Polycyclic *N*-Hetero Compounds. XIX. Synthesis of Novel Meso-ionic Benz[*h*]imidazo[1,2-*c*]quinazoline and Benzo[*h*]pyrrolo[1′,2′:3,4]imidazo[1,2-*c*]quinazoline Derivatives

Takashi Hirota*, Kimiko Katsuta, Tetsuto Namba, Kenji Sasaki and Shōhei Hayakawa

Faculty of Pharmaceutical Sciences, Okayama University,
Okayama, 700, Japan

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Benz[*h*]imidazo[1,2-*c*]quinazolinium-1-olate (**5**) and benzo[*h*]pyrrolo[1′,2′:3,4]imidazo[1,2-*c*]quinazolinium-8-olate (**9**) having novel meso-ionic ring systems were synthesized by the reaction of *N*-(5,6-dihydrobenzo[*h*]-quinazolin-4-yl)amino acids with acetic anhydride.

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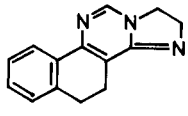
1,2,4,5-Tetrahydrobenz[*h*]imidazo[1,2-*c*]quinazoline (**1**) having a 11,13,15-triazasteroidal skeleton, which was synthesized in our laboratory [1], exhibited an antidepressive activity with a moderate toxicity in mice [2]. During the course of our chemical modification of **1**, we have reported the synthesis of a 16-substituted 11,13,15-triazasteroidal



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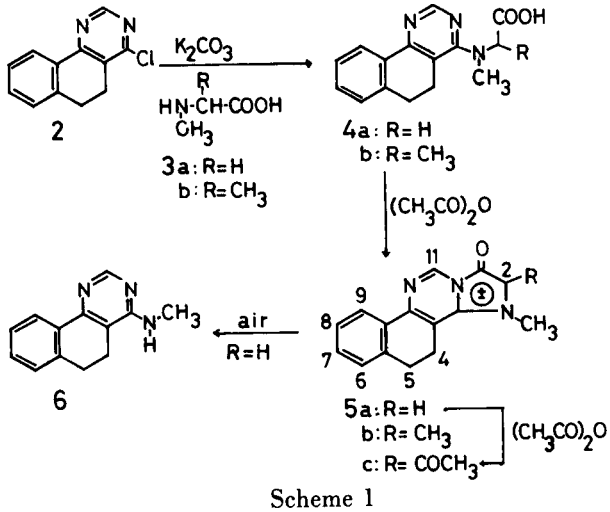
Structure 1

skeleton with an oxygen function at 17-position by the reaction of *N*-(5,6-dihydrobenzo[*h*]quinazolin-4-yl)amino acid with acetic anhydride [3]. The successful synthesis of this skeleton has prompted us to investigate whether the cyclization of the *N*-alkylated derivative of this amino acid with acetic anhydride can produce a meso-ionic 11,13,15-triazasteroidal skeleton.

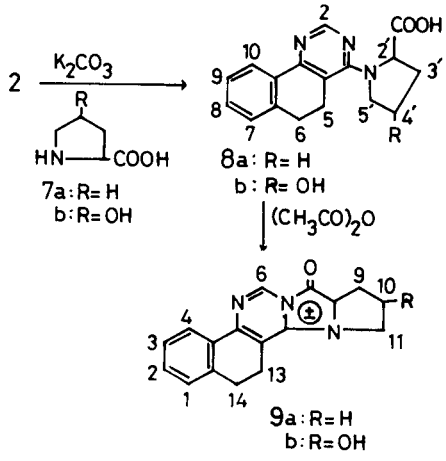
As shown in Scheme 1, the condensation of 4-chloro-5,6-dihydrobenzo[*h*]quinazoline (**2**) [1b] with *N*-methylglycine (**3a**) and *N*-methylalanine (**3b**) in a manner similar to that reported previously [3] afforded *N*-(5,6-dihydrobenzo-[*h*]quinazolin-4-yl)-*N*-methylglycine (**4a**) and alanine (**4b**), respectively.



Scheme 1

Treatment of **4a** with excess acetic anhydride at 100° afforded 2-acetyl-3-methyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]-quinazolinium-1-olate (**5c**) as stable orange needles. The pmr spectrum of **5c** showed the disappearance of an α-methylene signal of the glycine moiety and the new appearance of an acetyl group at δ 2.66 ppm, supporting the structure of **5c**. Also the *N*-methyl signal shifted 1.22 ppm to a down field comparing with that of **4a**. This can be interpreted through the additive effects of both anisotropic deshielding by a newly formed imidazole ring and inductive deshielding by a partial positive charge of the methylated nitrogen atom. The interpretation was further supported by the work of Lawson and Miles [4], who cyclized *N*-ethyl-*N*-(2-pyridyl)glycine with acetic anhydride to obtain an acetylated meso-ionic compound.

Although 2-acetylated derivative **5c** was obtained when a large excess of acetic anhydride was used, reaction of **4a** with 1.5 moles equivalent of acetic anhydride in pyridine-benzene gave 3-methyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]-quinazoliniuml-olate (**5a**) as brownish yellow crystals. The pmr spectrum of **5a** under argon showed one proton singlet at δ 6.06 ppm attributable to a proton of 2-position and *N*-methyl signal at δ 4.01 ppm. Compound **5a** seemed to be sensitive to air, for instance, the brownish yellow spot of **5a** on tlc change to colorless by exposure to air. Such color change was also caused by bubbling air into a dichloromethane solution of **5a**. In the latter treatment, the major product was isolated from the reaction mixture and identified as 4-methylamino-5,6-dihydrobenzo[*h*]quinazoline (**6**) by the synthesis of **6** from **2** and methylamine. A mechanism for the formation of **6** is not clear at present. Since it was considered from the structure of **5a** and **5c** that **5a** might be an intermediate in the formation of **5c** from **4a**, **5a** was heated with acetic anhydride under nitrogen to see if **5a** is transformed to **5c**. As expected, **5c** was obtained in 72% yield, although some other minor products were also formed.



Scheme 2

As described for the preparation of **5c**, treatment of **4b** with excess acetic anhydride afforded 2,3-dimethyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazolinium-1-olate (**5b**) as brownish yellow needles. However, no incorporation of an acetyl group occurred in this case.

As described above, **2** was successfully modified to tetracyclic meso-ionic compounds **5a-5c**. From both the view points of the chemical modification of **1** and the reactivity of **2**, therefore, it is interesting to see if **2** is converted into the corresponding pentacyclic meso-ionic compounds by using cyclic amino acid derivatives **7** instead of **3a** and **3b**. As shown in Scheme 2, reaction of **2** with proline derivatives **7a,b** in a manner similar to that described for the preparation of **4a** and **4b** gave *N*-(5,6-dihydrobenzo[*h*]-quinazolin-4-yl)proline derivatives **8a,b** in good yield, Scheme 2. Since an immediate color change of a reaction mixture (dark brown) occurred when **8a** was treated with excess acetic anhydride at 100°, the reaction was carried out at room temperature and gave 10,11,13,14-tetrahydro-9*H*-benzo[*h*]pyrrolo[1′,2′:3,4]imidazo[1,2-*c* quinazolinium-8-olate (**9a**). On the other hand, treatment of **8b** with excess acetic anhydride or pyridine-acetic anhydride gave a fairly complicated mixture of products. Therefore, the cyclization of **8b** in pyridine-benzene-acetic anhydride was conducted and afforded 10-hydroxy-10,11,13,14-tetrahydro-9*H*-benzo[*h*]pyrrolo[1′,2′:3,4]imidazo[1,2-*c*]quinazolinium-8-olate (**9b**) as yellow crystals, which showed a single spot on tlc.

The antidepressive activities of several compounds obtained here will be published in an early date.

EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The ir spectra were obtained with a Nihon Bunko A-102 spectrometer. The pmr spectra were measured with a Hitachi R22-FTS instrument (90 MHz) with tetramethylsilane as an internal standard (δ value). The mass spectra (70 eV) were taken with a Shimadzu LKB-9000 spectrometer. The uv spectra were taken on a Hitachi ESP-2 spectrophotometer.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)-*N*-methylglycine (**4a**).

A mixture of 540 mg (2.5 mmoles) of **2**, 890 mg of *N*-methylglycine (10 mmoles), and 690 mg (5 mmoles) of potassium carbonate in 15 ml of 2-methoxyethanol-water (1:1, v/v) was refluxed for 4 hours. After evaporation of the solvents, the residue was dissolved in water and neutralized with acetic acid. The deposited colorless crystals were recrystallized from ethanol giving 590 mg (88%) of **4a** as colorless needles, mp 163-165°; ir (potassium bromide): 3450 (broad) cm^{-1}, 2450 (broad), 1705, 1610, 1598; pmr (DMSO-d_6): δ 2.87 (br s, H-5 and 6, 4H), 3.15 (s, CH_3, 3H), 4.14 (s, N-CH_2, 2H), 7.36 (m, H-7, 8, and 9, 3H), 8.12 (m, H-10, 1H), 8.55 (s, H-2, 1H), 12.50 (br, COOH, 1H, exchanged with deuterium oxide); ms: 269 (M^+, 8), 268 (M^+-1, 14), 251 (M^+-18, 42), 225 (M^+-44, 81), 224 (M^+-45, 100).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 66.98; H, 5.56; N, 15.57.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)-*N*-methyl-DL-alanine (**4b**).

A mixture of 648 mg (3 mmoles) of **2**, 309 mg (3 mmoles) of *N*-methyl-DL-alanine, and 207 mg (1.5 mmoles) of potassium carbonate in 20 ml of dioxane-water (1:1, v/v) was refluxed for 2 days. After evaporation of the solvents, 20 ml of water was added to the residue. Insoluble fraction, which contained **2**, was filtered off and the mother liquor was evaporated. The residue was dissolved in saturated sodium hydrogen carbonate and insoluble fraction, which contained 4-hydroxy-5,6-dihydrobenzo[*h*]quinazoline (source of **2**, checked with tlc), was filtered off. The mother liquor was treated with charcoal and acidified with acetic acid. The resulting solution was kept in a refrigerator for 1 week. Gradually precipitated crystals of **4b** were collected. The mother liquor was concentrated to half volume to obtain second crystals. The combined crystals of **4b** weighed 391 mg (46%), mp 156-158°; ir (potassium bromide): 3450 (broad) cm^{-1}, 2450 (broad), 1710, 1611, 1595; pmr (DMSO-d_6): δ 1.45 (d, J = 7 Hz, CH-CH_3, 3H), 2.85 (br s, H-5 and 6, 4H), 3.00 (s, N-CH_3, 3H), 4.66 (q, J = 7 Hz, C*H*-CH_3, 1H), 7.37 (m, H-7, 8, and 9, 3H), 8.09 (m, H-10, 1H), 8.54 (s, H-2, 1H); ms: 283 (M^+, 4), 282 (M^+-1, 4), 265 (M^+-18, 80), 239 (M^+-44, 89), 238 (M^+-45, 100).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.59; H, 6.18; N, 14.61.

3-Methyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazolinium-1-olate (**5a**).

To a solution of 135 mg (0.5 mmole) of **4a** in 0.4 ml of pyridine was added 0.07 ml (0.75 mmole) of acetic anhydride in 3.4 ml of benzene and then the mixture was stirred for 5 minutes. The resulting solution was allowed to stand at 5-10° for 1 hour. The precipitated brownish yellow needles were filtered, washed with about 1 ml of cold benzene-cyclohexane (1:1, v/v), and dried under vacuum, which weighed 71 mg (56%) of **5a**, mp 129-131° dec; ir (potassium bromide): 1645 cm^{-1}; pmr (deuteriochloroform): δ 3.18 (m, H-4 and 5, 4H), 4.01 (s, N-CH_3, 3H), 6.06 (s, H-2, 1H), 7.33 (m, H-6, 7, and 8, 3H), 8.27 (m, H-9, 1H), 9.14 (s, H-11, 1H); ms: 251 (M^+, 100), 236 (M^+-15, 21), 222 (M^+-29, 36), 210 (M^+-41, 30), 208 (M^+-43, 9).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.24; H, 5.10; N, 16.63.

4-Methylamino-5,6-dihydrobenzo[*h*]quinazoline (**6**). Method A.

A mixture of 22 mg of **2** in 5 ml of ethanol and 1 ml of aqueous 40% methylamine in a sealed flask was stirred for 20 hours at room temperature. The resulting mixture was evaporated to dryness and the residue was recrystallized from aqueous acetone to give 15 mg (73%) of **6** as colorless scales, mp 133-135°; ir (potassium bromide): 3270 cm^{-1}; pmr (deuteriochloroform): δ 2.85 (m, H-5 and 6, 4H), 3.03 (s, N-CH_3, 3H), 6.18 (br, NH, 1H, exchanged with deuterium oxide), 7.33 (m, H-7, 8, and 9, 3H), 8.28 (m, H-10, 1H), 8.53 (s, H-2, 1H); ms: 211 (M^+, 100).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 74.00; H, 6.29; N, 19.97.

Method B.

A solution of 10 mg of **5a** in 100 ml of dichloromethane was stirred under bubbling of air at room temperature until the solution became colorless (about 1 day). After evaporation of dichloromethane, the residue was separated with preparative tlc (Wako-gel B5-FM, 20 cm × 20 cm × 1 mm, solvent system; ethanol:chloroform = 1:6, v/v). Fraction of Rf value *ca.* 0.75, which showed blueish violet with PAN-UV lamp, was collected and recrystallized from aqueous acetone giving 4 mg (48%) of **6** as colorless scales, mp 133-135°, identical with above **6** by mixed melting point, tlc, and ir.

2-Acetyl-3-methyl-4,5-dihydrobenz[*h*]imidazo[1,2-*c*]quinazolinium-1-olate (**5c**). Method A.

A mixture of 135 mg (0.5 mmole) of **4a** and 1 ml of acetic anhydride was heated at 100° for 2.5 hours. After evaporation of acetic anhydride, the resulting residue was recrystallized from benzene giving 86 mg (58%) of **5c** as orange needles, mp > 300°; ir (potassium bromide): 1690 cm^{-1}, 1610 (shoulder), 1595; pmr (deuteriochloroform): δ 2.66 (s, $COCH_3$, 3H), 3.23 (m, H-4 and 5, 4H), 4.37 (s, N-CH_3, 3H), 7.31 (m, H-6, 7, and 8, 3H), 8.24 (m, H-9, 1H), 9.13 (s, H-11, 1H); ms: 293 (M^+, 100) 292 (M^+-1, 73), 278 (M^+-15, 19), 250 (M^+-43, 16), 222 (M^+-71, 39), 208 (M^+-85, 39); uv (dichloromethane): λ max 243 nm (log ε 4.17), 258 (shoulder), 266 (4.14), 284 (shoulder), 348 (3.80), 416 (shoulder), 438 (4.15), 465 (shoulder).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.44; H, 5.16; N, 14.17.

Method B.

A mixture of 15.3 mg (0.06 mmole) of **5a** and 0.3 ml of acetic anhydride was heated at 90-95° for 1 hour. After evaporation of acetic anhydride, the residue was subjected to preparative tlc (Wako-gel B5-FM, 20 cm × 20 cm × 1 mm, solvent system; ethanol:chloroform = 1:9, v/v). The fraction of orange zone of Rf *ca.* 0.6-0.7 was collected and recrystallized from benzene to give 11.9 mg (72%) of **5c** as orange needles, which was identified with the above **5c** by the instrumental analyses and tlc.

2,3-Dimethyl-4,5-dihydrobenzo[*h*]quinazolinium-1-olate (**5b**).

A mixture of 162 mg (0.5 mmole) of **4b** and 1 ml of acetic anhydride was heated at 100° for 10 minutes. Colorless **4b** dissolved in acetic anhydride and the solution colored in orange during this 10 minutes. The resulting solution was evaporated to dryness. Two ml of xylene was added to the crystalline orange residue and evaporated around 50° to dryness for removal of acetic anhydride. The procedure was carried out twice. The residue was triturated with 2 ml of benzene and filtered off. After drying, it weighed 103 mg (77%) of **5b**, mp 161-163°; ir (potassium bromide): 1640 cm^{-1}, 1595; pmr (deuteriochloroform): δ 2.33 (s, C-CH_3, 3H), 3.20 (m, H-4 and 5, 4H), 4.03 (s, N-CH_3, 3H), 7.28 (m, H-6, 7, and 8, 3H), 8.26 (m, H-9, 1H), 9.13 (s, H-11, 1H); ms: 265 (M^+, 100), 250 (M^+-15, 35), 235 (M^+-30, 23); uv (ethanol): λ max 238 nm (log ε 3.80), 248 (3.74), 285 (3.30), 375 (3.58), 410 (3.66).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.15; H, 5.64; N, 15.71.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)-DL-proline (**8a**).

A mixture of 260 mg (1.2 mmoles) of **2**, 690 mg (6 mmoles) of DL-proline, and 331 mg (2.4 mmoles) of potassium carbonate in 10 ml of 2-methoxyethanol-water (1:1, v/v) was refluxed for 7 hours. After evaporation of the solvents, the residue was dissolved in a small amount of water and acidified with acetic acid. Since no solid precipitated in this stage, the solution was saturated with sodium chloride and extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from benzene to give 343 mg (97%) of **8a** as colorless needles, mp 118-120°; ir (potassium bromide): 3440 (broad) cm^{-1}, 2600 (broad), 1722, 1625, 1605 (shoulder); pmr (deuteriochloroform): δ 2.20 (m, H-3′ and 4′, 4H), 2.90 (m, H-5 and 6, 4H), 3.84 (m, H-5′, 2H), 4.80 (m, H-2′, 1H), 7.35 (m, H-7, 8, and 9, 3H), 8.15 (m, H-10, 1H), 8.56 (s, H-2, 1H); ms: 295 (M^+-1, 9), 251 (M^+-44, 57), 250 (M^+-45, 100).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 68.98; H, 5.76; N, 13.98.

N-(5,6-Dihydrobenzo[*h*]quinazolin-4-yl)-*trans*-4-hydroxy-L-proline (**8b**).

A mixture of 216 mg (1 mmole) of **2**, 655 mg (5 mmoles) of *trans*-4-hydroxy-L-proline, and 276 mg (2 mmoles) of potassium carbonate in 15 ml of 2-methoxyethanol-water (1:1, v/v) was refluxed for 4 hours. After evaporation of the solvents, the residue was dissolved in water and acidified with acetic acid. The precipitated crystals were recrystallized from aqueous ethanol to give 225 mg (72%) of **8b** as colorless needles, mp 155-157°; ir (potassium bromide): 3350 (broad) cm^{-1}, 2750 (broad), 1660 (shoulder), 1613; pmr (DMSO-d_6): δ 2.15 (m, H-3′, 2H), 2.93 (m, H-5 and 6, 4H), 3.51 (br d, $J_{5',5'}$ = 11 Hz, H-5′, 1H), 4.02 (dd, $J_{5',5'}$ = 11 Hz, $J_{4',5'}$ = 4 Hz, H-5′, 1H), 4.38 (br, H-4′, 1H), 4.74 (dd, $J_{2',3'}$ = 9 Hz, $J_{2',3'}$ = 7 Hz, H-2′, 1H), 5.04 (br, OH, 1H, exchanged with deuterium oxide), 7.37 (m, H-7, 8, and 9, 3H), 8.10 (m, H-10, 1H), 8.46 (s, H-2, 1H), 12.10 (br, COOH, 1H, exchanged with deuterium oxide); ms: molecular ion peak was not observed, 267 (M^+-44, 74), 266 (M^+-45, 63), 248 (M^+-63, 100), 222 (M^+-89, 92); ms of methyl ester of **8b**: 325 (M^+, 46), 266 (M^+-59, 100), 248 (M^+-77, 27), 222 (M^+-103, 55).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.39; H, 5.47; N, 13.35.

10,11,13,14-Tetrahydro-9*H*-benzo[*h*]pyrrolo[1′,2′:3,4]imidazo[1,2-*c*]quinazolinium-8-olate (**9a**).

A mixture of 90 mg (0.3 mmole) of **8a** and 0.5 ml of acetic anhydride was stirred for 30 minutes at room temperature. The colorless **8a** became brownish yellow during this 30 minutes under dissolving in acetic anhydride. After evaporation of acetic anhydride, xylene was added to the residue and evaporated again around 50° (twice). The residue was triturated with benzene and the resulting yellow powder was filtered off, which weighed 54 mg (64%) of **9a** after drying, mp 99-102°; ir (potassium bromide): 1660 (shoulder) cm^{-1}, 1640; pmr (deuteriopyridine): δ 2.26 (m, H-10, 2H), 2.85 (br s, H-13 and 14, 4H), 3.01 (br t, $J_{9,10}$ = 7 Hz, H-9, 2H), 4.05 (br t, $J_{10,11}$ = 7.5 Hz, H-11, 2H), 7.37 (m, H-1, 2, and 3, 3H), 8.51 (m, H-4, 1H), 9.82 (s, H-6, 1H); ms: 277 (M^+, 79), 249 (M^+-28, 69), 221 (M^+-56, 43), 181 (M^+-96, 100); uv (dichloromethane): λ max 238 nm (log ε 4.24), 248 (shoulder), 290 (shoulder), 310 (3.94), 388 (4.08), 439 (4.18).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.30; H, 5.35; N, 14.85.

10-Hydroxy-10,11,13,14-tetrahydro-9*H*-benzo[*h*]pyrrolo[1′,2′:3,4]imidazo[1,2-*c*]quinazolinium-8-olate (**9b**) Monohydrate.

To a solution of 59 mg (0.2 mmole) of **8b** in 0.5 ml of pyridine was added 0.022 ml (0.23 mmole) of acetic anhydride in 1 ml of dry benzene and the mixture was shaken for 10 minutes at room temperature. The precipitated yellow needles were filtered off and washed with dry benzene, which weighed 43.5 mg (74%) of **9b** after drying, mp 175-177°; ir (potassium bromide): 3430 (broad) cm^{-1}, 1640, 1606; pmr (DMSO-d_6): δ 2.90 (m, H-9, 2H), 3.06 (m, H-13 and 14, 4H), 4.28 (dd, $J_{11,11}$ = 12.5 Hz, $J_{10,11}$ = 3 Hz, H-11, 1H), 4.68 (dd, $J_{11,11}$ = 12.5 Hz, $J_{10,11}$ = 5 Hz, H-11, 1H), 4.90 (br, H-10, 1H), 7.30 (m, H-1, 2, and 3, 3H), 8.12 (m, H-4, 1H), 8.89 (s, H-6, 1H); ms: 293 (M^+, 18), 276 (M^+-18, 11), 249 (M^+-44, 100), 248 (M^+-45, 62), 247 (M^+-46, 20); uv (dichloromethane): λ max 238 nm (log ε 4.09), 250 (shoulder), 287 (3.79), 302 (3.76), 311 (3.75), 388 (3.69), 430 (3.67).

Anal. Calcd. for $C_{17}H_{15}N_3O_2 \cdot H_2O$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.32; H, 5.29; N, 13.37.

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