3-quinolinecarbonitrile (**2**) in a good yield, as shown in Chart 1.

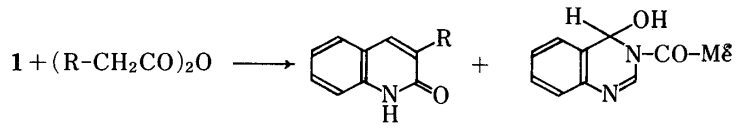


1 **2**

Chart 1

It was expected that use of alkanoic anhydrides (**3**) instead of active methylene compounds in the above reaction might lead to a similar ring transformation. In fact, we found that the reaction of **1** with **3** resulted in the ring transformation, giving 3-substituted 2(1*H*)-quinolinones (**4**). In the present paper, we describe in detail our investigation of the transformation.

When **1** was refluxed with anhydrides (**3a**—**c**) for 2 h, the corresponding **4a**—**c** were obtained, although the yields were unsatisfactory. In the case of acetic anhydride (**3a**), 3-acetyl-3, 4-dihydro-4-hydroxyquinazoline (**5**) was isolated together with 2(1*H*)-quinolinone (**4a**). The results are summarized in Chart 2.



3	R	4	yield (%)	5	yield (%)
3a	H	**4a**	18	5	34
3b	Me	**4b**	15		
3c	Et	**4c**	75		

Chart 2

Compounds **4a**—**c**[2] showed undepressed melting points on admixture with the corresponding authentic samples.

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The structure of **5** was suggested by the elemental analysis, and confirmed by analyses of the infrared absorption (IR), proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra. On hydrolysis or thermal decomposition, **5** was easily convertible into **1**. Moreover, on reaction with alumina in the presence of water, **5** gave 2′-formylformanilide (**6**) as a minor product and **1** as a major product.

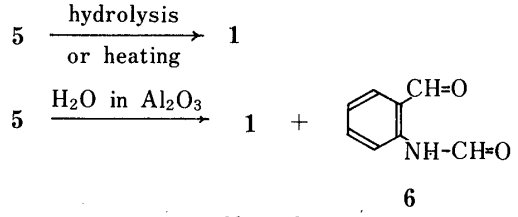

Chart 3

The mechanism of this ring transformation is assumed to involve sequential nucleophilic addition of **3**, ring fission and ring closure, as shown in Chart 4. This is similar to a mechanism[1] reported for the transformation of **1** with active methylene compounds. On the other hand, addition of acetate ion to the initially formed 3-acetylquinazolinium intermediate (G) leads to **5** *via* an intermediate (H).

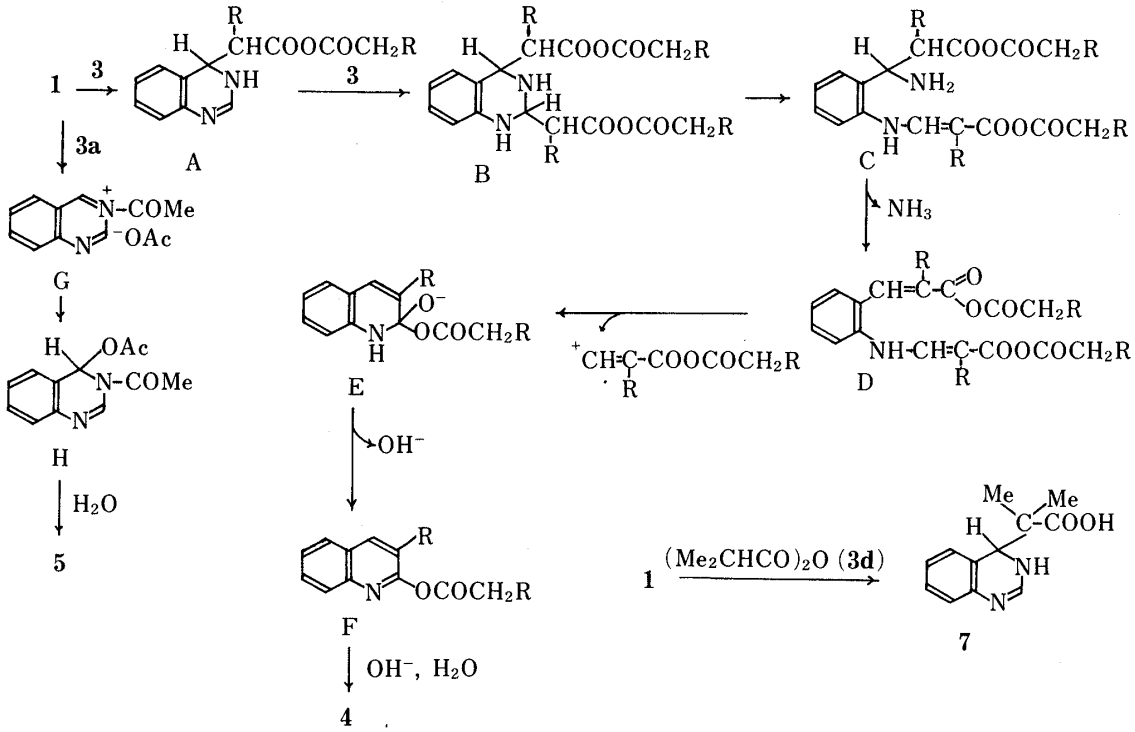

Chart 4

On the basis of our mechanism, it can be assumed that isobutyric anhydride (**3d**) might undergo the addition reaction, but the reaction would not proceed further, because **3d** has only one hydrogen present at the α position. In fact, under the same conditions as used for the transformation, **3d** gave only the addition product, α,α-dimethyl-3,4-dihydro-4-quinazolineacetic acid (**7**), which corresponds to intermediate (A) in Chart 4.

In order to establish the generality of the ring transformation with **3**, another fused pyrimidine ring system was examined. When 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8**)[3] was refluxed with **3a** for 2 h, no reaction product was isolated, and **8** was recovered in good yield. However, in the absence of alkali treatment during work-up of the reaction mixture, the reaction of more electrophilic 5-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidinium iodide

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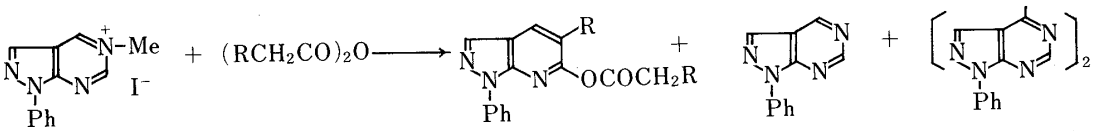
(**9**)[4] resulted in ring transformation to give 5-substituted 1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-6-yl alkanoates (**10a**—**c**), corresponding to intermediate (F) in Chart 4, together with **8** and a trace of 4,4′-bi[1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine] (**11**).[5] The results are summarized in Chart 5.



9	**3** R	**10** yield (%)	**8** yield (%)	**11** yield (%)
	3a H	**10a** 11	**8** 22	**11** trace
	3b Me	**10b** 4	**8** 43	**11** trace
	3c Et	**10c** 11	**8** 40	**11** trace

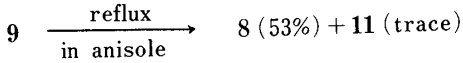


Chart 5

It is assumed that compounds **8** and **11** were formed through thermal decomposition of **9**. In fact, when a solution of **9** in anisole was refluxed for 2 h, **8** was obtained in 53% yield together with a trace of **11**. The structures of **10a**—**c** were suggested by the elemental analyses, and confirmed by analyses of IR, ^{1}H- and ^{13}C-NMR spectra, as described in the experimental section.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Jasco IRA-1 grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24 high-resolution NMR spectrometer, and ^{13}C-NMR spectra were taken at 90 MHz on a JEOL JNM-FX90Q FTNMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, m = multiplet, and br s = broad singlet.

Reaction of 1 with 3——A mixture of **1** (50 mg) and **3** (1000 mg) was refluxed for 2 h. After removal of the excess **3** under reduced pressure, the reaction mixture was poured into a large amount of ice–H_2O mixture, neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and concentrated to dryness. In the case of **3a**, the residue was dissolved in benzene, and allowed to stand overnight in a refrigerator. The deposited **5** was filtered off, and purified by recrystallization from benzene.

The residue (the filtrate in the case of **3a**) was chromatographed on a column of SiO_2 with benzene and $CHCl_3$. The $CHCl_3$ eluate gave **4**, which was recrystallized from ethyl acetate.

2(1*H*)-Quinolinone (**4a**)[2a]: mp 200 °C, colorless needles, yield 18% (100 mg).

3-Methyl-2(1*H*)-quinolinone (**4b**)[2b]: mp 233 °C, colorless needles, yield 15% (90 mg).

3-Ethyl-2(1*H*)-quinolinone (**4c**)[2c]: mp 170 °C, colorless needles, yield 75% (500 mg).

3-Acetyl-3,4-dihydro-4-hydroxyquinazoline (**5**): mp 153 °C, colorless scales, yield 34% (250 mg). *Anal.* Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.15; H, 5.29; N, 14.51. IR ν_{max}^{KBr} cm^{-1}: 3070 (OH), 1720 (C=O). ^{1}H-NMR ($(CD_3)_2SO$): 3.30 (3H, s, CH_3), 6.50 (1H, dd, $J_{4,2}=1.2$ Hz, $J_{4,OH}=7.6$ Hz, C^4-H), 6.78 (1H, d, $J_{4,OH}=7.6$ Hz, exchangeable with D_2O, C^4-OH), 7.1—7.3 (4H, m, aromatic H), 8.17 (1H, d, $J_{2,4}=1.2$ Hz, C^2-H). ^{13}C-NMR ($(CD_3)_2SO$): 21.86 (q), 71.87 (d), 125.40 (d), 125.99 (s), 126.58 (d), 127.84 (d), 129.19 (d), 139.32 (s), 140.51 (d), 171.23 (s).

Alkaline Hydrolysis of 5——A mixture of **5** (330 mg) and 10% NaOH (6 ml) was stirred at room temperature for 1.5 h. The reaction mixture was poured onto a large amount of ice, neutralized with AcOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2 with benzene. The benzene eluate gave **1**, which was recrystallized from petr. ether to give colorless needles, mp 48 °C, in 84% yield (190 mg).

Acid Hydrolysis of 5——A mixture of **5** (120 mg) and 1 N HCl (1.5 ml) was stirred overnight at room temperature. The reaction mixture was neutralized with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and passed through a column of SiO_2 to remove impurities. Compound **1** was obtained in 61%

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yield (50 mg).

Thermal Decomposition of 5——Compound **5** (230 mg) was heated at 165 °C for 3 h in a testtube, then allowed to cool. The reaction mixture was chromatographed on a column of SiO_2 with benzene. The benzene eluate gave **1** in 64% yield (100 mg).

Reaction of 1 with 3d——A mixture of **1** (500 mg) and **3d** (1000 mg) was refluxed for 2 h. After removal of the excess **3d**, the reaction mixture was poured onto a large amount of ice, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ then MeOH as eluents. The MeOH eluate gave **7**, which was recrystallized from EtOH to give colorless granules, mp above 300 °C, in 27% yield (230 mg). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.70; H, 6.44; N, 12.70. IR ν_{max}^{KBr} cm^{-1}: 2300—2950 ($=NH_2^+$ and OH), 1680 (C=O). ^{1}H-NMR (CF_3COOD): 1.30 (3H, s, CH_3), 1.40 (3H, s, CH_3), 5.25 (1H, s C^4-H), 6.94—7.54 (4H, m, aromatic H), 8.10 (1H, s, C^2-H).

Reaction of 9 with 3——A mixture of **9** (1000 mg, 3.0 mmol) and **3** (40 mmol) was refluxed for 2 h. After removal of the excess **3** under reduced pressure, the reaction mixture was poured onto a large amount of ice, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4, and concentrated to dryness. The residue was chromatographed on a column of SiO_2 with benzene then $CHCl_3$–AcOEt as eluents. The first fraction with benzene gave **10** which was recrystallized from petr. ether. The second fraction gave **8**, which was recrystallized from petr. ether to give colorless needles, mp 77—81 °C. The eluate with $CHCl_3$–AcOEt gave **11**, which was recrystallized from benzene to give yellow needles, mp 289 °C.

The yields of **10a—c**, **8**, and **11** are shown in Chart 5.

1-Phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl Acetate (**10a**): mp 97 °C, colorless needles. *Anal.* Calcd for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.00; H, 4.41; N, 16.26. IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). ^{1}H-NMR ($CDCl_3$): 2.30 (3H, s, CH_3), 6.83 (1H, d, $J_{4,5}=8.2$ Hz, C^5-H), 7.08—8.28 (7H, m, aromatic H). ^{13}C-NMR ($CDCl_3$): 21.02 (q), 110.80 (d), 115.57 (s), 121.09 (d), 126.08 (d), 128.84 (d), 132.80 (d), 133.66 (d), 139.03 (s), 147.18 (s), 156.85 (s), 168.55 (s).

5-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl Propionate (**10b**): mp 63.5 °C, colorless scales. *Anal.* Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.27; H, 5.42; N, 14.95. IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). ^{1}H-NMR ($CDCl_3$): 1.30 (3H, t, $J=7.0$ Hz, $CH_2\underline{CH_3}$), 2.23 (3H, s, Ar-CH_3), 2.71 (2H, q, $J=7.0$ Hz, CO-$\underline{CH_2}CH_3$), 7.11—8.24 (7H, m, aromatic H).

5-Ethyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl Butyrate (**10c**): mp 70 °C, colorless needles. *Anal.* Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.76; H, 6.19; N, 13.63. IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). ^{1}H-NMR ($CDCl_3$): 1.10 (3H, t. $J=7.0$ Hz, $CH_2\underline{CH_3}$), 1.25 (3H, t. $J=7.0$ Hz, $CH_2\underline{CH_3}$), 1.80 (2H, m, $CH_2\underline{CH_2}CH_3$), 2.64 (2H, q, $J=7.0$ Hz, Ar-$\underline{CH_2}CH_3$), 2.66 (2H, q, $J=7.0$ Hz, CO-$\underline{CH_2}$-CH_2), 7.10—8.29 (7H, m, aromatic H).

Thermal Decomposition of 9——A mixture of **9** (1000 mg) and anisole (2000 mg) was refluxed for 2 h, then allowed to cool. The precipitate was collected by filtration to recover **9** in 12% yield (120 mg). After removal of the excess anisole from the filtrate under reduced pressure, the residue was dissolved in MeOH. The insoluble crystals were collected by filtration to give a trace of **11**. The MeOH filtrate was concentrated to dryness to give **8** in 53% yield (310 mg).

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