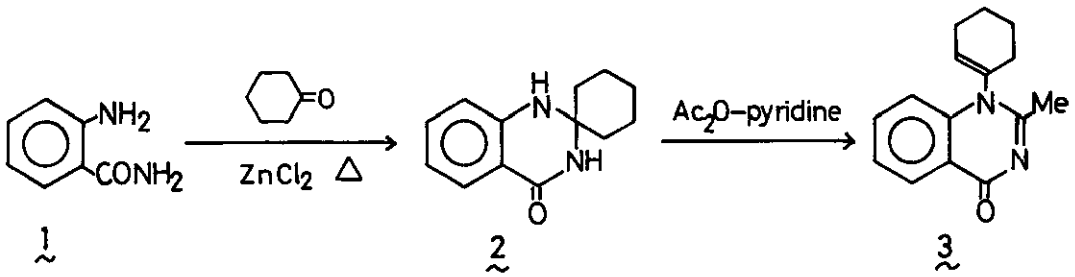
SYNTHESIS OF 1,2-DIPHENYLPYRROLO[1,2-a]QUINAZOLINES

Jiroh Horiuchi
Central Research Institute, Kantoishi Pharmaceutical Co. Ltd., 1780 Kitano, Tokorozawa 359, Japan
Masatoshi Yamato
Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka, 1-1-1, Okayama 700, Japan
Nobuya Katagiri and Tetsuzo Kato*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract —— Heating of 2-aminobenzamide (1) with benzoin (4) in the presence of anhydrous zinc chloride gave 2-(1-benzoyl-benzylamino)benzamide (5a) which, on treatment with acetic anhydride, was transformed to 1,2-diphenyl-4,5-dihydropyrrolo-[1,2-a]quinazolin-5-one (6).

Previously, we have reported the reaction of 2-aminobenzamide (1) with ketones to give 2,2-disubstituted 1,2,3,4-tetrahydroquinazolin-4-one.[1,2] For instance, heating of compound 1 with cyclohexanone in the presence of anhydrous zinc chloride afforded the 2-spiro compound (2), which, on treatment with acetic anhydride in pyridine, was transformed to 1-cyclohexenyl-2-methyl-1,4-dihydro-quinazolin-4-one (3).



1 2 3

As a continuation of this study, we investigated similar reaction of 2-aminobenzamide (1) with benzoin (4). Though the objective 2,2-disubstituted tetrahydroquinazoline corresponding to compound 2 could not be detected, the reaction gave the product (5a), which subsequently underwent cyclization, on treatment with acetic anhydride, to give the pyrrolo[1,2-a]quinazoline (6).

When a mixture of benzoin (4) and an equimolar amount of 2-aminobenzamide (1) was heated at 120 °C in the presence of anhydrous zinc chloride, 2-(1-benzoylbenzylamino)benzamide (5a)[3] was obtained, in 38% yield, colorless plates (from MeOH), m.p. 188 - 191 °C; $\nu_{max.}$ (KBr) 3 450 - 3 300, 1 680, and 1 640 cm^{-1}; ^{13}C-nmr δ (DMSO-d_6) 60.88 (d, -CH<), 171.79 (s, -$CONH_2$), and 196.80 (s, COPh); *m/e* 330 (M^+) and 225 (M^+-COPh).

Heating of 5a in acetic anhydride at 110 °C for 5 h gave 2-(1-benzoylbenzylamino)benzonitrile (5b), colorless prisms (from MeOH), m.p. 134 - 135 °C, and yellow needles (6) (from MeOH) of m.p. >300 °C in 34% and 64% yields, respectively. 5b: $\nu_{max.}$ (KBr) 3 350, 3 050, 2 210, and 1 675 cm^{-1}; ^{13}C-nmr δ ($CDCl_3$) 62.24 (d, -CH<), 117.47 (s, -CN), and 195.31 (s, COPh); *m/e* 312 (M^+).

Compound 6 was assigned to be 1,2-diphenyl-4,5-dihydropyrrolo[1,2-a]quinazolin-5-one on the basis of elemental analyses and spectroscopic data. 6: Found: C, 82.26; H, 4.76; N, 8.23. $C_{23}H_{16}N_2O$ requires C, 82.12; H, 4.79; N, 8.33; $\nu_{max.}$ (KBr) 1 670 cm^{-1} (CO); ^{1}H-nmr δ (DMSO-d_6) 5.87 (s, pyrrole ring proton); ^{13}C-nmr δ (DMSO-d_6) 88.51 (d, pyrrole-C_3) and 157.04 (s, CO); *m/e* 336 (M^+).

Compound 6 was heated in phosphoryl chloride at 100 °C for 1 h. Purification of the product by silica gel column chromatography afforded a 75% yield of 5-chloro-1,2-diphenylpyrrolo[1,2-a]quinazoline (7a), m.p. 193 °C (dec.) (from AcOEt), and a 20% yield of the bis-derivative (8), yellow powder (from benzene) of m.p. 300 °C. 7a: ^{1}H-nmr δ ($CDCl_3$) 6.92 (1H, s, 3-H) and 8.15 (1H, m, 6-H); ^{13}C-nmr δ (DMSO-d_6) 102.79 (d, 3-C) and 136.32 (s, 5-C); *m/e* 354 (M^+) and 356 (M^++2). 8: ^{13}C-nmr δ (DMSO-d_6) 102.11 (d, 3'-C) and 103.96 (s, 3-C); *m/e* 672 (M^+) and 674 (M^++2).

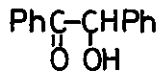
Similar treatment of compound 6 with an equimolar amount of phosphorus pentachloride afforded 3,5-dichloro-1,2-diphenylpyrrolo[1,2-a]quinazoline (7b), yellow needles (from MeOH) of m.p. 276 - 280 °C; ^{1}H-nmr δ (DMSO-d_6) 8.12 (1H, m, 6-H); ^{13}C-nmr δ (DMSO-d_6) 103.50 (s, 3-C) and 139.30 (s, 5-C); *m/e*

388 (M^+), 390 (M^++2), and 392 (M^++4).

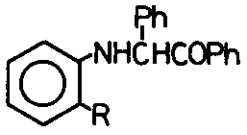
In the ^{1}H-nmr spectrum of 7b, the signal due to the proton at C_3-position was not detected. Upon catalytic reduction with Pd-C in methanol, compound 7a was transformed to 1,2-diphenyl-1,2,3,5-tetrahydropyrrolo[1,2-a]quinazolin-5-one (9) in 67% yield, pale yellow needles (from EtOH) of m.p. 280 °C (dec.); $\nu_{max.}$ ($CHCl_3$) 1 645 cm^{-1} (C=O); ^{1}H-nmr δ ($CDCl_3$) 3.0 - 4.9 (3H, m, 2,3-Hs) and 5.84 (1H, d, J = 8 Hz, 1-H); ^{13}C-nmr δ (DMSO-d_6) 38.83 (t, 3-C), 44.31 (d, 2-C), 67.18 (d, 1-C), 166.20 (s, 3a-C), and 168.20 (s, 5-C); m/e 338 (M^+).

The configuration of 9 was not determined.

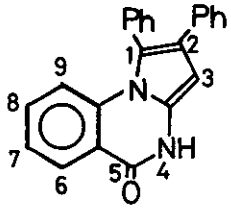
Catalytic reduction of compound 7a with Pd-C in methanol in the presence of magnesium oxide gave 1,2-diphenylpyrrolo[1,2-a]quinazoline (7c) in a quantitative yield, yellow needles (from MeOH) of m.p. 203 °C; ^{1}H-nmr δ ($CDCl_3$) 7.02 (1H, s, 3-H) and 8.48 (1H, s, 5-H); ^{13}C-nmr δ (DMSO-d_6) 102.40 (d, 3-C), 122.93 (s, 2-C), 127.48 (s, 1-C), 138.14 (s, 3a-C), and 146.32 (d, 5-C); m/e 320 (M^+).



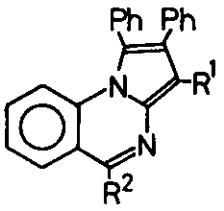
4



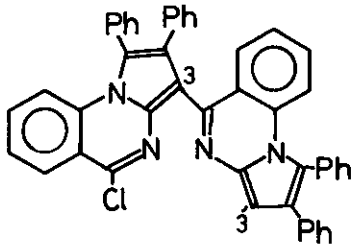
5 a : R=CONH$_2$
b : R=CN



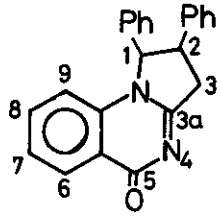
6



7 a : R^1=H, R^2=Cl
b : R^1=R^2=Cl
c : R^1=R^2=H



8



9

Acknowledgement

We thank Mrs. C. Koyanagi and Mr. K. Kawamura of the Central Analysis Room of Pharmaceutical Institute, Tohoku University, for elemental analyses and mass spectral measurements, respectively.

References and Notes

1. M. Yamato, J. Horiuchi, and Y. Takeuchi, *Chem. Pharm. Bull.*, 1980, 28, 2623.
2. M. Yamato, J. Horiuchi, and Y. Takeuchi, *Chem. Pharm. Bull.*, 1981, 29, 3055.
3. Satisfactory analytical data were obtained for all new compounds herein reported.

Received, 23rd October, 1981