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Preparation and Reaction of 3-Oxo-3*H*-pyrazolo[1,5-*a*]indole Derivatives[1)]

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An alternative method to prepare 3-oxo-2-phenyl-3*H*-pyrazolo[1,5-*a*]indoles starting from indoline-2-carboxylic acid was explored. The reaction with nucleophilic agents allowed us to introduce the properly substituted alkyl substituents at C-4 of the 4*H*-pyrazolo[1,5-*a*]indoles. The 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) oxidation of these products gave the 3-oxo-2-phenyl-3*H*-pyrazolo[1,5-*a*]indole derivatives. Selective keto-enol tautomerizations of these 1,5-diketo-monoene system were observed.

Keywords 3-oxo-3*H*-pyrazolo[1,5-*a*]indole; Michael addition; keto-enol tautomerization; 3-hydroxy-4*H*-pyrazolo[1,5-*a*]indole; dimeric product; 2-pyrazoline-4,5-dione-5-methide

We have reported the dark red ketone **1** as an intermediate for the preparation of 3*H*-pyrazolo[1,5-*a*]indole derivatives.[2)] This ketone is of particular interest because its resonance form **2** is stabilized by the formation of a stable pyrazole ring, which affords a highly electrophilic character at C-4, although this position corresponds to the nucleophilic C-3 of the indole nucleus. Also, the ketone **1** contains a 2-pyrazoline-4,5-dione-5-methide structural unit, a pyrazole analog of *o*-quinone monomethide.[3)] We have developed an alternative method to prepare this ketone based upon the reaction between hydrazonyl and carboxy groups[4)] and investigated its chemical behavior toward nucleophilic agents.

The reduction of the ketone **1** with $NaBH_4$ in methanol afforded the air-sensitive phenolic product **3**.[2)] As the quinone methides can be prepared from phenols,[5)] the phenol **3** was oxidized with 1 eq of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and the dark red product **1** was obtained in 95% yield. Thus, compounds **1** and **3** are interconvertible by reduction and oxidation reactions. Consequently an alternative method to prepare the phenol **3** was explored by employing Pilling's method to prepare 4-hydroxypyrazole from α-hydrazinoacid.[4a)] This pathway eventually allowed an easy access to the ketone **1** (Chart 1). As a starting material, indoline-2-carboxylic acid **5** was selected and transformed into the 1-carbamoyl compound **6** by treatment with NaOCN and CF_3COOH. This product was subjected to the Hofmann rearrangement with NaOCl/KOH.[6)] The basic reaction mixture was acidified with hydrochloric acid, then the N-amino compound **7** formed *in situ* was allowed to react with benzaldehyde. The hydrazone **8** (M^+ *m/z*: 266) isolated in 62% yield was cyclized intramolecularly by refluxing with a mixture of pyridine and acetic anhydride[4a)] to give the acetate **4** in 57% yield. The hydrolysis of the acetate with NaOH under an inert gas as described in a previous report[2)] afforded the phenol **3** in good yield. As the ketone **1** was in hand, its chemical properties were investigated.

The C-3 position of the indole nucleus is quite reactive to electrophilic reagents.[7)] This property can be reversed by introducing electron-withdrawing groups at N-1 and C-2, but examples are scarce.[8)] The C-3 of the ketone **1** retains this feature, as represented by the resonance form **2**. In contrast to the reduction with $NaBH_4$ in methanol,[2)] the reduction of the ketone **1** with di-isobutyl aluminum hydride (DIBAL-H) at −78 °C afforded two products after acetylation. The major product was identified as the acetate **4** (46%). The minor product **9** (10%) had M^+ at *m/z* 578 in the MS, which supported the dimeric structure of the acetate **4** (*m/z* 290 × 2 − 2 = 578). In the ^1H-NMR spectrum the minor product **9** showed a singlet signal at δ 5.02 (4-H), which is 1 ppm lower than the 4-H signal of **4**. The integration ratio between 4-H and acetyl methyl protons of the minor product **9** was 1 : 3, while that for **4** was 2 : 3. Thus, the dimeric structure **9** was assigned to the minor product. The base peak (P^+, *m/z* 247) in the MS can be rationalized in terms of the formation of the stable radical cation **11**, which is derived from the monomeric radical cation **10** formed by cleavage of the central bond of the dimeric product **9**. The formation of the dimeric product

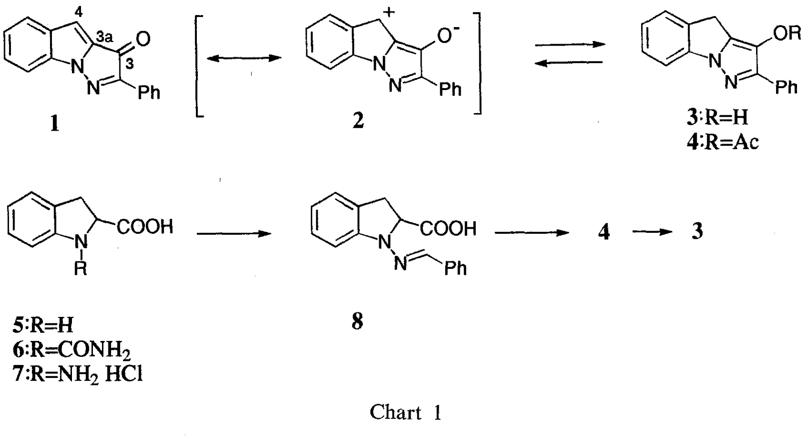

Chart 1

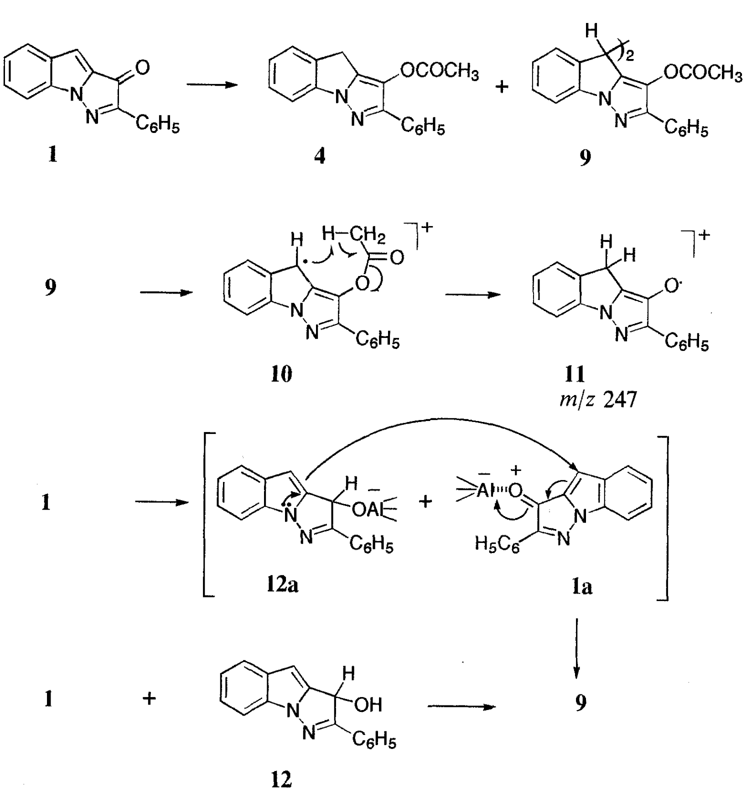

Chart 2

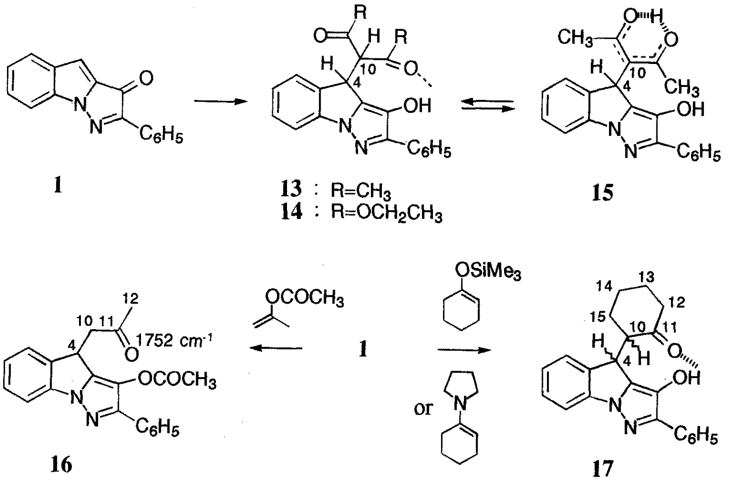

Chart 3

9 is illustrated in Chart 2. The initial *in situ* 1,2-reduction product **12a** works as a nucleophile and attacks the ketone complex **1a** formed by the association of **1** with DIBAL-H as a Lewis acid.[9] The complex **12a** is a derivative of the 3*H*-pyrazolo[1,5-*a*]indole, whose C-4 nucleophilic character was reported in the previous report.[2] The subsequent proton removal and isomerization of the coupled product gives the dimeric product **9**. This pathway was eventually confirmed by the independent reaction of these intermediates. When an equimolar mixture of the 3*H*-isomer **12**[2] and the ketone **1** was treated with 1 eq of boron trifluoride etherate at −50 °C, the dimeric product **9** was obtained in 89% yield after acetylation.

Then the reactions of the ketone **1** with anionic nucleophiles were investigated (Chart 3). When the ketone **1** was reacted with acetylacetone and ethyl malonate in the presence of sodium hydride at 0—3 °C, the Michael addition products **13** and **14** were obtained in 95% and 84% yields, respectively. The adduct **13** consisted mainly of the keto form (80%), as two acetyl groups (δ 1.81 and 2.41 ppm) and two distinct methine protons, 4-H (δ 4.57 ppm) and 10-H (δ 4.42 ppm) with $J=4.9$ Hz, were detected in the ^{1}H-NMR spectrum. The shift of one acetyl methyl signal to lower magnetic field (δ 2.41 ppm) is due to the intramolecular hydrogen bonding between 3-OH (δ 7.23) and one acetyl carbonyl group. The other acetyl methyl (δ 1.81 ppm) is subject to the anisotropic effect of the aromatic ring. The ^{1}H-NMR spectrum of **13** in solution

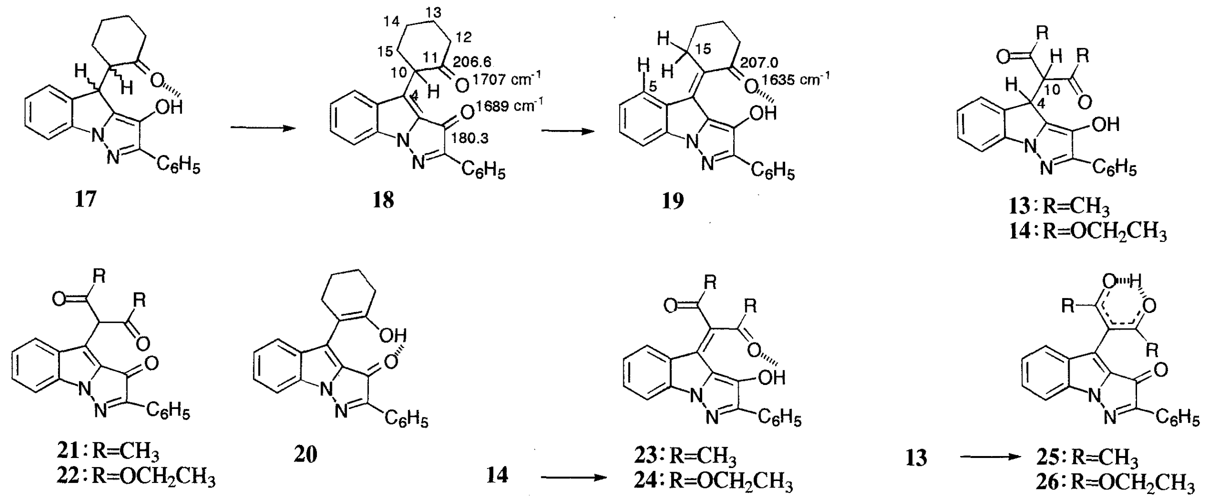

Chart 4

revealed contamination with the enol form **15** (20%), which showed two distinct methyl signals at δ 1.14 and 2.27 ppm, both as small singlets, because of restricted rotation at the single bond between C-4 and C-10. Also the signal of the tightly trapped enolic OH was seen at δ 16.96 ppm as a small singlet (0.2 H), in addition to 3-OH (δ 6.95, s). The methyl and OH groups for the enol form of 3-methyl-2,4-pentandione were reported to resonate at δ 2.08 and 16.50 ppm, respectively.[10] The small signals of the enol **15** were also distinctly detected in the ^{13}C-NMR spectrum. In contrast to the adduct from acetylacetone, the adduct **14** from ethyl malonate was found to be free from the enol form, consisting solely of the keto form. The ^{1}H-NMR spectrum of **14** showed two ethyl ester and 3-OH (δ 7.64) signals. In the IR spectrum ($CHCl_3$), two ester carbonyl (1740 and 1718 cm^{-1}) and weakly hydrogen-bonding 3-OH (3397 cm^{-1}) groups were also observed.

Next, acid-catalyzed nucleophilic addition reactions were investigated (Chart 3). When the ketone **1** was reacted with isopropenyl acetate in the presence of 1 eq of boron trifluoride etherate, nucleophilic addition and acetyl transfer took place consecutively and the adduct **16** was obtained in 97% yield. The introduction of the acetonyl group at C-4 was supported by the signal of 4-H (δ 4.64), which was coupled with the adjacent methylene protons (δ 2.96, J = 7.0 Hz) of the acetonyl group in the ^{1}H-NMR spectrum. Ketone carbonyl (1752 cm^{-1}) and ester carbonyl (1709 cm^{-1}) were readily distinguished in the IR spectrum. Similar reaction of the ketone **1** with 1-cyclohexenyl trimethylsilyl ether afforded the adduct **17** in 88% yield. This adduct is a mixture of diasteroisomers (85 : 15) according to the ^{1}H-NMR analysis. The same product **17** was obtained but in somewhat lower yield (44%), when the ketone **1** was reacted with an enamine, 1-pyrolidino-1-cyclohexene.

Table I. UV-VIS Spectra of 3-Oxo-3*H*-pyrazolo[1,5-*a*]indole Derivatives[a)]

Compound	λ_{max} nm (log ε)	λ_{max} nm (log ε)	λ_{max} nm (log ε)	λ_{max} nm (log ε)
1	238 (sh, 4.11)	291 (4.06)	391 (4.01)	504 (3.52)
18	236 (sh, 4.24)	295 (4.20)	391 (4.12)	511 (3.73)
19	214 (sh, 4.38)[b)]	294 (4.42)	391 (3.88)	489 (3.67)
24	258 (4.17)	293 (4.39)	368 (3.90)	490 (3.59)
25	240 (sh, 4.18)	291 (4.19)	401 (4.01)	523 (3.77)

a) Measured in acetonitrile. *b)* End absorption.

Since the above products are phenols, they were subjected to DDQ oxidation as in the case of the phenol **3**. When the cyclohexanone adduct **17** was oxidized with 1 eq of DDQ in THF and the reaction mixture was carefully worked up with aqueous 0.5 M NaOH (1 eq), the dark red crystalline product **18** was obtained in 82% yield (Chart 4). The UV-VIS absorption pattern of this dark red product was essentially identical with that of the ketone **1**, with a slight bathochromic shift (Table I). Thus the structure **18**, involving the same conjugated system as in **1**, was assigned to this product. Two ketone carbonyls were detected at 1707 cm^{-1} (six-membered ketone) and 1689 cm^{-1} (five-membered conjugated ketone) in the IR spectrum. The observation of 10-H at δ 4.22 (dd, J = 12.1, 6.0 Hz) in the NMR spectrum also favors the diketo-structure **18** over the monoketo-enol structures, **19** and **20**. When the solution of the diketone **18** in dichloromethane was stirred vigorously with aqueous 10% NaOH solution, the isomeric dark red product **19** was isolated in quantitative yield. The 3-OH of **19** appeared at around 3000 cm^{-1} as a broad shallow band due to hydrogen-bonding, and one carbonyl absorption was detected at 1635 cm^{-1} in the IR spectrum. In the ^{1}H-NMR spectrum 3-OH was seen at δ 8.13 ppm as a singlet. The differentiation of the enol-form **19** from **20** was accomplished by ^{13}C-NMR analyses. Of two keto carbonyls of the diketone **18**, the 3-keto carbonyl carbon appeared at δ 180.3 ppm but this signal is no longer present in the isomerized product. However, a carbonyl carbon (δ 206.6 ppm) of the isomerized product corresponded well with the 11-ketone carbon (δ 207.0 ppm) of **18**, although double bond conjugation shifts the carbonyl carbon to higher magnetic field as deduced from the conjugated resonance form. These comparisons allowed us to assign the structure **19** for the isomerized product. In the NOESY spectrum of the product **19**, nuclear Overhauser effect

(NOE) was detected between 5-H (δ 7.71) and 15-H_2 (δ 3.18). The highest VIS absorption band of **19** appeared at 489 nm, which is at 22 nm shorter wavelength than that of the diketone **18** (Table I).

The similar oxidation of the malonate adduct **14** with DDQ gave the red needles **24** in 78% yield (Chart 4). Three structures are possible for this oxidation product, the triketone (**22**), the diketone (**24**) and the monoketone (**26**). The UV-VIS absorption pattern was quite similar to that of the monoketo-enol **19** (Table I). The presence of two non-equivalent ethyl esters could eliminate the structures **22** and **26** if there is free rotation around the single bond between C-4 and C-10. In fact, two signals for $OCH_2C\underline{H}_3$ were detected at δ 1.38 (t, $J=7.0$ Hz) and 1.41 ppm (t, $J=7.0$ Hz) in the ^{1}H-NMR spectrum, and there was no methine proton, which should be present in the triketone **22**. In the ^{13}C-NMR spectrum no carbonyl carbon other than the ester carbonyls (δ 166.2 and 167.0 ppm) was detectable. Based on these observations, the structure **24** was assigned to the red product. In the IR spectrum 3-OH is detected as a broad band (3451 cm^{-1}) due to intramolecular hydrogen-bonding. Also the appearance of 3-OH at comparatively low magnetic field (δ 10.2, s) in the ^{1}H-NMR spectrum also supported the presence of intramolecular hydrogen-bonding.

Dehydrogenation of the acetylacetone adduct **13** with DDQ also produced a similar dark red product. Among the three possible structures for this product, **21**, **23** and **25**, the monoketone structure **25** was assigned for this product, based on the following observations. In the IR spectrum only one carbonyl absorption was detected at 1688 cm^{-1}, which corresponded well with the 3-keto carbonyl absorption of the diketone **18** (1689 cm^{-1}). Two or more carbonyl absorptions should appear in the other isomers, **21** and **23**. The enolic OH appeared around 3000 cm^{-1} as a broad shallow band because of strong hydrogen-bonding, as in acetylacetone.[11] In the ^{1}H-NMR spectrum two methyl groups appeard as a singlet (δ 2.10 ppm), like those of acetylacetone.[10] This is because the 3-keto group of **25** does not hinder the free rotation of the enolic acetylacetone unit, although 3-OH of the enol form of the acetylacetone adduct **15** does restrict free rotation of the enolic portion. The signal of the tightly trapped enolic OH was detected at quite low magnetic field (δ 17.35 ppm). In the ^{13}C-NMR spectrum the position of the 3-keto carbon signal (δ 180.0 ppm) was in good accord with that in the diketone **18** (δ 180.3 ppm). The chemical shifts of 2 eq enol carbons (δ 192.3 ppm) and methyl carbons (δ 24.1 ppm) are comparable with those for the enol form of acetylacetone (δ 190.5 and 22.5 ppm).[12] Since this enolic structure of **25** is quite stable, **25** did not undergo further keto-enol isomerization and was recovered intact when treated with 10% aqueous NaOH solution.

In summary, we have found a useful method to introduce alkyl substituents at C-4 of 4*H*-pyrazolo[1,5-*a*]indole derivatives by the reaction of 3-oxo-3*H*-pyrazolo[1,5-*a*]-indole derivatives with nucleophilic agents. This method, in combination with the electrophilic reactions at C-4 of 3*H*- and 1*H*-pyrazolo[1,5-*a*]indole derivatives,[2,13] makes it possible to introduce a variety of substituents at C-4 of the 4*H*-isomers *via* both nucleophilic and electrophilic reactions. An interesting keto-enol tautomerization of the 1,5-diketo-monoene system, in which a conjugated ketone unit is constructed in the 3-oxo-pyrazolo[1,5-*a*]indole skeleton, was also observed.

Experimental[14]

3-Oxo-2-phenyl-3*H*-pyrazolo[1,5-*a*]indole (1) A mixture of the phenol **3** (69 mg, 0.28 mmol) and DDQ (63 mg, 0.28 mmol) in THF (5 ml) was stirred at room temperature (r.t.) for 2 h. The dark red solution was diluted with dichloromethane, then washed with 10% aqueous NaOH and saturated brine. After drying over anhydrous $MgSO_4$ the solution was evaporated and the crude product was recrystallized from ethyl acetate to give the conjugated ketone **2**[2] (65 mg, 95%).

Preparation of 3-Acetoxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (4) from Indoline-2-carboxylic Acid (5) 1) To a mixture of indoline-2-carboxylic acid **5** (6.80 g, 41.7 mmol), NaOCN (5.52 g, 84.9 mmol) and MeCN (50 ml) were added CF_3COOH (6.6 ml, 85.7 mmol). The suspension was stirred at r.t. for 3 h, then NaOCN (2.61 g; total 8.13 g, 125.1 mmol) and CF_3COOH (3.1 ml; total 9.7 ml, 125.9 mmol) were added again and stirring was continued overnight. The reaction mixture was concentrated and the residual solution was acidified with 1 M HCl. The solid was collected, washed with water, dried and recrystallized from ethanol to give 1-carbamoylindoline-2-carboxylic acid (**6**, 7.10 g, 82%), mp 171.0—173.0 °C (from ethanol). MS *m*/*z*: 206 (M^+, 8), 163 (27), 118 (100), 91 (7). IR: 3397, 3227, 2928, 2503 (br), 1911 (br), 1702, 1684, 1607, 1489, 1451, 1254, 751 cm^{-1}. ^{1}H-NMR (d_6-DMSO) δ: 3.06 (1H, dd, $J=16.6$, 2.6 Hz, 3-H), 3.37 (1H, br s, COOH), 3.50 (1H, dd, $J=16.6$, 11.0 Hz, 3-H), 4.91 (1H, dd, $J=11.0$, 2.6 Hz, 2-H), 6.32 (2H, s, NH_2), 6.85 (1H, t, $J=7.3$ Hz, 5-H), 7.10 (1H, t, $J=7.8$ Hz, 6-H), 7.13 (1H, d, $J=7.3$ Hz, 4-H), 7.77 (1H, d, $J=7.8$ Hz, 7-H). ^{13}C-NMR (d_6-DMSO) δ: 32.6 (C-3), 59.7 (C-2), 114.1 (C-7), 121.1 (C-5), 124.2 (C-4), 127.0 (C-6), 128.4 (C-3a), 143.6 (C-7a), 155.5 (C=O, carbamoyl), 173.0 (COOH). 2) The 1-carbamoyl compound **6** (4.12 g, 20.0 mmol) was dissolved in a solution of aqueous KOH (85%, 4.62 g, 70.0 mmol) and ethanol–water (1 : 1, 80 ml), and the whole was cooled to 0 °C. Into this solution, 1.6 M sodium hypochlorite (16 ml, 25.6 mmol) was introduced and the resulting solution was further stirred at r.t. for 1 h, then warmed at 50 °C for 30 min. After it had cooled, the solution was acidified with 6 M HCl and warmed at 40 °C for 30 min. It was cooled to r.t., then benzaldehyde (2.54 g, 24.0 mmol) was added, and the reaction mixture was stirred overnight at r.t. The precipitates were collected, washed with water and dried to give 1-benzylideneaminoindoline-2-carboxylic acid (**8**, 3.30 g, 62%), mp 174.5—175.5 °C (from ethyl acetate). MS *m*/*z*:266 (M^+, 19), 221 (54), 220 (24), 118 (100), 117 (83), 105 (10), 104 (11), 91 (9). IR: 3030, 2940, 1708, 1611, 1589, 1563, 1483, 1269, 1230, 1213, 754, 746, 690 cm^{-1}. ^{1}H-NMR (d_6-DMSO) δ: 3.19 (1H, dd, $J=16.6$, 4.4 Hz, 3-H), 3.34 (1H, br s, COOH), 3.65 (1H, dd, $J=16.6$, 11.2 Hz, 3-H), 4.98 (1H, dd, $J=11.2$, 4.4 Hz, 2-H), 6.81 (1H, td, $J=7.4$, 1.2 Hz, 5-H), 7.10—7.19 (3H, m, 4,6,7-H), 7.28 (1H, tt, $J=7.3$, 1.2 Hz, 4′-H), 7.37 (1H, s, N=CH), 7.38 (2H, m, 3′,5′-H), 7.66 (2H, m, 2′,6′-H). ^{13}C-NMR (d_6-DMSO) δ: 32.5 (C-3), 60.3 (C-2), 108.2 (C-7), 120.2 (C-5), 124.6 (C-4), 125.4 (C-3a), 125.6 (C-2′, 6), 127.7 (C-6), 127.8 (C-4′), 128.5 (C-3′, 5′), 133.0 (N=C), 135.7 (C-1′), 147.4 (C-7a), 171.7 (COOH). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.17; H, 5.21; N, 10.50. 3) A solution of hydrazone **8** (2.25 g, 8.4 mmol) in a mixture of pyridine (30 ml) and acetic anhydride (1.75 ml) was refluxed for 2 h under a nitrogen atmosphere. The reaction mixture was poured onto ice (20 g) and the solution was extracted with ether. The usual work-up of the extracts yielded a colorless crystalline product **4**[2] (1.40 g, 57%).

Reduction of the Ketone 1 with DIBAL-H The ketone **1** (246 mg, 1 mmol) was dissolved in dry CH_2Cl_2 (20 ml) and the solution was cooled to −78 °C. A 1 M solution of DIBAL-H in hexane (1.5 ml, 1.5 mmol) was introduced into the ketone solution at −78 °C in an atmosphere of argon and the resulting solution was stirred at the same temperature for 1 h, then the reaction was quenched with NaF (63 mg, 1.5 mmol) and water (2 drops). The suspension was vigorously stirred for 30 min and filtered. The inorganic material was washed with CH_2Cl_2. The filtrate and washings were combined and dried over $MgSO_4$. After usual work-up, the product was dissolved in CH_2Cl_2 (10 ml) and acetylated with acetic anhydride (0.20 ml, 2.12 mmol) and DMAP (122 mg, 1.00 mmol) at r.t. for 6 h. The solution was poured into a mixture of 1 M HCl and ice, and extracted with ether. Work-up and chromatographic purification (petroleum ether–ethyl acetate, 9 : 1) gave **4** (133 mg, 46%) and the dimeric product **9** (26 mg, 10%), colorless crystals, mp 244.0—244.5 °C (from ethyl acetate). MS *m*/*z*: 578 (M^+, 7), 290 (18), 247 (100), 143 (9), 104 (11), 89 (8). IR: 3059, 1761, 1626, 1477, 1202, 751, 696 cm^{-1}. ^{1}H-NMR δ: 2.18 (6H, s, $COCH_3$), 5.02 (2H, s, 4-H), 6.92 (2H, d, *J*=7.4 Hz, 5 H), 7.06 (2H, td, *J*=7.4, 0.9 Hz, 6-H), 7.26—7.45 (8H, m, Ar-H), 7.61 (2H, d, *J*=7.8 Hz, 8-H), 7.86 (4H, m, 2′,6′-H). ^{13}C-NMR δ: 20.9 ($CO\underline{C}H_3$), 44.7 (C-4), 110.6 (C-8), 124.8 (C-5), 125.0 (C-6), 126.6 (C-2′, 6′), 128.0 (C-4′), 128.6 (C-3′, 5′, 3), 129.1 (C-7), 131.9 (C-1′), 134.2 (C-4a), 136.0 (C-3a), 140.2 (C-8a), 145.1 (C-2), 167.8 (C=O). *Anal.* Calcd for $(C_{18}H_{13}N_2O_2)_2$: C, 74.73; H, 4.53; N, 9.68. Found: C, 75.00; H, 4.51; N, 9.62.

Lewis Acid-Catalyzed Reaction of the Ketone 1 with the 3*H*-Isomer (12) A solution of **1** (123 mg, 0.50 mmol) and **12**[2] (124 mg, 0.50 mmol) in CH_2Cl_2 (10 ml) was cooled to −50 °C under an argon atmosphere. To this solution, borontrifluoride etherate (0.13 ml, 1.06 mmol) was added and the solution was stirred at −50 °C for 30 min. After addition of aqueous $NaHCO_3$, the basic solution was neutralized with 1 M HCl, then extracted with CH_2Cl_2. The extracts were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was dissolved in dry CH_2Cl_2 and acetylated with acetic anhydride (0.20 ml, 2.12 mmol) and DMAP (26 mg, 0.21 mmol) at r.t. for 6 h. Work-up as described above gave the dimeric product **9** (259 mg, 89%).

3-[4-(3-Hydroxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indolyl)]pent-2,4-dione (13) A mixture of the ketone **1** (70 mg, 0.28 mmol) and sodium hydride (60% dispersion in mineral oil, 12 mg, 0.30 mmol) in dry THF (10 ml) was stirred at 0—3 °C in a nitrogen atmosphere. Then acetylacetone (0.04 ml, 0.90 mmol) was added and the resulting solution was kept at the same temperature for 5 min. Aqueous ammonium chloride was added, and the resulting solution was extracted with ether. The crude product thus obtained was purified by flash column chromatography (petroleum ether–ethyl acetate, 3 : 1) to give the adduct **13** (94 mg, 95%) as a readily coloring amorphous solid, which was shown to contain the enol form (20%) in solution by ^{1}H-NMR analysis. MS *m*/*z*: 346 (M^+, 15), 303 (21), 261 (22), 247 (19), 246 (36), 144 (16), 143 (100), 134 (23), 128 (21), 119 (74), 115 (82), 105 (39), 100 (19), 91 (31), 85 (33), 70 (57), 61 (54). HRMS: Calcd for $C_{21}H_{18}N_2O_3$: 346.1316. Found M^+: 346.1372. IR: 3360, 3060, 1721, 1700, 1623, 1474, 1304, 1247, 1147, 774, 754, 698 cm^{-1}. ^{1}H-NMR δ (keto form: 80%): 1.81 (s, CH_3), 2.41 (s, CH_3), 4.42 (d, *J*=4.9 Hz, 10-H), 4.56 (d, *J*=4.9 Hz, 4-H), 7.23 (s, 3-OH); δ (enol form: 20%): 1.14 (s, CH_3), 2.23 (s, CH_3), 4.99 (s, 4-H), 6.95 (br s, 3-OH), 16.96 (s, OH); δ (common signals): 7.15 (1H, m, 6-H), 7.28 (1H, m, 4′-H), 7.33 (1H, d, *J*=7.3 Hz, 5-H), 7.38—7.45 (3H, m, Ar-H), 7.64 (1H, d, *J*=7.8 Hz, 8-H), 8.10 (2H, m, 2′,6′-H). ^{13}C-NMR δ (ket form): 30.5 (CH_3), 31.6 (CH_3), 38.4 (C-4), 69.3 (C-10), 110.7 (C-8), 124.3 (C-6), 124.8 (C-5), 126.3 (C-2′, 6′), 127.4 (C-4′), 128.1 (C-3), 128.4 (C-3′, 5′), 129.5 (C-7), 132.7 (C-1′), 133.5 (C-4a), 136.4 (C-3a), 140.1 (C-8a), 143.6 (C-2), 202.8 (CO), 206.7 (CO); δ (enol form): 23.1 (CH_3), 23.6 (CH_3), 38.8 (C-4), 106.4 (C-10), 110.4 (C-8), 124.5 (C-6), 124.7 (C-5), 126.5 (C-2′, 6′), 127.7 (C-4′), 128.6 (C-3′, 5′), 128.7 (C-7), 133.1 (C-1′), 134.1 (C-4a), 136.8 (C-3a), 139.6 (C-8a), 145.2 (C-2), 189.3 (s), 195.3 (s). It was not possible to see the C-3 signal.

Diethyl 2-[4-(3-Hydroxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indolyl)]-malonate (14) The ketone **1** (85 mg, 0.35 mmol) and ethyl malonate (0.07 ml, 0.46 mmol) in dry THF (10 ml) were reacted in the presence of sodium hydride (60% dispersion, 15 mg, 0.38 mmol) as described above to give the adduct **14** (118 mg, 84%) as a readily coloring amorphous solid. MS *m*/*z*: 406 (M^+, 5), 262 (4), 246 (9), 133 (69), 115 (100), 88 (44), 61 (33). HRMS: Calcd for $C_{23}H_{22}N_2O_5$: 406.1527. Found M^+: 406.1475. IR ($CHCl_3$): 3397, 2986, 1740, 1718, 1625, 1481, 1472, 1307 cm^{-1}. ^{1}H-NMR δ: 0.92 (3H, t, *J*=7.1 Hz, $OCH_2C\underline{H}_3$), 1.37 (3H, t, *J*=7.1 Hz, $OCH_2C\underline{H}_3$), 3.96 (2H, q, *J*=7.1 Hz, $OC\underline{H}_2CH_3$), 4.01 (1H, d, *J*=5.4 Hz, 10-H), 4.40 (2H, m, $OC\underline{H}_2CH_3$), 4.59 (1H, d, *J*=5.4 Hz, 4-H), 7.15 (1H, t, *J*=7.6 Hz, 6-H), 7.23—7.48 (5H, m, Ar-H), 7.61 (1H, d, *J*=8.1 Hz, 8-H), 7.64 (1H, s, OH), 8.12 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 13.5 ($OCH_2\underline{C}H_3$), 14.0 ($OCH_2\underline{C}H_3$), 39.1 (C-4), 54.6 (C-10), 62.3 ($O\underline{C}H_2CH_3$), 63.0 ($O\underline{C}H_2CH_3$), 110.2 (C-8), 124.0 (C-6), 124.9 (C-5), 126.3 (C-2′, 6′), 127.2 (C-4′), 127.8 (C-3), 128.4 (C-3′, 5′), 129.1 (C-7), 133.1 (C-1′), 133.4 (C-4a), 136.7 (C-3a), 140.3 (C-8a), 143.3 (C-2), 167.4 (C=O), 170.7 (C=O).

4-Acetonyl-3-acetoxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (16) Borontrifluoride etherate (0.05 ml, 0.41 mmol) was introduced into a solution of the ketone **1** (88 mg, 0.36 mmol) and isopropenyl acetate (0.08 ml, 0.73 mmol) in dry CH_2Cl_2 (15 ml), which was stirred and cooled at −30 °C in nitrogen atmosphere, and the resulting solution was kept at the same temperature for 1 h. After addition of ether, the solution was washed with aqueous $NaHCO_3$, 1 M HCl and brine successively. Flash column chromatography (petroleum ether–ethyl acetate, 4 : 1) of the crude product gave **16** (119 mg, 96%) as a syrup. MS *m*/*z*: 346 (M^+, 23), 304 (100), 261 (91), 247 (47), 246 (75), 143 (36), 130 (19), 129 (21), 117 (16), 104 (24), 86 (41), 84 (61), 77 (16). HRMS: Calcd for $C_{21}H_{18}N_2O_3$: 346.1316. Found M^+: 346.1354. IR (neat): 3061, 2961, 2932, 1752, 1709, 1624, 1599, 1477, 1368, 1206, 1177, 759, 694 cm^{-1}. ^{1}H-NMR δ: 2.21 (3H, s, $CH_2COC\underline{H}_3$), 2.33 (3H, s, $OCOC\underline{H}_3$), 2.96 (2H, d, *J*=7.0 Hz, $C\underline{H}_2COCH_3$), 4.64 (1H, t, *J*=7.0 Hz, 4-H), 7.19 (1H, td, *J*=7.6, 1.0 Hz, 6-H), 7.28—7.48 (5H, m, Ar-H), 7.66 (1H, d, *J*=7.8 Hz, 8-H), 7.84 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 21.0 ($OCO\underline{C}H_3$), 29.9 (C-12), 36.4 (C-4), 45.9 (C-10), 110.5 (C-8), 124.9 (C-6), 124.9 (C-5), 126.8 (C-2′,6′), 127.9 (C-3), 128.0 (C-4′), 128.6 (C-3′,5′,7), 132.0 (C-1′), 136.7 (C-4a), 139.0 (C-3a), 139.9 (C-8a), 146.6 (C-2), 169.0 ($O\underline{C}OCH_3$), 205.9 (C-11).

2-[4-(3-Hydroxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indolyl]cyclohexanone (17) 1) Borontrifluoride etherate (0.13 ml, 1.06 mmol) was added to a solution of the ketone **1** (246 mg, 1.00 mmol) and trimethylsiloxycyclohexene (0.21 ml, 1.10 mmol) in dry CH_2Cl_2 (20 ml) at −30 °C and the reaction mixture was kept at the same temperature for 30 min. After dilution with CH_2Cl_2, the solution was worked up as described above to give the product **17** (277 mg, 80%) as a diastereoisomeric mixture (85 : 15) and a readily coloring amorphous solid. MS *m*/*z*: 344 (M^+, 26), 326 (7), 247 (30), 246 (35), 143 (28), 134 (15), 128 (16), 119 (49), 105 (34), 91 (28), 84 (32), 73 (100). HRMS: Calcd for $C_{22}H_{20}N_2O_2$: 344.1524. Found M^+: 344.1527. IR: 3372, 3058, 2938, 1697, 1623, 1477, 1305, 1246, 773, 752, 697 cm^{-1}. ^{1}H-NMR δ (major isomer: 85%): 1.08—1.18 (m, 15-H), 1.47—1.78 (m, 13, 15-H and 14-H_2), 2.17 (m, 13-H), 2.58 (m, 12-H_2), 3.22 (ddd, *J*=13.0, 5.2, 2.7 Hz, 10-H), 4.48 (d, *J*=2.7 Hz, 4-H), 7.16 (t, *J*=7.6 Hz, 6-H), 7.25 (1H, s, OH), 7.26—7.44 (5H, m, Ar-H), 7.60 (1H, d, *J*=8.0 Hz, 8-H), 8.13 (m, 2′,6′-H); δ (minor isomer: 15%): 1.94 (m, 14-H), 2.36 (m, 13-H), 2.54 (m, 12-H_2), 2.64 (m, 10-H), 4.20 (d, *J*=9.0 Hz, 4-H), 7.09 (t, *J*=7.6 Hz, 6-H), 8.10 (m, 2′,6′-H). ^{13}C-NMR δ (major isomer): 25.0 (C-14), 28.9 (C-13), 29.1 (C-15), 39.0 (C-4), 42.9 (C-12), 54.0 (C-10), 110.2 (C-8), 124.0 (C-6), 124.1 (C-5), 126.1 (C-2′, 6′), 127.2 (C-4′), 128.4 (C-3′, 5′), 128.7 (C-7), 128.9 (C-3), 133.2 (C-1′), 135.0 (C-4a), 136.1 (C-3a), 140.7 (C-8a), 143.0 (C-2), 218.7 (C=O). δ (minor isomer): 25.1 (C-14), 28.2 (C-13), 33.1 (C-15), 39.9 (C-4), 54.5 (C-10), 123.2 (C-6), 126.3 (C-2′, 6′), 127.4 (C-4′), 132.0 (C-1′), 134.6 (C-4a), 135.5 (C-3a), 140.6 (C-8a), 143.4 (C-2), 217.4 (C=O). 2) A solution of the ketone **1** (246 mg, 1.00 mmol) and 1-pyrrolidino-1-cyclohexene (0.19 ml, 1.18 mmol) in dry CH_2Cl_2 (20 ml) was treated with borontrifluoride etherate (0.15 ml, 1.22 mmol) at −30 °C for 1 h in an argon atmosphere. Work-up as described above gave **17** (152 mg, 44%).

2-[4-(3-Oxo-2-phenyl-3*H*-pyrazolo[1,5-*a*]indolyl]cyclohexanone (18) DDQ (183 mg, 0.80 mmol) was added to a solution of the phenol **17** (277 mg, 0.80 mmol) in THF (10 ml), and the resulting solution was stirred at r.t. overnight. The reaction mixture was dissolved in CH_2Cl_2 and the solution was washed with 0.5 M NaOH solution (2 ml), water and brine successively. After drying over $MgSO_4$, the solution was evaporated and the crude product was recrystallized to give the dark red crystalline **18** (226 mg, 82%), mp 178.5—179.5 °C (from ethyl acetate). MS *m*/*z*: 342 (M^+, 100), 314 (28), 286 (6), 273 (7), 239 (12), 211 (30), 183 (33), 182 (29), 168 (19), 167 (13), 155 (17), 154 (17), 142 (7), 141 (8), 140 (11), 129 (7), 128 (9), 127 (12), 115 (11), 104 (8), 103 (6), 84 (7), 77 (7), 69 (10). IR: 3070, 2948, 2857, 1707, 1689, 1615, 1543, 1342, 1314, 1294, 1150, 1141, 1124, 1023, 872, 747, 689 cm^{-1}. ^{1}H-NMR δ: 1.73—2.72 (8H, m, 4×CH_2), 4.11 (1H, dd, *J*=12.1, 6.0 Hz, 10-H), 7.07 (1H, td, *J*=7.5, 1.3 Hz, 6-H), 7.38—7.55 (6H, m, Ar-H), 8.21 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 25.3 (C-14), 27.4 (C-13), 33.8 (C-15), 42.1 (C-12), 49.3 (C-10), 110.2 (C-8), 122.0 (C-6), 124.0 (C-5), 127.1 (C-4), 127.4 (C-2′, 6′), 127.9 (C-1′), 128.7 (C-3′, 5′), 128.7 (C-3a), 130.2 (C-7, 4a), 130.4 (C-4′), 134.5 (C-8a), 152.6 (C-2), 180.3 (C-3), 206.6 (C-11). *Anal.* Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.15; N, 8.12.

3-Hydroxy-4-(2-oxo-1-cyclohexylidene)-2-phenyl-4*H*-pyrazolo[1,5-*a*]indole (19) A heterogeneous solution of **18** (37 mg, 0.11 mmol) in a mixture of CH_2Cl_2 (10 ml) and aqueous 10% NaOH (4 ml) was stirred vigorously at r.t. for 2 h. The organic layer was collected and washed with water and brine successively. Recrystallization of the crude product gave **19** (37 mg, 100%), dark red crystals, mp 137.5—139.0 °C (from ethanol). MS *m*/*z*: 342 (M^+, 100), 314 (13), 286 (9), 239 (18), 211 (56), 183 (60), 182 (52), 168 (40), 155 (45), 154 (37), 142 (15), 141 (25), 140

(19), 129 (13), 128 (15), 127 (22), 115 (27), 114 (12), 83 (21), 77 (22), 69 (29). IR: 3000 (broad shallow band), 3057, 2944, 1635, 1621, 1553, 1478, 1469, 1406, 1248, 1156, 1096, 975, 766, 742, 694 cm^{-1}. ^{1}H-NMR δ: 1.93 (4H, m, 13,14-H$_2$), 2.67 (2H, t, $J=5.9$ Hz, 12-H$_2$), 3.18 (2H, t, $J=5.7$ Hz, 15-H$_2$), 7.07 (1H, td, $J=7.9$, 1.1 Hz, 6-H), 7.32 (1H, tt, $J=7.3$, 1.2 Hz, 4′-H), 7.39 (1H, td, $J=7.9$, 1.0 Hz, 7-H), 7.43 (2H, m, 3′,5′-H), 7.51 (1H, d, $J=7.9$ Hz, 8-H), 7.71 (1H, d, $J=7.9$ Hz, 5-H), 8.13 (1H, s, OH), 8.13 (2H, m, 2′,6′-H). ^{13}C-NMR δ: 22.4 (C-14), 23.2 (C-13), 32.0 (C-15), 41.5 (C-12), 110.1 (C-8), 123.8 (C-6), 126.4 (C-2′, 6′), 127.6 (C-4′), 128.4 (C-3′, 5′), 128.8 (C-5), 129.8 (C-3), 131.2 (C-7), 132.3 (s), 132.6 (s), 134.5 (s), 140.2 (s), 142.5 (s), 145.0 (s), 165.3 (s), 207.0 (C=O). *Anal.* Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.16; H, 5.15; N, 8.14.

Diethyl 2-[3-Hydroxy-2-phenyl-4*H*-pyrazolo[1,5-*a*]indol-4-ylidene]malonate (24) The adduct **14** (162 mg, 0.40 mmol) was reacted with DDQ (100 mg, 0.44 mmol) in THF (10 ml) at r.t. for 30 min and worked up as described above to give **24** (125 mg, 78%), red needles, mp 120.0—121.0 °C (from ethyl acetate). MS *m/z*: 404 (M$^+$, 60), 358 (100), 286 (6), 227 (31), 183 (53), 154 (18), 128 (23), 127 (46). IR: 3451 (br), 3073, 2982, 1725, 1678, 1620, 1605, 1473, 1266, 1246, 1081, 1031, 777, 763, 699 cm^{-1}. ^{1}H-NMR δ: 1.38 (3H, t, $J=7.0$ Hz, $\mathrm{OCH_2C\underline{H}_3}$), 1.41 (3H, t, $J=7.0$ Hz, $\mathrm{OCH_2C\underline{H}_3}$), 4.41 (2H, q, $J=7.0$ Hz, $\mathrm{OC\underline{H}_2CH_3}$), 4.48 (2H, q, $J=7.0$ Hz, $\mathrm{OC\underline{H}_2CH_3}$), 7.04 (1H, td, $J=7.5$, 1.4 Hz, 6-H), 7.27—7.53 (6H, m, Ar-H), 8.11 (2H, m, 2′,6′-H), 10.27 (1H, s, OH). ^{13}C-NMR δ: 13.9 ($2\times\mathrm{CH_2\underline{C}H_3}$), 62.3 ($\mathrm{\underline{C}H_2CH_3}$), 63.2 ($\mathrm{\underline{C}H_2CH_3}$), 110.2 (C-8), 115.0 (s), 124.2 (C-6), 124.7 (s), 125.4 (C-4′), 126.3 (C-2′, 6′), 127.8 (C-3, 5), 128.4 (C-3′, 5′), 131.9 (s), 132.6 (C-7), 135.6 (s), 139.8 (s), 143.7 (s), 145.3 (s), 166.2 (C=O), 167.0 (C=O). *Anal.* Calcd for $C_{23}H_{20}N_2O_5$: C, 68.30; H, 4.99; N, 6.97. Found: C, 68.25; H, 4.90; N, 6.68.

4-Oxo-3-[4-(3-oxo-2-phenyl-3*H*-pyrazolo[1,5-*a*]indolyl]pent-2-en-2-ol (25) A solution of the adduct **13** (331 mg, 0.96 mmol) and DDQ (217 mg, 0.96 mmol) in THF (5 ml) was stirred at r.t. for 30 min then diluted with ether. After usual work-up, the crude product was purified by flash column chromatography (petroleum ether–ethyl acetate, 9 : 1) to give **25** (278 mg, 85%), dark red needles, mp 204.0—205.0 °C (from ethyl acetate–pentane). MS *m/z*: 344 (M$^+$, 100), 326 (7), 302 (7), 223 (15), 213 (34), 198 (16), 171 (29), 170 (63), 156 (50), 149 (16), 143 (36), 142 (34), 129 (22), 128 (37), 127 (22), 115 (51), 101 (20), 83 (28), 81 (22), 77 (18). IR: 3000 (broad shallow band), 3076, 1684, 1614, 1551, 1421, 1336, 1279, 1144, 766, 748, 689 cm^{-1}. ^{1}H-NMR δ: 2.10 (6H, s, $2\times\mathrm{CH_3}$), 7.16 (1H, td, $J=7.6$, 1.2 Hz, 6-H), 7.42—7.55 (5H, m, Ar-H), 7.61 (1H, d, $J=8.3$ Hz, 8-H), 8.25 (2H, m, 2′,6′-H), 17.35 (1H, s, OH). ^{13}C-NMR δ: 24.1 ($2\times\mathrm{CH_3}$), 103.4 (C-10), 110.4 (C-8), 122.4 (C-4), 122.8 (C-6), 124.4 (C-5), 126.6 (C-3a), 127.5 (C-2′,6′), 128.4 (C-1′), 128.8 (C-3′, 5′), 130.5 (C-7), 130.7 (C-4′), 130.8 (C-4a), 134.3 (C-8a), 152.7 (C-2), 180.0 (C-3), 192.3 ($2\times$C=O). *Anal.* Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.14. Found: C, 73.49; H, 4.58; N, 8.02.

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