4, H-6), 5.70 (1 H, br s, H-2); MS (low resolution, 70 eV, 85 °C), m/e (relative intensity) 178 (80, $M^+ - 18$), 163 (44), 153 (12), 140 (30), 139 (13), 135 (31), 111 (100), 109 (47), 107 (27), 95 (36); CI (methane), MS (low resolution) 237 (7, M + 41), 225 (21, M + 29), 197 (100, M + 1), 179 (17, M + 1 - H_2O).

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Registry No. 1, 2873-36-1; **2**, 2854-40-2; **3**, 36357-32-1; **4**, 87013-76-1; **5**, 87013-77-2; **6**, 87039-25-6; batyl alcohol, 544-62-7; chimyl alcohol, 506-03-6; δ-valerolactam, 675-20-7; *p*-hydroxybenzaldehyde, 123-08-0.

Supplementary Material Available: Data for **5** from X-ray analysis: Table S1, bond angles; Table S2, endocyclic torsion angles; Table S3, positional parameters for the carbon and oxygen atoms (3 pages). Ordering information is given on any current masthead page.

Mechanism of Acylation of Dilithium Salts of β-Keto Esters: An Efficient Synthesis of Anibine

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Condensation of the dianion of ethyl acetoacetate, generated by LDA in ether solution, with ethyl benzoate furnished ethyl 5-phenyl-3,5-dioxopentanoate (**7b**) in only 35% yield. Addition of TMEDA (0.02 M) dramatically increased the yield to 85%. The method was extended to the synthesis of ethyl 5-(3′-pyridyl)-3,5-dioxopentanoate (**7d**) in high yield. The latter on thermal cyclization followed by methylation with diazomethane yielded anibine (**1**).

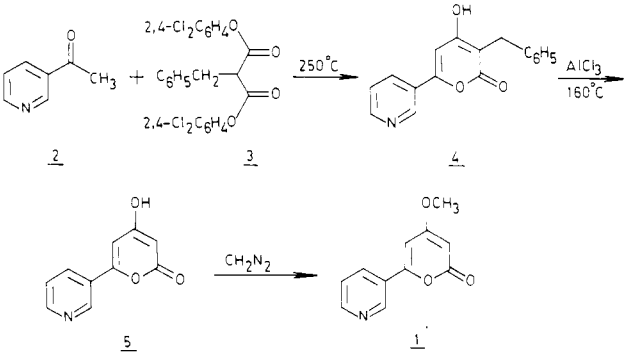
Anibine, an alkaloid from South American rosewood trees, *Aniba duekei* and *Aniba rosaeodora*, was isolated by Mors and co-workers and was shown to be 4-methoxy-6-(3′-pyridyl)-α-pyrone (**1**).[1] Its pharmacological properties[2] are similar to that of nikethamide. The camphorsulfonate[3] is used as an antispasmodic agent in the treatment of cardiac and respiratory failures and also in morphine and barbituric coma.

A synthesis of **1** has been reported by Ziegler and Nolken (Scheme I).[4] A simpler synthesis of the benzene analogue (**9**) of **1** through the intermediacy of **7a** or **7b** is known (Scheme II, Ar = Ph).[5] There is, however, no report of the application of this method to obtain **1** itself. This could be due to difficulties in obtaining **7c**, which is an amino acid. Mors and co-workers[1] indeed failed to obtain **7c** in the hydrolysis of **1**.

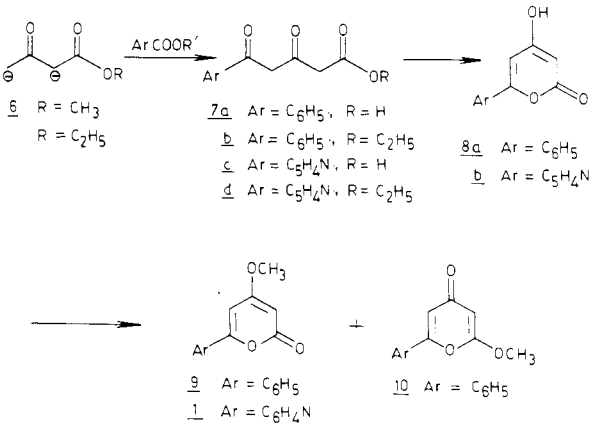
Synthesis of **1** by cyclization of **7d** was more promising. In the case of the benzene analogue (**7b**), the cyclization was achieved with concentrated sulfuric acid,[5] but only in poor yield (11%). Our plan was to achieve the cyclization thermally. This was attempted, in the first instance, with **7b**.

To obtain **7b**, the dianion of ethyl acetoacetate was prepared by using LDA and was then treated with ethyl benzoate. Aqueous workup furnished acid **7a** in 35% yield, 55% of ethyl benzoate being recovered. The reaction also

Scheme I



Scheme II



furnished another compound, $C_{19}H_{20}O_5$, mp 102–103 °C, whose spectral properties (see Experimental Section) indicated that it was diethyl 5-phenyl-3-hydroxyhomophthalate (**12b**). The methyl ester **12a**, corresponding to

(1) (a) Mors, W. B.; Gottlieb, O. R.; Djerassi, C. *J. Am. Chem. Soc.* **1957**, *79*, 4507. (b) Mors, W. B.; Gottlieb, O. R. *Chem. Abstr.* **1960**, *54*, 12181h.
(2) Bofafogo Gonealves, N.; Joao Canali carrea Fo *Nature (London)* **1958**, *182*, 938.
(3) Boissier, J. R.; Combes, G.; Gottlieb, O. R. *Chem. Abstr.* **1964**, *61*,15940g.
(4) Ziegler, E.; Nolken, E.; *Monatsh. Chem.* **1958**, *89*, 391, 716.
(5) Wolfe, J. F.; Harris, T. M.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 3249.

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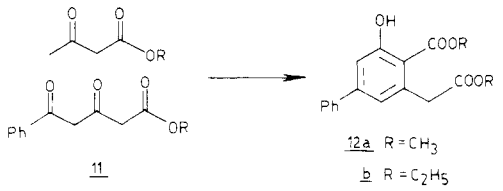


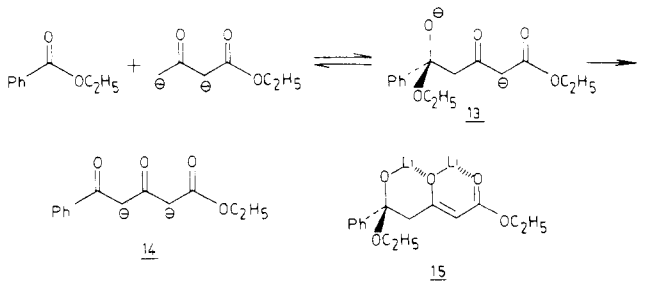
11 12a R = CH_3 b R = C_2H_5

12b, is known in the literature[6] but was obtained in a different way.

Formation of **7a**, in the above experiment, indicated that **7b** had formed in the reaction but had been hydrolyzed in the alkaline medium during aqueous workup. In order to avoid the hydrolysis, the reaction mixture was first decomposed with the calculated amount of glacial acetic acid dissolved in ether. Further workup gave ester **7b** in 35% yield as a mixture of enol isomers (^{1}H NMR), which were sensitive to heat and were characterized by hydrolysis to **7a** in high yield (isolated yield 80%). The recovery of ethyl benzoate was again 55%. This reaction also furnished the compound **12b** obtained in the earlier experiment.

The structure of **12b** indicated that it might have been formed by further reaction of **7b** with the dianion of ethyl acetoacetate, the latter being always present in excess. To avoid this a mixture of ethyl benzoate and ethyl acetoacetate was added to the LDA solution in ether. Acetic acid workup, indeed, did not give any **12b**. However, the yield of the ester **7b** was once again only 30–35%, and ethyl benzoate was recovered in 50–55% yield.

These results could be rationalized as follows. Initial reaction of the dianion with ethyl benzoate would yield **13**, which *could decompose before workup* into product **14** *irreversibly* and into starting materials *reversibly*. In the end, however, due to thermodynamic control, all the reactants would be converted to **14**. Actually, however,



13 is a species in which oxygen anions are strongly coordinated to lithium cations and might be represented better by **15**. It is possible that **15** has considerable stability and *does not decompose in the reaction medium but only during workup*. The decomposition during workup would be irreversible and in parallel reactions would furnish product **7b** and ethyl benzoate in fixed proportion.

The way to promote the formation of **7b** then appeared to be to sequester the lithium cations so that formation of species **13** is favored and hence its decomposition to product **14** *in the reaction medium itself before workup*. Sequestration of lithium cations can be readily achieved by electron-donor chelating agents like TMEDA (tetramethylethylenediamine). Hence a mixture of ethyl acetoacetate and ethyl benzoate was added to a solution of LDA in ether containing TMEDA. Acetic acid workup, in agreement with our expectation, now gave **7b** in high yield (80–85%).

Having obtained **7b** in high yield, its thermal cyclization was carried out. Thus, on heating under vacuum (3 mm) at 150 °C, the ester **7b** cyclized to the α-pyrone **8a** in 92% yield. The latter was methylated with diazomethane and as reported[7] gave the two possible isomers **9** and **10**, in a 4:1 ratio and a total yield of 85%.

After the successful synthesis of the benzene analogue **9**, the same synthetic strategy was adopted for the synthesis of **1**. A mixture of ethyl acetoacetate and ethyl nicotinate was added to a solution of LDA in ether containing TMEDA. The acetic acid workup gave a compound which, like **7b**, was sensitive to heat and was not characterized by elemental analysis. However, the IR and the ^{1}H NMR spectra indicated it to be the expected mixture of the enol isomers of **7d**. Ester **7d** on heating under vacuum (3 mm) at 150 °C gave a compound in 85–90% yield whose ^{1}H NMR was in agreement with structure **8b**. It was difficult to purify the compound, and hence it was converted to **1** by methylation with diazomethane. The yield was 66% from **7d**. Interestingly, unlike in the case of **9**, only one of the possible isomers **1** was obtained in this reaction.

Experimental Section

Capillary melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were obtained by using a Perkin-Elmer R32 (90 MHz) spectrometer with tetramethylsilane as an internal standard.

Reaction of the Dianion of Ethyl Acetoacetate with Ethyl Benzoate. To a solution of LDA at 0 °C (prepared from 5 g (0.05 M) of diisopropylamine and *n*-butyllithium (0.05 M in ether) at 0 °C), 2.6 g (0.02 M) of ethyl acetoacetate in 20 mL of ether was added dropwise (under N_2). The pale yellow reaction mixture was warmed to room temperature (25 °C), when a reddish brown suspension resulted. It was again quickly cooled to 0 °C and stirred for 10 min and 3.75 g (0.025 M) of ethyl benzoate in 20 mL of ether was added dropwise. The reaction mixture was allowed to slowly warm to room temperature and stirred for 16–18 h.

The reaction mixture was decomposed with 6 g (0.1 M) of glacial acetic acid dissolved in 75 mL of dry ether. The pale yellow (sometimes white) ppt was filtered and washed with 50 mL of dry ether. The residue was suspended in 30 mL of ether and 30 mL of ice-cold water was added. The ether layer was separated and combined with the filtrate. The total organic layer was quickly washed with 20 mL of ice water and dried over sodium sulfate. Removal of the solvent gave a red oil. The oil was chromatographed on silica gel (100–200 mesh). Elution with hexane gave ethyl benzoate (2 g, 55% recovery). Further elution with *n*-hexane–ethyl acetate (9:1) gave diethyl 5-phenyl-3-hydroxyhomophthalate (**12b**) (0.250 g, 10%). The sample was crystallized from hexane: mp 102–103 °C; IR (Nujol) 3150, 1710, 1625, and 1590 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H), 1.36 (t, 3 H), 3.92 (s, 2 H), 4.13 (q, 2 H), 4.36 (q, 2 H), 6.92 (d, 1 H, J = 1.8 Hz), 7.17 (d, 1 H, J = 1.8 Hz), 7.5 (m, 5 H, phenyl), 11.32 (s, 1 H, exchanges with D_2O).

Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.55; H, 6.14. Found: C, 69.81; H, 6.16.

On further elution with *n*-hexane–ethyl acetate (3:1) ester **7b** (1.1 g, 35%) was obtained as a pale yellow oil, which was a mixture of enol isomers: IR (neat) 3400–3200, 3050, 1740, 1720, 1600, and 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1–1.3 (t and m, 3 H, OCH_2CH_3 of the enol isomers), 3.45 and 3.6 (two singlets, 2 H, $COCH_2C{=}C$ of the enol isomers), 4.05–4.5 (m, 2 H, OCH_2CH_3 of the enol isomers), 6.17 and 6.3 (two singlets, 1 H, olefinic protons of the enol isomers), 7.4–7.7 (m, 3 H, phenyl protons at the 3, 4, and 5 positions of the enol isomers), 7.8–8.15 (m, 2 H, phenyl protons at the 2 and 6 positions of the enol isomers).

Ethyl 5-Phenyl-3,5-dioxopentanoate (7b). To a solution of LDA (prepared from 5 g (0.05 M) of diisopropylamine and *n*-butyllithium (0.05 M in ether) at 0 °C) containing 2 mL (0.02 M)

(6) Chan, T. H.; BrownBridge, P.; *J. Chem. Soc., Chem. Commun.* **1981**, 1, 20.

(7) Herbst, D.; Mors, W. B.; Gottlieb, O. R.; Djerassi, C. *J. Am. Chem. Soc.* **1959**, *81*, 2427.

of TMEDA a mixture of 2.6 g (0.02 M) of ethyl acetoacetate and 3.75 g (0.025 M) of ethyl benzoate in 50 mL of ether was added dropwise at room temperature (under N_2). Initially the color of the reaction mixture was reddish brown. Then it turned pale yellow at the end of the addition. The reaction mixture was stirred at room temperature for 16–18 h. Acetic acid workup, as above, gave an oil, which upon flash chromatography on a silica gel column (>200 mesh without binder), with *n*-hexane for the eluting solvent gave 0.350 g (10% recovery) of ethyl benzoate. Further elution with *n*-hexane–ethyl acetate (3:1) gave 4.5 g (85%; 87% on the basis of recovery) of ethyl 5-phenyl-3,5-dioxopentanoate (**7b**) as a pale yellow oil, identical with the earlier sample.

5-Phenyl-3,5-dioxopentanoic Acid (7a). To a solution of potassium hydroxide (0.560 g) in 5 mL of absolute alcohol was added 0.4 g of ethyl 5-phenyl-3,5-dioxopentanoate (**7b**) dissolved in 2 mL of absolute alcohol at room temperature. The reaction mixture was stirred for 15 min, decomposed with crushed ice, and acidified with ice-cold 3 N HCl. The precipitated acid was filtered, washed with 20 mL of ice-cold water, and dried. The acid was crystallized from ether–petroleum ether (1:2) to give 0.350 g (80%) of 5-phenyl-3,5-dioxopentanoic acid (**7a**): mp 94–95 °C (lit.[5] 94–96 °C); IR (Nujol) 3300–3000, 1740, 1625, 1575, 1200, 1140, and 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.55 (s, 2 H), 3.72 (br s, 1 H, D_2O exchangeable), 6.30 (s, 1 H, D_2O exchangeable), 7.45 (m, 3 H, phenyl protons at the 3, 4, and 5 positions), 7.85 (m, 2 H, phenyl protons at the 2 and 6 positions), 12.00 (br s, 1 H, D_2O exchangeable).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.32; H, 4.93.

6-Phenyl-4-hydroxy-α-pyrone (8a). Ester **7b** (0.5 g) was heated slowly under vacuum (3 mmHg) to 150 °C (ca. 45 min), kept at this temperature for an additional 5 min, and slowly cooled to room temperature. A pale yellow solid was obtained, which was crystallized from ethyl methyl ketone, mp 254–255 °C (lit.[5] 258–259 °C dec); IR (Nujol) 3650–3200, 1650, 1620, 1550, 1250, and 1070 cm^{-1}; ^1H NMR ($CDCl_3$, Me_2SO-d_6) δ 3–5 (br s, 1 H, exchanges with D_2O), 5.41 (d, 1 H, J = 2.8 Hz, exchanges with D_2O), 6.65 (d, 1 H, J = 2.5 Hz), 7.5 (m, 3 H, phenyl protons at the 3, 4, and 5 positions), 7.8 (m, 2 H, phenyl protons at the 2 and 6 positions).

Anal. Calcd for $C_{11}H_8O_3$: C, 70.21; H, 4.29. Found: C, 70.11; H, 4.31.

Anibine (1). To a solution of LDA (prepared from 5 g (0.05 M) of diisopropylamine and *n*-butyllithium (0.05 M) at 0 °C in ether) containing 2 mL (0.02 M) of TMEDA a mixture of 2.6 g (0.02 M) of ethyl acetoacetate and 3.4 g (0.025 M) of ethyl nicotinate in 50 mL of ether was added dropwise at room temperature (under N_2). Initially the reaction mixture was reddish brown, and it turned to yellow or reddish yellow. The reaction mixture was stirred at room temperature for 16–18 h. Workup, as above, gave a red oil which upon flash chromatography on a silica gel column (>200 mesh without binder) with hexane–ethyl acetoacetate (9:1) for the eluting solvent gave 1.5 g (44% recovery) ethyl nicotinate. Further elution with hexane–ethyl acetate (1:1) yielded 2.6 g (47%; 83% on the basis of recovery) of ethyl 5-(3′-pyridyl)-3,5-dioxopentanoate (**7d**): IR (neat) 3600–3200, 1750, 1700, 1610, 1300, 1035, and 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1–1.5 (t and m, 3 H, OCH_2CH_3 of the enol isomers), 3.4, 3.9 (s, 2 H, $COCH_2C{=}C$ of the enol isomers), 4–4.5 (m, 2 H, OCH_2CH_3 of the enol isomers), 6.35 and 6.87 (two singlets, 1 H, olefinic protons of the enol isomers), 7.3–8.9 (m, 4 H, pyridyl protons of the enol isomers).

As in the case of **7b**, 0.5 g of ester **7d** on cyclization gave a light brown solid, which was crystallized from dioxane–hexane (1:1) to give 0.360 g (90%) of 4-hydroxy-6-(3′-pyridyl)-α-pyrone (**8b**): mp 207–209 °C (lit.[4] 212 °C dec); IR (Nujol) 3650–3200, 1730, 1720, 1600, 1250, and 1225 cm^{-1}; ^1H NMR ($CDCl_3$, Me_2SO-d_6) δ 3–4 (br s, 1 H, exchanges with D_2O), 5.45 (d, 1 H, J = 2.5 Hz, exchanges with D_2O, H_3), 6.60 (d, 1 H, J = 2.5 Hz, H_5), 7.35 (dd, 1 H, $J_{5',6'}$ = 5 Hz, $J_{5',4'}$ = 8 Hz, $H_{5'}$), 8.10 (m, 1 H, $H_{4'}$), 8.67 (dd, 1 H, $J_{6',5'}$ = 5 Hz, $J_{6',4'}$ = 1.5 Hz, $H_{6'}$), 8.9 (d, 1 H, $J_{2',4'}$ = 2.5 Hz, $H_{2'}$). A satisfactory analytical sample could not be obtained for the compound.

α-Pyrone **8b** (0.280 g) was treated with an ethereal solution of diazomethane at room temperature. The reaction mixture was left at room temperature for 2 h. Removal of the solvent and crystallization of the residue from 95% ethanol gave 0.180 g (66%) of anibine (**1**): mp 176–177 °C (lit.[1] 177–178 °C); IR (Nujol) 3150, 1730, 1645, and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H, OCH_3), 5.5 (d, 1 H, J = 2.5 Hz, H_3), 6.5 (d, 1 H, J = 2.5 Hz, H_5), 7.35 (dd, 1 H, $J_{5',6'}$ = 5 Hz, $J_{5',4'}$ = 8 Hz, $H_{5'}$), 8.10 (m, 1 H, $H_{4'}$), 8.67 (dd, 1 H, $J_{6',5'}$ = 5 Hz, $J_{6',4'}$ = 1.5 Hz, $H_{6'}$), 9.0 (d, 1 H, $J_{2',4'}$ = 2.5 Hz, $H_{2'}$).

Anal. Calcd for $C_{11}H_9O_3N$: C, 65.02; H, 4.43. Found: C, 65.00; H, 4.50.

Registry No. 1, 643-91-4; **7a**, 5526-43-2; **7b**, 86969-12-2; **7d**, 86969-13-3; **8a**, 5526-38-5; **8b**, 80601-69-0; **12b**, 86969-14-4; ethyl acetoacetate, 141-97-9; ethyl benzoate, 93-89-0; ethyl nicotinate, 614-18-6; TMEDA, 110-18-9.

Synthesis of the Major Pheromonal Component of the Monarch Butterfly (*Danaus plexippus*) via Palladium-Catalyzed 1,4-Functionalization of Isoprene

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4-Chloroprenyl acetate (**2**), regioselectively prepared by palladium(II)-catalyzed 1,4-acetoxychlorination of isoprene, was selectively functionalized in the 1- and 4-positions to afford **6**, which is readily transformed to the dimethyl ester of the pheromone (*E,E*)-3,7-dimethyldeca-2,6-diene-1,10-dioic acid (**1a**) of the Monarch butterfly. The allylic chloro group in **2** was chemoselectively substituted with sodium dimethyl malonate (classically or with palladium(0) catalysis) without affecting the allylic acetoxy group, which subsequently was replaced with sodium methyl acetoacetate using palladium(0) catalysis to give **5**. The configuration of the double bond in **5** is >95% *E* when triphenylphosphine is used as ligand. A double alkylation of **2** to **5** can also be performed as a one-pot sequence. Selective double decarboxylation of **5** gave methyl (*E*)-4-methyl-8-oxo-4-nonenoate (**6**) in 35% overall yield from isoprene. Transformation of **6** to the dimethyl ester of **1** has been described elsewhere.

Pheromones of certain butterflies contain a degraded sesquiterpenoid skeleton. For example, Meinwald and co-workers were able to isolate **1a** (major) and **1b** (minor) from the hairpencils of males of the Monarch butterfly

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