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CHEMISTRY OF INDOLES CARRYING A BASIC FUNCTION. PART VI.[1] SYNTHESIS OF A NEW RING SYSTEM WITH INDOLE NUCLEUS

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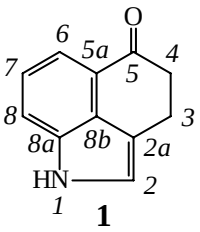
Abstract **—** Stobbe condensed product half ester (**2*E***; *E*-1,3,4,5-tetrahydrobenz[*c*,*d*]indole-5-ylidene-3′-ethoxycarbonylpropionic acid) afforded a monomer tetracyclic indole derivative (**4**; 5-ethoxycarbonyl-7-acetoxy-1*H*,9c*H*-3,4-dihydronaphto[*c*,*d*,*e*]indole) and a dimer (**5**; 5-ethoxycarbonyl-1*H*,9c*H*-3,4-dihydronaphto[*c*,*d*,*e*]indole-7-(*O*-*E*-1,3,4,5-tetrahydrobenz[*c*,*d*]indole-5-ylidene-3′-ethoxycarbonylethylpropionate) in an unexpected cyclisation.

Stobbe condensation is widely used to prepare α,β-unsaturated acids from ketones.[2] In the hope of constructing ergoline skeleton by *intramolecular* version of the Stobbe condensation, a few succinic diester derivatives were prepared by Uhle[3] and Stoll[4,5] early in the fifties but the expected cyclizations have never been published. (Recently we described the formation of a few tetra- and pentacyclic products starting from similar type of compounds).[6] On the other hand a successful *intermolecular* reaction of Uhle′s ketone (**1**), leading to the usual half ester (**2**) in a good yield, was also described by Stoll′s group. To elaborate the half ester side chain at C-5, the ester group was hydrolysed to the dicarboxylic acid and then the latter was attempted to transform into a conjugated monocarboxylic acid. However, the end product proved to be an acid anhydride (**3**), and this approach was finished at this level.[4]



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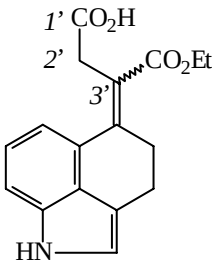

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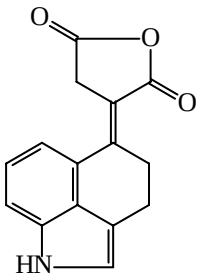

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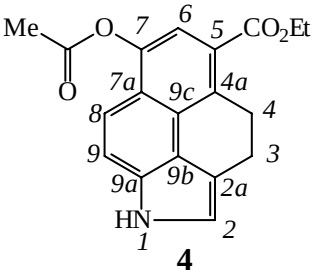
Nevertheless the half ester (**2**) seemed to be a valuable intermediate to build up the ring D of the ergoline skeleton. One of our conceptions was to perform an allylic bromination with NBS at C-4, followed by bromine-amine exchange. The starting material (**2**) was prepared by a modified Stobbe condensation (NaH, benzene + EtOH)[7] in 92 % yield. The crude product was formed as an isomeric mixture (**2*E***:**2*Z*** ≈ 8:2; established by NMR examinations) and the dominant **2*E***-isomer (where the carboxyl group is oriented toward the aromatic ring) was obtained in pure form by column chromatography. (After a few days the purified isomer (**2*E***) was isomerised in solution to an equilibrium mixture of the two isomers, where the ratio of **2*E***:**2*Z*** turned out to be similar to that in the crude product).

Despite our expectation, the bromination of **2** with NBS gave an unseparable, and unstable mixture which was unsuitable for any further transformation. In order to enhance the chance of the bromination process, *N*-acetylation of Stobbe product (**2**) was attempted. Adopting the Bowman′s procedure[8] for protection, **2*E*** was treated with acetyl chloride in the presence of K_2CO_3 in methyl ethyl ketone (4 h, rt). After working-up the reaction mixture (extraction, column chromatography), two unexpected products (**4** yield: 20 %; and **5** yield: 15 %) were obtained as crystals. Not a trace of *N*-acetyl derivative of **2** could be isolated. To the best of our knowledge compounds (**4**) and (**5**) represent a new ring system with indole nucleus.



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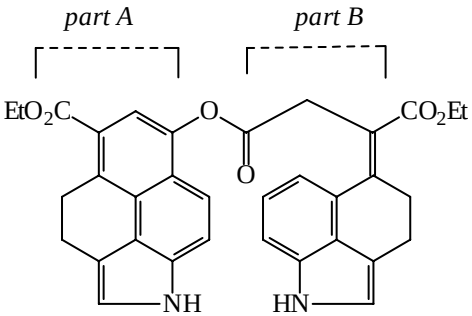

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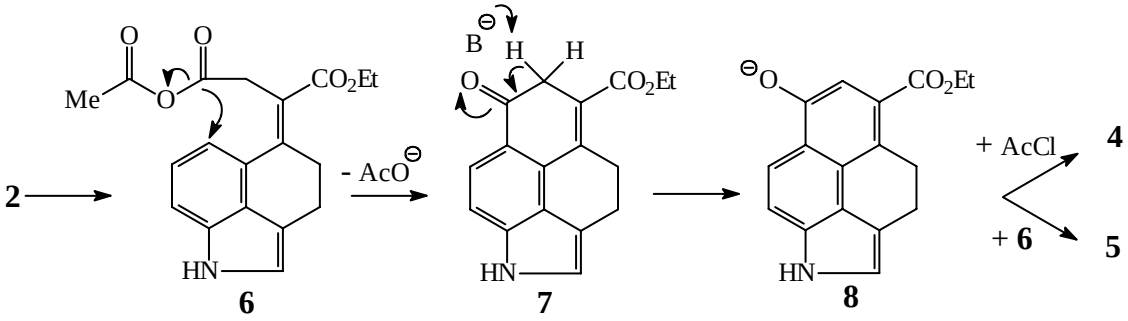
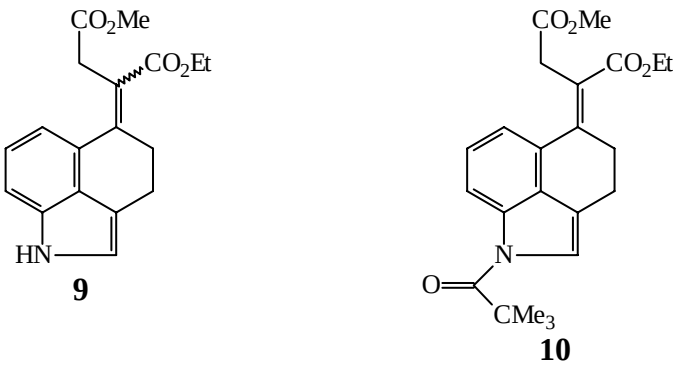
Concerning the reaction sequence, at the outset we can assume the formation of mixed anhydride (**6**) which attacks the aromatic ring at carbon-6 forming keto ester (**7**). This latter compound isomerises and affords phenoxide (**8**), subsequently acylated with acetyl chloride to afford monomer (**4**), or with mixed anhydride (**6**) yielding dimer (**5**).



To avoid the above undesired cyclisation during the *N*-protection of **2**, the carboxyl group was esterified with diazomethane (2 h, 0 ^{o}C) affording diester (**9)** (yield: 93 %) as an isomer mixture in about the same ratio as the starting half ester. (Nevertheless, the pure **9*E***-isomer could be isolated by crystallization). Diester (**9**) was allowed to react with acetyl chloride in the presence of K_2CO_3 but after 2 days only the starting material could be detected. For the *N*-acylation, diester (**9**) was treated with pivaloyl chloride applying the procedure of Goto′s group[9] for protection of 3-indolepropionic acid (n-BuLi, - 78 ^{o}C, pivaloyl chloride, 2 h, 0 ^{o}C $\rightarrow$ rt). In this case *N*-pivaloyl diester (**10**) was obtained as a single *E*-isomer in 37.5 % yield. (The stereochemical arrangment of **10** was verified by NOE measurements).



EXPERIMENTAL

Mps are uncorrected. MS spectra were run on an AEI-MS-902 (70 eV; direct insertion) and on a Kratos MS-902 mass spectrometers. IR spectra were taken on a Nicolet 205 and Nicolet 7795 FT-IR spectrophotometers. NMR measurements were carried out on a Varian Unity Inova (400 MHz) instrument. Chemical shifts are given relative to TMS = 0.00 ppm.

Glassware was flame dried before use. THF and benzene were distilled from sodium/benzophenone; CH_2Cl_2 was distilled from P_2O_5 and EtOH was distilled from Mg.

E/Z-1,3,4,5-Tetrahydrobenz[*c,d*]indole-5-ylidene-3′-ethoxycarbonylpropionic acid (**2**)

Uhle′s ketone (**1**, 1.7 g; 10 mmol) was suspended in diethyl succinate (5.0 mL; 30 mmol) at rt. Sodium hydride (1.2 g; 30 mmol; 60% suspension in oil) was washed with dry benzene and added to the above suspension in benzene (5 mL). The reaction mixture was stirred for 0.5 h, then a mixture of benzene and ethanol (10 mL + 0.1 mL) was dropped while stirring the mixture. After 2 h the red crystals (sodium salt of **2**) were filtered off, washed with hexane to remove the excess of the reagent. The crystals were dissolved in a mixture of chloroform (100 mL) and aqueous HCl solution (0.5 N; 30 mL). After extraction, the organic phase was washed with water (3x10 mL), dried (Na_2SO_4), filtered and the filtrate evaporated to dryness under reduced pressure. The residue was chromatographed (eluent: chloroform + methanol, 10:1). As a result of this purification isomer-**2*E*** (2.0 g; 66.9 %) and the mixture of isomers (0.75 g; 25.0 %) were obtained.

Compound (**2*E***): mp 158-162 ^{o}C (ether). IR (KBr): 3381 (νNH indole), 3300-2500 (νOH carboxylic acid), 1711 (νC=O carboxylic acid), 1688 (νC=O conjugated ester), 1618 (νC=C), 1445 ($\beta_s CH_2$), 1193 (ν_{as}COC ester), 1087 (ν_sCOC ester), 755 ($\gamma C_{Ar}H$) cm^{-1}. MS (*m/z*, %): 299 (M^+, 67). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.37 (3H, t, *J*=7.1 Hz, -CH_2CH_3), 3.02 (2H, t, *J*=6.1 Hz, H-3), 3.22 (2H, t, *J*=6.1 Hz, H-4), 3.63 (2H, s, H-2′), 4.32 (2H, q, *J*=7.1 Hz, -CH_2CH_3), 6.92 (1H, br s, H-2), 7.12 (1H, dd, *J*=7.2 + 1.2 Hz, H-8), 7.18 (1H, dd, *J*=7.2 + 7.5 Hz, H-7), 7.32 (1H, dd, *J*=7.5 + 1.2 Hz, H-6), 8.02 (1H, br s, NH). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.13 (-CH_3), 23.49 (C-4), 31.43 (C-3), 37.70 (C-2′), 61.03 (-OCH_2), 111.62 (C-8), 113.44 (C-2a), 117.66 (C-6), 118.21 (C-7), 121.37 (C-3′), 122.40 (C-2), 129.00 (C-8b), 134.11 (C-8a), 148.31 (C-5), 169.30 (-CO_2Et), 177.18 (C-1′). Anal. Calcd. for $C_{17}H_{17}NO_4$, C, 68.21, H, 5.72, N, 4.68. Found C, 68.13, H, 5.68, N, 4.72.

The NMR data of minor isomer (**2*Z***) was determined in the equilibrium of the solution. ^{1}HNMR($CDCl_3$), δ (ppm): 1.15 (3H, t, *J*=7.1 Hz, -CH_2CH_3), 2.80 (2H, t, *J*=6.0 Hz, H-3), 3.10 (2H, t, *J*= 6.0 Hz, H-4), 3.90 (2H, s, H-2′), 4.20 (2H, q, J= 7.1 Hz, -CH_2CH_3), 6.90 (1H, br s, H-2), 7.08-7.25 (3H, m, H-8, H-7, H-6), 8.0 (1H, br s, NH).

5-Ethoxycarbonyl-7-acetoxy-1*H*,9c*H*-3,4-dihydronaphto[*c,d,e*]indole (**4**)

5-Ethoxycarbonyl-1*H*,9c*H*-3,4-dihydronafto[*c,d,e*]indole-7-(*O*-*E*-1,3,4,5-tetrahydrobenz[*c,d*]indole-5-ylidene-3′-ethoxycarbonylethylpropionate) (**5**)

To a solution of **2*E*** (782 mg; 2.6 mmol) in methyl ethyl ketone (35 mL) at rt, dry potassium carbonate (2.0 g; 14.5 mmol) and acetyl chloride (0.5 mL; 7.0 mmol) was added. The reaction mixture was stirred at the above temperature for 4 h. (After 2 h, a further portion of acetyl chloride (0.2 mL) was added). The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in a mixture of chloroform and water (50 mL + 10 mL). The phases were separated and the organic layer was washed with water (2x5 mL), and dried (Na_2SO_4). The filtrate was evaporated and the residue (730 mg) was chromatographed (eluent: hexane + ethyl acetate, 1/1).

The first fraction gave **4** (160 mg; 20 %). From the second fraction, **5** was obtained (211 mg; 15 %).

Compound (**4**): mp 186-192 ^{o}C (from hexane + ethyl acetate, 1/1). IR (KBr): 3480, 1785, 1710, 1480, 1400, 1390 cm^{-1}. MS (*m/z*, %): 323 (M^+, 42.5), 313 (6.4), 281 (100), 252(17). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.42 (3H, t, *J*=7.0 Hz, -CH_2CH_3), 2.48 (3H, s, $COCH_3$), 3.18 (2H, t, *J*=6.1 Hz, H-3), 3.80 (2H, t, *J*=6.1 Hz, H-4), 4.40 (2H, q, *J*=7.0 Hz, -CH_2-CH_3), 6.94 (1H, br s, H-2), 7.43 (1H, d, *J*=8.1 Hz, H-8), 7.54 (1H, d, *J*=8.1 Hz, H-9), 7.68 (1H, s, H-6), 8.32 (1H, br s, NH). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.37 (CH_3), 20.04 (C-3), 20.99 ($COCH_3$), 26.46 (C-4), 60.84 (-OCH_2), 113.20 (C-2a), 114.61 (C-8), 115.21 (C-9), 116.86 (C-6), 117.58 (C-2), 121.66 (C-7a), 124.01 (C-9b), 124.64 (C-5), 127.13 (C-9c), 129.94 (C-9a), 134.81 (C-4a), 144.56 (C-7), 167.14 (-CO_2Et), 169.86 (-$OCOCH_3$). Anal. Calcd. for $C_{19}H_{17}NO_4$, C, 70.57, H, 5.29, N, 4.33. Found C, 70.55, H, 5.32, N, 4.32.

Compound (**5**): mp 156-162 ^{o}C (from hexane + ethyl acetate, 1/1). IR (KBr): 3410, 1790, 1700, 1600 cm^{-1}. FAB-MS (DMSO+NOBA): 563 (M+H). ^{1}H NMR ($CDCl_3$), δ (ppm): part A: 1.38 (3H, t, *J*=7.0 Hz, -CH_2CH_3), 3.15 (2H, t, *J*=6.0 Hz, H-3), 3.78 (2H, t, *J*=6.0 Hz, H-4), 4.39 (2H, q, *J*=7.0 Hz, -CH_2CH_3), 6.88 (1H, br s, H-2), 7.38 (1H, d, *J*=8.0 Hz, H-9), 7.45 (1H, d, *J*=8.0 Hz, H-8), 7.72 (1H, s, H-6), 8.35

(1H, br s, NH); part B: 1.44 (3H, t, *J*=7.0 Hz, -CH_2CH_3), 3.03 (2H, t, *J*=6.0 Hz, H-3), 3.28 (2H, t, *J*=6.0 Hz, H-4), 4.28 (2H, s, -$COCH_2$), 4.41 (2H, q, *J*=7.0 Hz, -CH_2CH_3), 6.85 (1H, br s, H-2), 7.21 (1H, t, *J*=7.4 + 7.1 Hz, H-7), 7.28 (1H, dd, *J*=7.1 + 1.1 Hz, H-8), 7.32 (1H, dd, *J*=7.4 + 1.1 Hz, H-6), 8.04 (1H, br s, NH). ^{13}C NMR ($CDCl_3$), δ (ppm): part A: 14.39 (-CH_3), 20.03 (C-3), 26.46 (C-4), 60.84 (-OCH_2), 113.28 (C-2a), 114.65 (C-8), 115.23 (C-9), 116.76 (C-6), 117.58 (C-2), 121.69 (C-7a), 123.88 (C-9b), 124.51 (C-5), 127.09 (C-9c), 129.93 (C-9a), 134.81 (C-4a), 144.62 (C-7), 169.10 (-CO_2Et); part B: 14.27 (-CH_3), 23.51 (C-4), 31.50 (C-3), 61.03 (-OCH_2), 111.73 (C-8), 113.04 (C-2a), 117.55 (C-6), 118.39 (C-7), 121.57 (C-3′), 122.28 (C-2), 128.81 (C-8b), 129.07 (C-5a), 134.16 (C-8a), 148.54 (C-5), 167.19 + 170.96 (2xCO_2). Anal. Calcd. for $C_{34}H_{30}N_2O_6$, C, 72.58, H, 5.37, N, 4.98. Found C, 72.55, H, 5.48, N, 4.95.

***E/Z*-Methyl-1,3,4,5-tetrahydrobenz[*c,d*]indolylidene(5)-3′-ethoxycarbonylpropionate** (**9**):

Half ester (**2**) (450 mg; 1.5 mmol) was dissolved in CH_2Cl_2 (50 mL) at 0 °C and diazomethane (10 mmol in 10 mL of CH_2Cl_2) was dropped. The mixture was stirred for 2 h. The reaction mixture was diluted with methanol (10 mL) and the mixture was evaporated to dryness under reduced pressure. The residue was purified with column chromatography (silica-Merck 9385, eluent: chloroform + methanol, 20/1) to yield **9** (439 mg, 93.0 %). Pure **9*E***-isomer could be obtained by crystallization from ether.

Compound (**9*E***): mp 111-112 °C. IR (KBr): 3401, 2981, 2951, 2845, 1736, 1715, 1604, 1437 cm^{-1}. MS (*m/z*, %): 312 (M^+, 56). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.31 (3H, t, *J*=7.0 Hz, -CH_2CH_3), 3.01 (2H, t, *J*=6.1 Hz, H-3), 3.19 (2H, t, *J*=6.1 Hz, H-4), 3.78 (3H, s, -OCH_3), 3.84 (2H, s, H-2′), 4.30 (2H, q, *J*=7.0 Hz, -CH_2CH_3), 6.91 (1H, br s, H-2), 7.09 (1H, dd, *J*=7.2 + 1.1 Hz, H-8), 7.17 (1H, dd, *J*=7.5 + 7.1 Hz, H-7), 7.29 (1H, dd, *J*=7.5 + 1.2 Hz, H-6), 8.0 (1H, br s, NH). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.18 (-CH_3), 23.46 (C-4), 31.33 (C-3), 37.73 (C-2′), 52.09 (-OCH_3), 60.74 (-OCH_2), 111.45 (C-8), 113.40 (C-2a), 117.56 (C-6), 118.16 (C-7), 122.27 (C-2), 122.14 (C-3′), 128.67 (C-8b), 129.04 (C-5a), 134.04 (C-8a), 147.25 (C-5), 169.07 (-CO_2Et), 172.44 (C-1′). Anal. Calcd. for $C_{18}H_{18}NO_4$, C, 69.22, H, 5.80, N, 4.48. Found C, 69.17, H, 5.77, N, 4.51.

The NMR data of the minor **9*Z***-isomer was determined from the isomer mixture.

Compound (**9*Z***): ^{1}H NMR ($CDCl_3$), δ (ppm): 1.16 (3H, t, *J*=7.0 Hz, -CH_2CH_3), 2.79 (2H, t, *J*=6.2 Hz, H-3), 3.03 (2H, t, *J*=6.2 Hz, H-4), 3.77 (2H, s, H-2′), 3.81 (3H, s, -OCH_3), 4.18 (2H, q, *J*=7.0 Hz, -CH_2CH_3),

6.89 (1H, br s, H-2), 6.99 (1H, dd, *J*=7.2 + 1.1 Hz, H-8), 7.08 (1H, dd, *J*=7.4 + 7.2 Hz, H-7), 7.24 (1H, dd, *J*=7.4 + 1.1 Hz, H-6), 7.91 (1H, br s, NH). ^{13}C NMR ($CDCl_3$), δ (ppm): 13.71 (-*C*H_3), 22.68 (C-4), 29.98 (C-3), 36.70 (C-2′), 51.85 (-O*C*H_3), 61.04 (-O*C*H_2), 110.84 (C-8), 113.00 (C-2a), 116.46 (C-6), 118.07 (C-7), 122.10 (C-2), 128.05 (C-8b), 128.46 (C-5a), 134.00 (C-8a), 149.60 (C-5), 167.60 (-*C*O_2Et), 171.70 (C-1′).

***E*-Methyl-*N*-pivaloyl-1,3,4,5-tetrahydrobenz[*c,d*]indolylidene(5)-3′-ethoxycarbonylpropionate** (**10**): Diester (**9**) (624 mg; 2.0 mmol) was disolved in THF (40 mL) and the solution was cooled at -78 ^{o}C. To the solution of **9**, n-BuLi solution (2.0 mL; 3.2 mmol, 1.6 mol/L in hexane) was added through siringe and the reaction mixture was stirred for 10 min. Then a solution of pivaloyl chloride (0.4 mL; 3.2 mmol) in THF (10 mL) was added and the mixture was stirred for further 3 h, while the temperature of the reaction mixture was allowed to warm up to rt. The mixture was diluted with aqueous 10 % NH_4Cl solution (50 mL) and ethyl acetate (30 mL). After extraction the phases were separated, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed (Merck 9385, eluent: hexane + ethyl acetate, 8/2) to yield **10** (297 mg, 37.5 %) as an oil.

IR (KBr): 2971, 2934, 2873, 1736, 1740, 1714, 1693, 1611, 1588, 1478, 1434, 1404, 1343, 1371 cm^{-1}. MS (*m/z*, %): 396 (M^+, 82). ^{1}H NMR ($CDCl_3$), δ (ppm): 1.35 (3H, t, *J*=7.0 Hz, -CH_2C*H*$_3$), 1.51 (9H, s, -C/C*H*$_3$/$_3$), 2.95 (2H, t, *J*=6.2 Hz, H-3), 3.16 (2H, t, *J*=6.2 Hz, H-4), 3.76 (3H, s, -OC*H*$_3$), 3.80 (2H, s, H-2′), 4.32 (2H, q, *J*=7.1 Hz, -C*H*$_2$CH$_3$), 7.25 (1H, dd, *J*=7.3 + 1.2 Hz, H-6), 7.32 (1H, dd, *J*=7.3 + 7.2 Hz, H-7), 7.42 (1H, br s, H-2), 8.32 (1H, dd, J=7.2 + 1.2 Hz, H-8). ^{13}C NMR ($CDCl_3$), δ (ppm): 14.18 (-*C*H_3), 23.30 (C-4), 28.61 (-C/*C*H$_3$/$_3$), 30.16 (C-3), 37.58 (C-2′), 40.97 (-*C*/CH$_3$/$_3$), 52.12 (-O*C*H_3), 60.88 (-O*C*H_2), 118.36 (C-8), 118.81 (C-2a), 119.34 (C-7), 121.74 (C-6), 123.08 (C-3′), 125.49 (C-2), 129.07 (C-5a), 129.92 (C-8b), 135.51 (C-8a), 145.91 (C-5), 168.73 (-*C*O_2Et), 172.11 (C-1′), 177.05 (N*C*O). Anal. Calcd. for $C_{23}H_{27}NO_5$, C, 69.50, H, 6.84, N, 3.52. Found C, 69.48, H, 6.79, N, 3.53.

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