Preparation of 6-(Nitron-C-yl)- and 6-(1,3-Butadienyl)-2-pyrones and Their Cycloaddition Reactions

Tetsuro Shimo* and Kenichi Somekawa

Department of Applied Chemistry and Chemical Engineering,
Faculty of Engineering, Kagoshima University,
Korimoto, Kagoshima 890, Japan

Otohiko Tsuge

Department of Industrial Chemistry, Kumamoto Institute of Technology,
Ikeda, Kumamoto 860, Japan

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6-(*N*-Substituted nitron-C-yl)-2-pyrones 1 and 6-(4-substituted 1,3-butadienyl)-2-pyrone **2** were prepared and their cycloaddition reactions with three kinds of diene systems were investigated. Namely, the reactions of **1** with methyl acrylate, vinyl crotonate and divinylsulfone took place at the nitrone moiety to afford 3-substituted isoxazolidines **9-14**, and that of **2** with maleimide took place at the 2-pyrone moiety to give a bis-adduct **17** *via* elimination of carbon dioxide.

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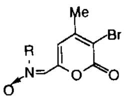
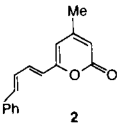
Nitrones have been known to undergo [3 + 2] cycloaddition reaction with olefins to afford isoxazolidines [1], which can be converted into β-amino alcohols [2] by subsequent reductive N-O bond cleavage, and to utilize for construction of natural products [3]. On the other hand, 2-pyrones have been known to be subjected to [4 + 2] cycloaddition reaction with olefins to give mono- and/or bis-adducts [4]. Hence, the cycloaddition reactions of 6-(*N*-substituted nitron-C-yl)-2-pyrones, which are 4π-4π systems of the combination of 2-pyrone-nitrone, are interesting concerning the reactivity and the products which may contain the double cycloadducts with diene components at the two conjugated diene moieties of 6-(nitron-C-yl)-2-pyrones.

We previously reported that the Diels-Alder reaction of 3-(2*H*-pyran-2-on-6-yl)indolizines, which are 4π-8π systems, with dienophiles gave 3-substituted indolizines [5].

In this paper, the cycloaddition reactions of 6-(*N*-phenylnitron-C-yl)-2-pyrone **1a** with olefinic dipolarophiles are investigated, in addition to the comparison of the reactivity of 6-(1,3-butadienyl)-2-pyrone.



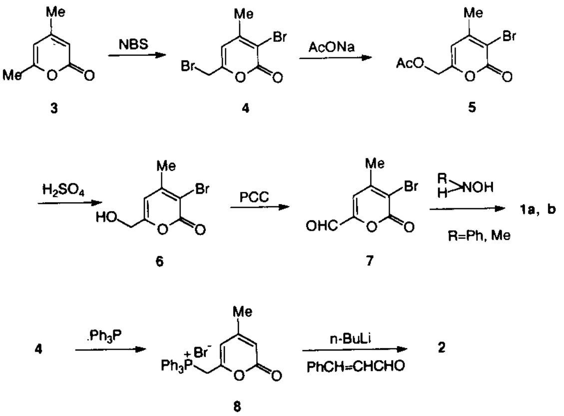
1a R=Ph
1b R=Me



2

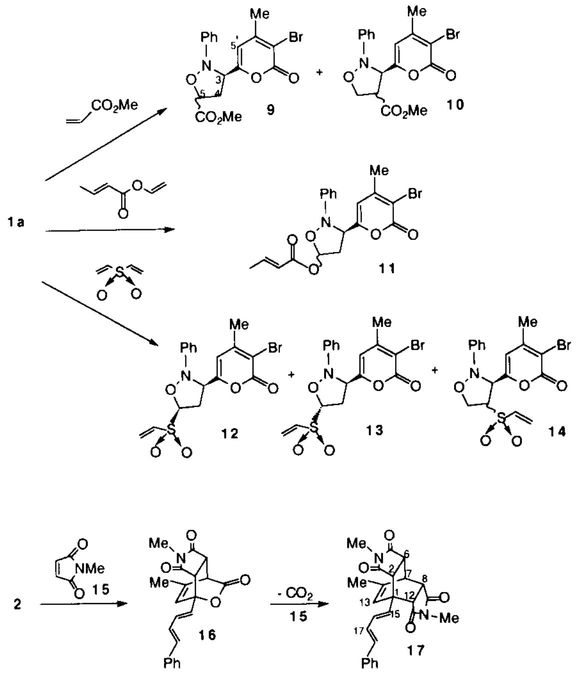
6-(*N*-Substituted nitron-C-yl)-2-pyrones **1a,b** were synthesized from the reaction of hydroxylamines with 6-(2*H*-pyran-2-one)carbaldehyde **7**, which were prepared from 4,6-dimethyl-2-pyrone (**3**) by bromination with NBS, followed by acetoxylation, hydrolysis and oxidation (Scheme 1). 6-(1,3-Butadienyl)-2-pyrone **2** was also prepared from Wittig reaction of cinnamaldehyde with phosphonium bromide **8**, which was formed from the reaction of 3-bromo-6-bromomethyl-4-methyl-2-pyrone with triphenylphosphine accompanied by debromination.

Scheme 1



The next step is a 1,3-dipolar cycloaddition reaction of 6-(*N*-phenylnitron-C-yl)-2-pyrone **1a**. The reaction of **1a** with methyl acrylate at 110° gave four adducts whose yields were estimated to 87% of **9** and 11% of **10** from the ^{1}H nmr analysis (Scheme 2). The crude residue was chromatographically separated, and major cycloadducts **9** could be isolated as a mixture of two stereoisomers. The regiochemistry of **9** was inferred from the ^{1}H nmr spectral data whose chemical shifts at the position of 3-H and 5-H occurred at δ 4.61 ($J_{3,4}$ = 5.3, $J_{3,5'}$ = 1.0 Hz) and *ca* 4.7 ($J_{5,4}$ = 6.5 Hz), respectively. We next investigated the reaction of **1a** with dienes which were expected to afford double cycloadducts with two 4π systems. 2-Pyrone **1a** reacted with vinyl crotonate at the vinyl moiety at 80° to give a product **11**, which was chromatographically purified. The reaction of **1a** with divinyl sulfone at 45° gave a mixture of three products. The mixture was separated to **12** (14%), **13** (25%) and **14** (7%) by column chromatography.

Scheme 2



The structures of **11-14** were assigned from the spectroscopic evidence. The regiochemistry of **11** was inferred from the ^{1}H nmr data of 5-H showing lower-field chemical shift at δ 6.71 (doublet-doublet) which could be seen in the similar skeleton [1c]. The regio- and stereochemistry of **12-14** were deduced as follows. Compounds **12** and **13** showed lower-field ^{1}H nmr signals at δ 5.12 and 5.11 of the 5-H protons, respectively. On the other hand, compound **14** showed higher-field signals at δ 4.3-4.5 of 3-H and 5-CH$_2$. A distinction between the two stereoisomers **12** and **13** can be made on the basis of the ^{1}H nmr data because **13** showed a higher-field signal of 3-H (δ 4.48, td, $J_{3,4}$ = 7.2, $J_{3,5'}$ = 1.0 Hz) compared to that of 12 (δ 4.74, bt, J = 6.3 Hz) owing to anisotropic effect of the 5-substituted C=C or S=O double bond.

The compound **12** was expected to afford a double cycloadduct, which was an intramolecular [4+2] cycloadduct between 2-pyrone and vinyl sulfone, from the HGS model consideration. But the reaction of **12** in refluxing benzene gave a complex mixture.

Compound **2** reacted with *N*-methylmaleimide at 110° to give a bis-adduct **17** in 54% yield. The stereochemistry of **17** was inferred to be endo-endo configuration of the imide groups from the ^{1}H nmr spectral data whose chemical shifts at the position of 2-H and 12-H, and 6-H and 8-H occurred at δ 2.86 and 3.05, respectively. It is inferred that **17** was formed by way of the elimination of carbon dioxide of the mono-adduct **16**, followed by addition of another molecule of *N*-methylmaleimide. In the similar reactions of **2** with acrylonitrile, methyl acrylate and dimethyl fumalate, **2** was recovered quantitatively.

As mentioned above, 6-(nitron-C-yl)-2-pyrone **1a** bearing a 4π-4π system reacted with dipolarophiles to give products *via* 1,3-dipolar cycloaddition reactions of the nitrone ring. And 6-(1,3-butadienyl)-2-pyrone reacted with *N*-methylmaleimide to give a product *via* Diels-Alder reaction of 2-pyrone ring. The results show that cycloaddition reactivity of the nitrone moiety is electrophilic. And it is higher than that of the 2-pyrone and 1,3-butadiene parts for simple olefins.

EXPERIMENTAL

All melting points were measured on a Yanagimoto Mel-temp apparatus and are uncorrected. The ir spectra were taken with a JASCO A-702 spectrometer. The ^{1}H nmr spectra were recorded on a Hitachi R-40 or a JEOL FX-100 instrument using TMS as internal reference. Mass spectra as well as high-resolution mass spectra were measured with a JEOL JMS-OISG-2 spectrometer at 70 eV of ignition energy.

3-Bromo-4-methyl-6-(*N*-phenylnitron-C-yl)-2-pyrone (**1a**) and 3-Bromo-4-methyl-6-(*N*-methylnitron-C-yl)-2-pyrone (**1b**).

1) A solution of 3-bromo-6-bromomethyl-4-methyl-2-pyrone (**4**) [5] (0.28 g, 1.0 mmole) and sodium acetate (0.08 g, 1.0 mmole) in ethanol (10 ml) was refluxed for 1.5 hours. After concentration of the reaction mixture, chloroform (10 ml) was added and the filtrate was concentrated to give **5** (0.256 g, 98%) which was recrystallized from ethyl acetate. Compound **5** had mp 124-125°; ir (potassium bromide): 1740, 1715, 1650, 1525 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.10, 2.27 (each s, 3H), 4.76 (s, 2H), 6.10 (s, 1H); ms: m/z (relative intensity) 262 (M+2, 21), 260 (M$^+$, 20), 43 (100).

Anal. Calcd. for $C_9H_9O_4Br$: C, 41.40; H, 3.45. Found: C, 41.19; H, 3.41.

2) A solution of **5** (0.256 g, 0.98 mmole) in ethanol (10 ml) containing a catalytic amount of concentrated sulfuric acid was fluxed for 3 hours. The reaction mixture was washed with 10% sodium carbonate solution and extracted with diethyl ether to give **6** (0.16 g, 74%) which was recrystallized from benzene. Compound **6** had mp 104-105°; ir (potassium bromide): 3430, 1680, 1630, 1525 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.29 (s, 3H), 2.80 (bs, 1H), 4.40 (bs, 2H), 6.22 (s, 1H); ms: m/z (relative intensity) 220 (M+2, 45), 218 (M$^+$, 46), 189 (100).

Anal. Calcd. for $C_7H_7O_3Br$: C, 38.37; H, 3.20. Found: C, 38.38; H, 3.24.

3) To a suspension of pyridinium chlorochromate (3.58 g, 16.6 mmoles) in dichloromethane (50 ml) under nitrogen atmosphere was added dichloromethane solution (10 ml) containing **6** (1.82 g, 8.3 mmoles). The reaction mixture was stirred for 2 hours at room temperature, washed with 10% sodium carbonate solution, and extracted with diethyl ether. The combined organic layer was dried (magnesium sulfate) and concentrated to give **7** (1.2 g, 67%), which was recrystallized from benzene. Compound **7** had mp 116-117°; ir (potassium bromide): 1720, 1685, 1630 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.41 (s, 3H), 6.90 (s, 1H), 9.49 (s, 1H); ms: m/z (relative intensity) 218 (M+2, 45), 216 (M$^+$, 46), 131 (100).

Anal. Calcd. for $C_7H_5O_3Br$: C, 38.73; H, 2.31. Found: C, 38.76; H, 2.38.

4) A solution of **7** (1.4 g, 6.4 mmoles) and phenylhydroxyl-

amine (0.70 g, 6.4 mmoles) in ethanol (40 ml) was refluxed for 2 hours. The solvent was removed under reduced pressure and the resulting solid was recrystallized from ethanol to give **1a** (0.96 g, 49%). A solution of **7** (0.11 g, 0.50 mmole) and methylhydroxylamine hydrochloride (0.042 g, 0.50 mmole) in ethanol (2 ml) was refluxed for 1 hour. The same workup afforded **1b** (0.03 g, 24%).

Compound **1a** had mp 163-165°; ir (potassium bromide): 1720, 1600, 1485 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.38 (s, 3H), 7.52 (m, 3H), 7.68 (m, 2H), 7.86 (s, 1H), 8.62 (s, 1H); ms: m/z (relative intensity) 309 (M + 2, 15), 307 (M$^+$, 16), 104 (100).

Anal. Calcd. for $C_{13}H_{10}NO_3Br$: C, 50.67; H, 3.25; N, 4.55. Found: C, 50.68; H, 3.43; N, 4.64.

Compound **1b** had mp 200-202°; ir (potassium bromide): 1705, 1607, 1563 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.33, 3.85 (each s, 3H), 7.27 (s, 1H), 8.02 (s, 1H); ms: m/z (relative intensity) 247 (M + 2, 22), 245 (M$^+$, 23), 42 (100).

Anal. Calcd. for $C_8H_8NO_3Br$: C, 39.04; H, 3.25; N, 5.69. Found: C, 38.82; H, 3.40; N, 5.68.

4-Methyl-6-(4-phenyl-1,3-butadienyl)-2-pyrone (**2**).

1) A solution of **4** (3.25 g, 11.5 mmoles) and triphenylphosphine (3.63 g, 13.8 mmoles) in benzene (60 ml) was refluxed for 4 days. The resulting solid was filtered and recrystallized from acetone-ethanol 7:3 v/v mixture to give **8** (2.8 g, 52%), which was difficult to purify by repeated recrystallization. Compound **8** had mp >250° dec; ir (potassium bromide): 1725, 1630, 1500 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.00 (s, 3H), 5.55 (d, 2H), 5.80, 6.90 (each bs, 1H), 7.73 (m, 15H); ms: m/z (relative intensity) 384 (M-HBr, 100).

2) To a THF (3 ml) solution of **8** (0.465 g, 1.0 mmole) was slowly added *n*-butyllithium (0.48 ml, 1.2 mmoles, 2.5 *M* solution in THF) at −78°. The solution was stirred at −78° for 0.3 hour and then cinnamaldehyde (0.16 g, 1.2 mmoles) was added. Stirring was continued for 3 days at room temperature. The reaction mixture was washed with water, the organic layer was separated and aqueous layer was extracted with diethyl ether. The combined organic layers were concentrated and resulting oil was chromatographed on a silica gel column (Wakogel C-200) using benzene as the eluent to afford **2** (0.15 g, 63%). Compound **2** had mp 143-145°; ir (potassium bromide): 1700, 1630, 1615, 1520 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 5.92, 5.96 (each bs, 1H), 6.12 (d, 1H, J = 14.9 Hz), 6.80 (m, 2H), 7.30 (m, 6H); ms: m/z (relative intensity) 238 (M$^+$, 100).

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88. Found: C, 80.25; H, 5.90.

3-(3-Bromo-4-methyl-2*H*-pyran-2-on-6-yl)-5-methoxycarbonyl-2-phenylisoxazolidine (**9**) and 3-(3-Bromo-4-methyl-2*H*-pyran-2-on-6-yl)-4-methoxycarbonyl-2-phenylisoxazolidine (**10**).

A solution of **1a** (0.102 g, 0.33 mmole) and methyl acrylate (0.142 g, 1.65 mmoles) in toluene (2 ml) was refluxed for 1 hour and the solvent was removed *in vacuo*. The residue was submitted to column chromatography using benzene to give **9** (0.095 g, 73%), which contained two stereoisomers (2:1 mixture from the ^{1}H nmr data), and four adducts containing **9** and **10** (0.033 g, 25%), each total yield of **9** and **10** was 87% and 11%, respectively, from the calculation of the ^{1}H nmr data.

Compound **9** had mp 40-42° (epimer ratio = 2:1); ir (potassium bromide): 1720, 1640, 1595 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.26 (s, 3H, Me), 2.85 (m, 2H, 4-H), 3.66, 3.75 (each s, 3H, CO$_2$Me), 4.61 (td, 1H, 3-H, $J_{3,4}$ = 5.3, $J_{3,5'}$ = 1.0 Hz), 4.77, 4.75 (each t, 5-H, $J_{5,4}$ = 6.5 Hz), 6.43, 6.54 (each s, 1H, 5'-H), 7.02 (m, 3H, Ph), 7.35 (m, 2H, Ph); ms: m/z (relative intensity) 395 (M + 2, 77), 393 (M$^+$, 79), 206 (100).

Anal. Calcd. for $C_{17}H_{16}NO_5Br$: C, 51.79; H, 4.06; N, 3.55. Found: C, 51.80; H, 4.13; N, 3.29.

3-(3-Bromo-4-methyl-2*H*-pyran-2-on-6-yl)-5-crotonyloxy-2-phenylisoxazolidine (**11**).

A solution of **1a** (0.154 g, 0.50 mmole) and vinyl crotonate (0.084 g, 0.50 mmole) in benzene (2 ml) was refluxed for 16 hours. The same workup mentioned above gave **11** (0.104 g, 50%).

Compound **11** had mp 42-45°; ir (potassium bromide): 1720, 1643, 1597 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 1.84 (dd, 3H, Me), 2.31 (s, 3H, Me), 2.78 (m, 2H, 4-CH$_2$), 4.48 (ddd, 3-H, $J_{3,4}$ = 6.5, 4.8, $J_{3,5'}$ = 1.2 Hz), 5.68 (dq, C*H*=CHMe), J = 15.5, J = 1.7 Hz), 6.63 (d, 1H, 5'-H, $J_{5',3}$ = 1.2 Hz, 6.71 (dd, 1H, 5-H, $J_{5,4}$ = 6.5, 4.0 Hz), 6.88 (dq, 1H, CH=C*H*Me, J = 15.5, J = 6.9 Hz), 7.00 (m, 3H, Ph), 7.26 (m, 2H, Ph); ms: m/z (relative intensity) 421 (M + 2, 7), 419 (M$^+$, 6), 69 (100).

Anal. Calcd. for $C_{19}H_{18}NO_5Br$: C, 54.30; H, 4.28; N, 3.33. Found: C, 54.48; H, 4.47; N, 3.23.

cis-3-(3-Bromo-4-methyl-2*H*-pyran-2-on-6-yl)-2-phenyl-5-vinylsulfonylisoxazolidine (**12**), *trans*-3-(3-Bromo-4-methyl-2*H*-pyran-2-on-6-yl)-2-phenyl-5-vinylsulfonylisoxazolidine (**13**) and 3-(3-Bromo-4-methyl-2*H*-pyran-2-on-6-yl)-2-phenyl-4-vinylsulfonylisoxazolidine (**14**).

A solution of **1a** (0.20 g, 0.65 mmole) and divinylsulfone (0.077 g, 0.65 mmole) in chloroform (2 ml) was heated at 45° for 13 hours. After concentration, resulting residue was submitted to column chromatography using hexane-ethyl acetate 5:1 v/v mixture to give **12** (0.039 g, 14%), **13** (0.069 g, 25%) and **14** (0.019 g, 7%).

Compound **12** had mp 57-60°; ir (potassium bromide): 1720, 1642, 1595, 1320, 1134 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.24 (s, 3H, Me), 3.04 (ddd, 1H, 4-H, $J_{4,4'}$ = 14.0, $J_{4,5}$ = 8.0, $J_{4,3}$ = 6.3 Hz), 3.34 (ddd, 1H, 4-H', $J_{4,4'}$ = 14.0, $J_{4',3}$ = 6.3, $J_{4',5}$ = 4.5 Hz), 4.74 (bt, 3-H, $J_{3,4}$ = $J_{3,4'}$ = 6.3 Hz), 5.12 (dd, 1H, 5-H, $J_{5,4}$ = 8.0, $J_{5,4'}$ = 4.5 Hz), 6.08 (d, 1H, =CH$_2$, J = 16.0 Hz), 6.26 (d, 1H, =CH$_2$, J = 9.0 Hz), 6.50 (s, 1H, 5'-H), 6.69 (dd, 1H, CH$_2$=C*H*, J = 16.0, 9.0 Hz), 7.06 (m, 3H, Ph), 7.28 (m, 2H, Ph); ms: m/z; (relative intensity) 428 (M + 3, 1), 426 (M + 1, 1), 65 (100). High-resolution ms: Calcd. for $C_{17}H_{16}NO_5SBr$: 424.9932. Found: 424.9938.

Compound **13** had mp 64-66°; ir (potassium bromide): 1710, 1640, 1590, 1327, 1135 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.26 (s, 3H, Me), 3.09 (t, 2H, 4-CH$_2$, $J_{4,3}$ = $J_{4,5}$ = 7.2 Hz), 4.48 (td, 1H, 3-H, $J_{3,4}$ = 7.2, $J_{3,5'}$ = 1.0 Hz), 5.11 (t, 1H, 5-H, $J_{5,4}$ = 7.2 Hz), 6.26 (dd, 1H, =CH$_2$, J = 9.0, 1.0 Hz), 6.42 (d, 1H, 5'-H, $J_{5',3}$ = 1.0 Hz), 6.44 (dd, 1H, =CH$_2$, J = 16.4, 1.0 Hz), 6.58 (dd, 1H, CH$_2$=C*H*, J = 16.4, 9.0 Hz), 7.01 (m, 3H, Ph), 7.20 (m, 2H, Ph); ms: m/z (relative intensity) 427 (M + 2, 2), 425 (M$^+$, 4), 317 (100).

Anal. Calcd. for $C_{17}H_{16}NO_5SBr$: C, 47.91; H, 3.75; N, 3.29. Found: C, 47.72; H, 3.71; N, 3.25.

Compound **14** had mp 60-64°; ir (potassium bromide): 1722, 1643, 1595, 1315, 1135 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.28 (s, 3H, Me), 4.26-4.50 (m, 3H, 4-H, 5-CH$_2$), 4.78 (d, 1H, 3-H, $J_{3,4}$ = 4.0), 6.22 (d, 1H, =CH$_2$, J = 9.0 Hz), 6.40 (s, 1H, 5'-H), 6.42 (d, 1H, =CH$_2$, J = 16.0 Hz), 6.69 (dd, 1H, CH$_2$=C*H*, J = 16.0, 9.0 Hz), 7.03 (m, 3H, Ph), 7.31 (m, 2H, Ph); ms: m/z (relative intensity) 427 (M + 2, 3), 425 (M^+, 2), 85 (100). High-resolution ms: Calcd. for $C_{17}H_{16}NO_5SBr$: 424.9932. Found: 424.9914.

4,10-Dimethyl-1-(4-phenyl-1,3-butadienyl)-4,10-diazatetracyclo-[5.5.2.$0^{2,6}$.$0^{8,12}$]tetradec-13-en-3,5,9,11-tetraone (**17**).

A solution of **2** (0.12 g, 0.50 mmole) and *N*-methylmaleimide (0.06 g, 0.54 mmole) in toluene (2 ml) was refluxed for 78 hours. The solvent was removed *in vacuo* and resulting solid was recrystallized from chloroform-ethanol 2:1 v/v mixture to give **17** (0.06 g, 54%).

Compound **17** had mp 276-278°; ir (potassium bromide): 1765, 1685 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 1.73 (d, 3H, Me), 2.80 (m, 2H, 2-H, 12-H), 2.86 (s, 6H, Me), 3.05 (dd, 2H, 6-H, 8-H, $J_{6,2} = J_{8,12} = 7.6$, $J_{6,7} = J_{8,7} = 2.8$ Hz), 3.60 (bs, 1H, 7-H), 5.80 (bs, 1H, 13-H), 6.10 (bd, 1H, 15-H (or 18-H), J = 15.3 Hz), 6.43 (dd, 1H, 16-H (or 17-H), J = 15.3, 9.0 Hz), 6.73 (d, 1H, 18-H (or 15-H), J = 18.0 Hz), 7.26 (m, 6H, Ph and 17-H (or 16-H)); ms: m/z (relative intensity) 416 (M^+, 70), 305 (100).

Anal. Calcd. for $C_{25}H_{24}N_2O_4$: C, 72.11; H, 5.77; N, 6.73. Found: C, 72.04; H, 5.82; N, 6.74.

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