PYRROLO[2,1-*a*]ISOINDOL-5-ONES AND BENZ[3,4]AZOCIN-1(2*H*)-1,4,6-TRIONES

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Abstract - Pyrrolo[2,1-*a*]isoindol-5-ones (**8**) have been obtained by base catalyzed cyclization and *O*-alkylation of *N*-phthalimido-substituted β-keto ester (**1**) *via* intermediate (**7**). Reaction of **1** with MeI/acetone/K_2CO_3 gave the *C*-alkylation product (**3**). With bulkier reagents than MeI in a variety of solvents and in the presence of various bases, compounds (**8**) were isolated. In the absence of an alkylating agent, reaction of **1** with NaH/DMF gave pyrrolo[2,1-*a*]isoindol-5-one derivative (**6**), found at room temperature in its keto form (**6a**) and at higher temperatures in the enol form pyrrolo[2,1-*a*]isoindol-5-one-1-carboxy-2-hydroxy-3-methyl methyl ester (**6b**), and **11** which at room temperature already appeared in the enol form. Reaction of acyl chloride (**14**) with ethyl cyanoacetate/NaH did not stop at ethyl-2-cyano-4-*N*-isoindol-3-oxopentanoate (**15**) but proceeded to rearrange to a single diastereomeric benz[3,4]azocin-1(2*H*)-1,4,6-trione (**17**).

Pyrrolo[2,1-*a*]isoindol-5-ones have been prepared by photocyclization of *N*-alkylated phthalimides,[1] reaction of substituted-1,4-diketones[2] with ammonia, intramolecular cyclization of an intermediate 2-(2-aminoethyl)indane-1,3-dione,[3] intramolecular acylations of pyrroles[4] and condensation of iminium ions derived from phthalimide and allenic silanes.[5]

This paper describes a simple, one step synthesis of pyrrolo[2,1-*a*]isoindol-5-ones (**8**) involving base catalyzed cyclization of *N*-phthalimido-substituted β-keto ester (**1**). These compounds have been found to be useful intermediates in the synthesis of statine and its analogues. In the course of attempted base

catalyzed alkylation of **1**, in a variety of solvents (acetone, DMF, toluene, *tert*-BuOH) and in the presence of various bases (K_2CO_3, *tert*-BuOK, NaH), a rapid, deep red coloration of the reaction mixture took place. A similar observation was made even in the absence of an alkylating agent when the reaction was carried out in the presence of NaH/DMF or *tert*-BuOK/*tert*-BuOH. Isolation and identification of the products revealed that instead of the desired *C*-alkylation, an unexpected cyclization had taken place to give compounds (**8**) or (**11**). *C*-Alkylation to give **3** was feasible only with MeI/acetone/K_2CO_3 (Figure 1) and even then a small amount of cyclized by-product (**8a**) formed. Replacement of MeI by bulkier alkyl halides resulted in exclusive formation of cyclized products such as **8b** (Figure 2). In the absence of an alkylating agent with stronger bases (NaH/DMF), rapid cyclization of **2** gave **6**, capable of existing in keto-**6a** and enol-**6b** forms. The former is favored at lower temperature, as evidenced by the minor coloration (pale yellow) of the reaction solution at 25 °C. At higher temperature, *ca.* 80 °C, the deeply red colored enol form **6b** prevailed. In the presence of alkylating agents enolate (**7**) underwent facile *O*-alkylation to give strongly colored **8** (Figure 2).

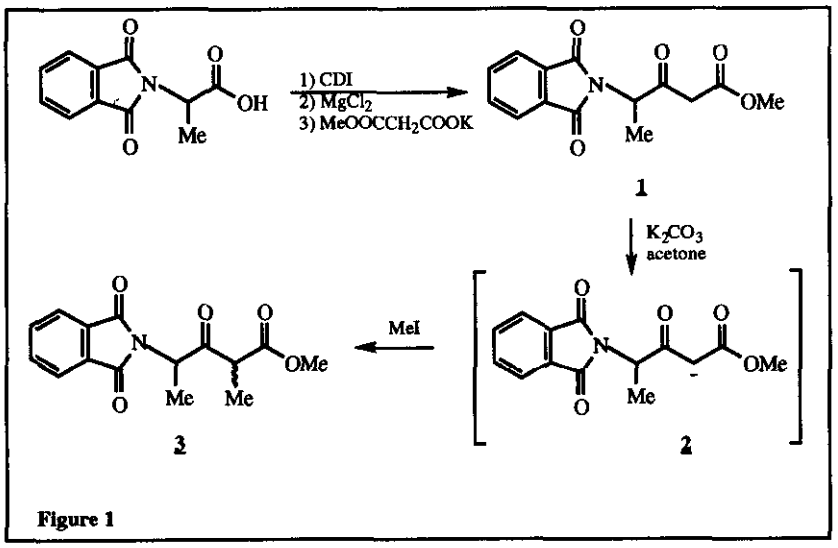


Figure 1

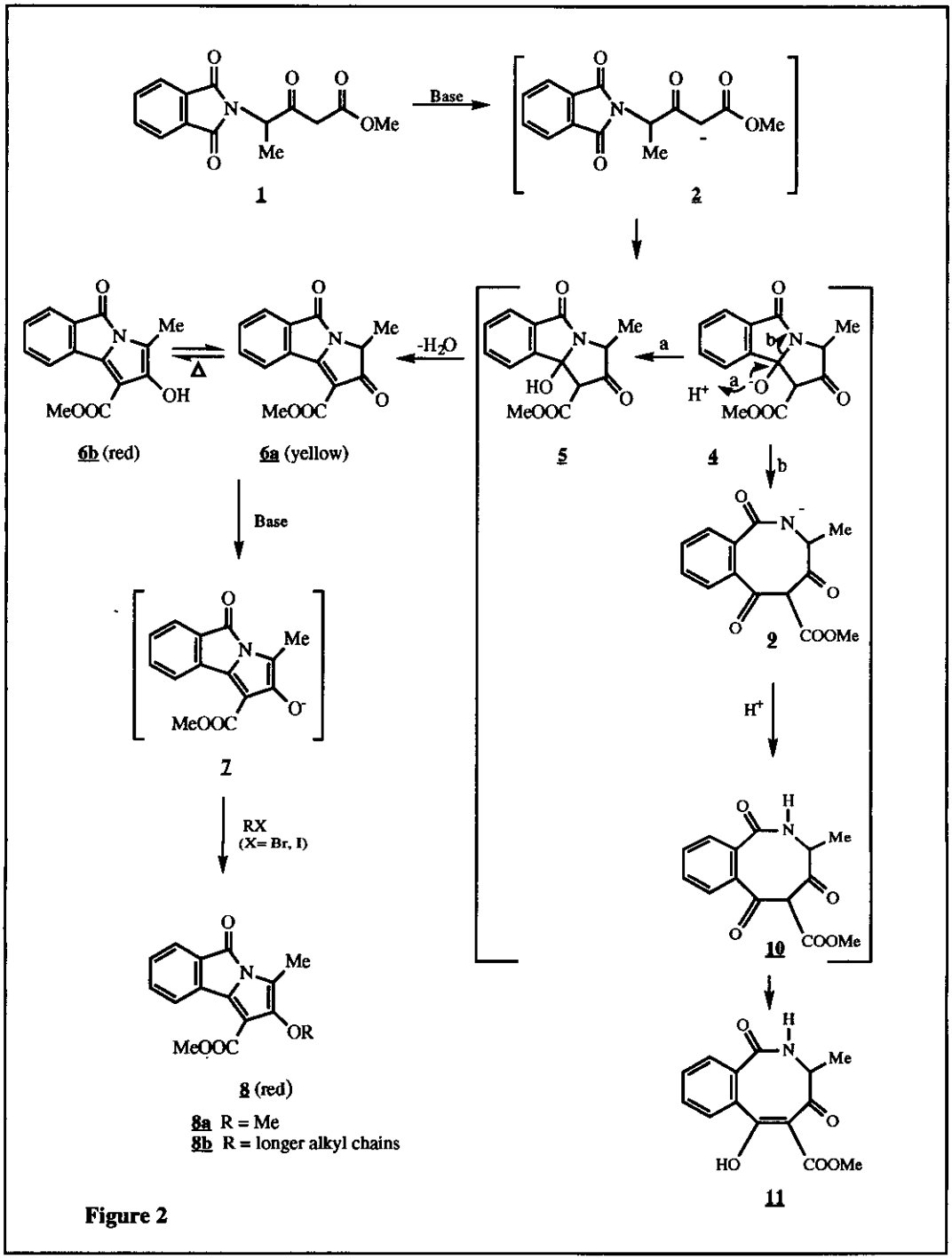
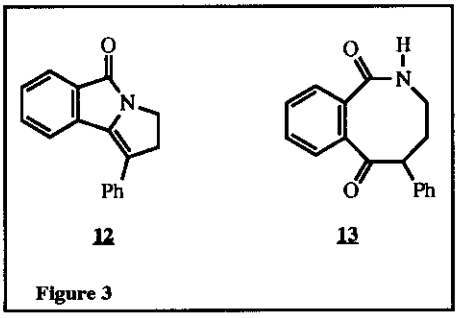

Base
1
2
-H2O
a
b
6b (red)
6a (yellow)
5
4
Base
9
H+
7
RX
(X= Br, I)
10
8 (red)
8a R = Me
8b R = longer alkyl chains
11

Figure 2

The isolation of **11** was possible because of the prevailing *enolic* character of the β-keto ester intermediate (**10**). This is in contrast to the formation of 2,3-dihydro-1-phenylpyrrolo[2,1-*a*]isoindol-5-ones (**12**) obtained *via* intramolecular ring contraction of the *ketonic* intermediate 3,4-dihydro-6-hydroxy-5-phenylbenz[3,4]azocin-1(2*H*)-one (**13**), postulated by Crabb and Patel (Figure 3).[3]



12 **13**

Figure 3

In an effort to achieve *C*-alkylation and prevent the rearrangement reaction leading to **6** or **8**, an attempt was made to prepare a derivative such as **15** possessing a readily removable acidic hydrogen. The intermediate anion (**16**) was expected to form readily and be capable of undergoing *C*-alkylation. However, when the acyl chloride (**14**) reacted with ethyl cyanoacetate/NaH, the reaction did not stop at **15** but readily rearranged to give a single diastereomer of structure (**17**) (Figure 4). The facile intramolecular cyclization may be attributed to the high electrophilic character of one of the phthalimido carbonyl groups. Structure elucidation of the rearrangements products was based primarily on nmr spectra. ^{1}H-Nmr of compounds (**8**), (**11**) and (**17**) showed characteristic asymmetric aromatic patterns in contrast to that of the symmetric phthalimido derivative (**1**). Compounds (**8**) lacked methine protons both α to the N and α to the ester groups and the C*Me* (singlet) was shifted downfield by about 1 ppm in comparison to the CH*Me* (doublet) in **1**. The absence of a ketonic *C*=O in the ^{13}C-nmr spectrum of **8** gave further support to the assigned structure. The structure of **11** was consistent with the presence of a CH*Me* doublet, a C*H*Me quintet, an N*H* doublet in the ^{1}H-nmr spectrum, and a ketonic *C*=O in the ^{13}C-nmr spectrum. In general, the ^{1}H-nmr of **17** was similar to that of **11**, however, in the ^{13}C-nmr the presence of two ketonic *C*=O's and a nitrile carbon was instrumental in the structure determination. The stereochemistry of **17** was not elucidated, however only one diastereomer was detected, as evidenced by the single patterns of both the ^{1}H-nmr and ^{13}C-nmr spectra.

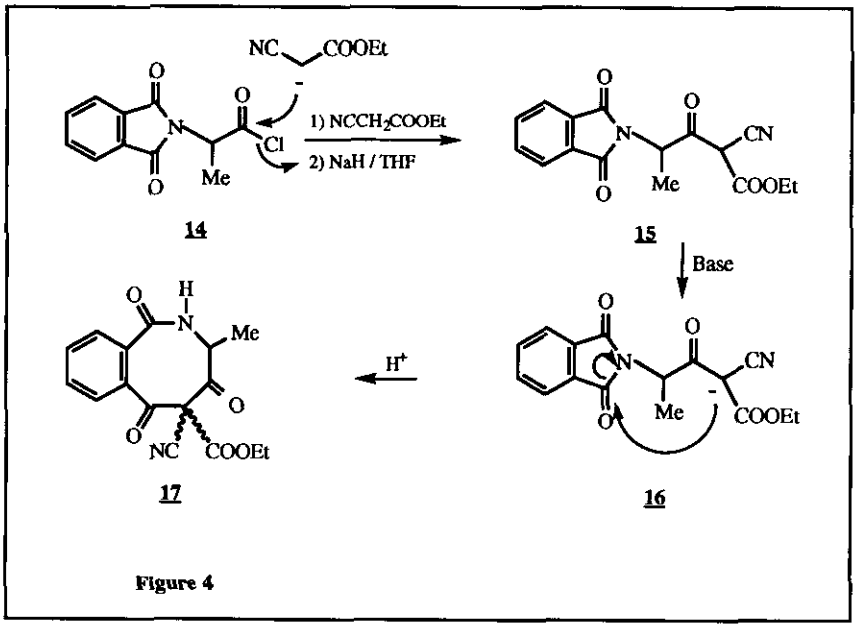


Figure 4

EXPERIMENTAL

^{1}H-Nmr spectra 200-MHz and 300-MHz were obtained on Brucker AC-200 and AM-300 spectrometers respectively. Chemical shifts were expressed in ppm downfield from Me_4Si used as internal standard. The values are given in δ scale. Mass spectra were obtained on a Varian Mat 731 spectrometer (CI=chemical ionization). Progress of the reactions was monitored by tlc on silica gel (Merck, Art. 5554). Flash chromatography was carried out on silica gel (Merck, Art 9385).

Methyl-4-*N*-isoindol-3-oxopentanoate (1). To a solution of *N*-phthalimido-L-alanine[6] (0.22 g, 1 mmol) in dry THF (15 ml) was added *N,N'*-carbonyldiimidazole (0.195 g, 1.2 mmol) and the solution was stirred at room temperature under N_2 for 0.5 h, followed by addition of $MgCl_2$ (0.1 g, 1 mmol) and monomethyl malonate potassium salt[7] (0.16 g, 1 mmol) and the resulting slurry was stirred at 50 °C overnight. The mixture was evaporated and the residue was partitioned between 1N HCl and EtOAc. The aqueous layer was extracted with EtOAc (3x15 ml). The combined organic layer was washed with 1N HCl (15 ml), 5% $NaHCO_3$ (3x15 ml), brine (15 ml), dried ($MgSO_4$) and evaporated to give the product as yellow crystals which were not further purified, mp 73-75 °C. ^{1}H-Nmr ($CDCl_3$) δ ppm 1.64 (d, J = 7 Hz,

3H, Me), 3.54 (ABq, *JAB* = 16 Hz, 2H, CH_2), 3.69 (s, 3H, OMe), 5.00 (q, *J* = 7 Hz, 1H, CH), 7.70-7.80 (m, 2H, Ar), 7.85-7.95 (m, 2H, Ar). ^{13}C-Nmr ($CDCl_3$) δ 14.25 (Me), 45.79 (CH_2), 52.45 (OMe), 54.08 (CH), 123.63 (C-2), 131.85 (C-1), 134.37 (C-3), 166.80 (CO-N), 167.42 (COO), 197.73 (CO). Ms (CI/i-Bu) m/z 276 (MH^+, 100), 244 (MH^+-MeOH, 42), 174 (MH^+-$C_4H_5O_3$, 2).

Pyrrolo[2,1-*a*]isoindol-5-one-1-carboxy-2-[butoxy-(4-ethoxycarbonyl)]-3-methyl methyl ester (8b). Method I: A solution of **1** (0.85 g, 3 mmol) in dry DMF (2.5 ml) was added to hexane-washed NaH (0.11 g, 2.8 mmol). A vigorous evolution of gas was observed and the solution turned deep red-brown. Ethyl 5-bromovalerate (0.87 g, 0.42 mmol) was added followed by a small amount of NaI. The mixture was stirred and heated to 90 °C for 6 h, during which the color changed to a dark orange. The reaction mixture was poured into water, acidified with 1N HCl and extracted with ether. The etheral layer was dried ($MgSO_4$), filtered and chromatographed (hexane:AcOEt 2:1) to give 0.5 g, 43%. **Method II**: A light yellow mixture of **1** (0.1 g, 0.36 mmol), K_2CO_3 (55 mg, 0.36 mmol), 18-crown-6 (97 mg, 0.36 mmol) and ethyl 5-bromovalerate (80 mg, 0.36 mmol) in dry toluene (15 ml) was heated for 10 min at 90 °C. The mixture was worked up as described in Method I, to give 52 mg, 38%. The red crystals obtained were recrystallized from EtOH, mp 55-57 °C. ^{1}H-Nmr ($CDCl_3$) δ 1.26 (t, *J* = 8 Hz, 3 H, $COOCH_2$*Me*), 1.83 (m, 4 H, $CH_2CH_2CH_2CO$), 2.35 (s, 3 H, Ar*Me*), 2.40 (t, *J* = 7 Hz, 2 H, CH_2CO), 3.92 (t, *J* = 7 Hz, 2 H, OCH_2CH_2), 3.94 (s, 3 H, COOMe), 4.14 (q, *J* = 7 Hz, 2 H, $COOCH_2$Me), 7.25 (ddd, *J* = 9, 7.5, 2 Hz, 1 H, H-3), 7.50 (ddd, *J* = 9, 7.5, 2 Hz, 1 H, H-2), 7.66 (dd, *J* = 7.5, 2 Hz, 1 H, H-4), 7.98 (dd, *J* = 7.5, 2 Hz, 1 H, H-1). ^{13}C-Nmr δ 8.25(Ar*Me*), 14.11 (*Me*CH_2), 21.46 (CH_2CH_2O), 29.27 ($CH_2CH_2CH_2O$), 33.88 (CH_2COOEt), 51.29 (OMe), 60.11 (CH_2Me), 74.60 (CH_2CH_2O), 108.49 (NCMe), 119.58 (CCOMe), 123.03 (Ar, C-9), 124.94 (Ar, C-7), 130.42 (Ar, C-6), 134.69 (Ar, C-8), 134.75 (*Ar*CO), 134.95 (*Ar*CN), 145.74 (CN), 163.08 (COOMe), 164.18 (COOEt), 173.29 (CON). Ms (CI/*i*-Bu) m/z 386 (MH^+, 65), 354 (MH^+-MeOH, 34), 340 (MH^+-EtOH, 11).

Pyrrolo[2,1-*a*]isoindol-5-one-1-carboxy-2-one-3-methyl methyl ester (6a). A solution of **1** (0.184 g, 0.66 mmol) in dry DMF (5 ml) was added to hexane-washed NaH (16 mg, 0.66 mmol). A vigorous evolution of gas was observed and the solution turned deep red-brown. The mixture was stirred at 80 °C for 1 h after which the DMF was evaporated. The orange residue was acidified with 1N HCl and

extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, evaporated and recrystallized from EtOH to give 99 mg, 57 % of **6**, mp 158-160 °C. ^{1}H-Nmr ($CDCl_3$) δ ppm 1.68 (d, *J* = 7 Hz, 3 H, CH*Me*), 3.97 (s, 3 H, COOMe), 4.38 (q, *J* = 7 Hz, 1 H, C*H*Me), 7.78 (m, 2 H, H-2, H-3), 7.93 (m, 1 H, H-4), 8.78 (m, 1 H, H-1); Ms (EI) m/z 257(M^+, 75), 226 (M^+-MeO, 55), 197 (M^+-MeOCOH, 63), 174 (M^+-$C_4H_5O_2$, 100).

Methyl-4-(*N*-phthalimido)-2-methyl-3-oxopentanoate (3). A suspension of K_2CO_3 (0.21 g, 1.5 mmol), **1** (0.1 g, 0.37 mmol) and MeI (62 mg, 0.44 mmol) in dry acetone (15 ml) was stirred under reflux for 2 h after which it was filtered. The filtrate was evaporated and chromatographed (hexane:AcOEt 2:1). The product was obtained as a mixture of 2 diastereomers in 56 % yield (59 mg). ^{1}H-Nmr ($CDCl_3$) (major diastereomer) δ ppm 1.32 (d, *J* = 7.5 Hz, 3 H, COOCH*Me*), 1.66 (d, *J* = 7.5 Hz, 3 H, COCH*Me*), 3.62 (s, 3 H, COOMe), 3.76 (q, *J* = 7.5 Hz, 1 H, COOC*H*Me), 5.04 (q, *J* = 7.5 Hz, 1 H, COC*H*Me), 7.70 (two symmetrical m, 4 H, Ar); (minor diastereomer) δ ppm 1.28 (d, *J* = 7.5 Hz, 3 H, COOCH*Me*), 1.51 (d, *J* = 7.5 Hz, 3 H, COCH*Me*), 3.58 (s, 3 H, COOMe), 3.59 (q, *J* = 7.5 Hz, 1 H, COOC*H*Me), 4.96 (q, *J* = 7.5 Hz, 1 H, COC*H*Me), 7.70 (two symmetrical m, 4 H, Ar). ^{13}C-Nmr (major diastereomer) δ ppm 12.57 (COOCH*Me*), 14.01 (COCH*Me*), 48.08 (CHNCO), 52.26 (OMe), 53.04 (CO*C*HCO), 123.36 (C-2), 131.55 (C-1), 134.26 (C-3), 167.30 (Ar*C*O), 170.10 (*C*OOMe), 200.78 (CO); (minor diastereomer) δ ppm 12.99 (COOCH*Me*), 14.07 (COCH*Me*), 48.40 (CHNCO), 52.26 (OMe), 53.38 (CO*C*HCO), 123.22 (C-2), 131.63 (C-1), 134.05 (C-3), 167.23 (Ar*C*O), 169.73 (*C*OOMe), 200.45 (CO); Ms (CI/*i*-Bu) m/z 290 (MH^+, 100), 258 (MH^+-OMe, 28), 174 (MH^+-$C_5H_7O_3$, 2.8).

5-Cyano-5-ethoxycarbonyl-3-methyl benz[3,4]azocin-1(2*H*)-1,4,6-trione (17). A solution of *N*-phthalimido-L-alanine chloride (0.48 g, 2 mmol), in dry THF (5 ml) under N_2 was added to ethyl cyanoacetate anion, generated from ethyl cyano acetate (0.23 g, 2 mmol) and NaH (96 mg, 2 mmol) in dry THF (10 ml), and the resulting mixture was refluxed for 6 h. The reaction was quenched by adding EtOH (3 ml), and the reaction mixture was allowed to stand at room temperature overnight. The mixture was washed with 1N NaOH (30 ml). The combined aqueous layers were extracted with ether (30 ml), acidified with 1N HCl and extracted with EtOAc (30 ml). The combined organic layer was dried over $MgSO_4$, filtered and evaporated to give the product as a tan-colored powder. ^{1}H-Nmr ($CDCl_3$) δ 1.36 (t, *J* = 7 Hz,

3 H, $COOCH_2Me$), 1.58 (d, J = 7 Hz, 3H, $CHMe$), 4.33 (q, J = 7 Hz, 2 H, $COOCH_2Me$), 5.16 (quintet, J = 7 Hz, 1H, CH), 6.72 (d, J = 7 Hz, 1H, NH), 7.55 (m, 3 H, H-7, H-8, H-9), 8.02 (d, J = 7, Hz, 1 H, H-10). ^{13}C-Nmr provided information regarding the structure as it showed two ketones (189.18 and 195.09). Ms (EI) m/z 314 (M^+, 2), 268 (M^+-EtOH, 2).

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