Studies on the Synthesis of the Benzo[a]quinolizidin-2-one Ring System. Preparation of a 1,1-Dimethyl Derivative[1]

Joan Bosch,*† Antonio Domingo,‡ and Ana Linares‡

Departments of Organic Chemistry, Faculty of Pharmacy, University of Valencia, Valencia-10, Spain, and University of Barcelona, Barcelona-28, Spain

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The first synthesis of a 1,1-dialkyl-substituted benzo[a]quinolizidin-2-one is reported. Condensation of mescaline and ethyl 2-(chloroformyl)-2-methylpropionate followed by Bischler–Napieralski cyclodehydration and sodium cyanoborohydride reduction gave tetrahydroisoquinoline **20**, which was converted into amido ester **21** by reaction with ethyl acrylate. Dieckmann cyclization of **21** gave the desired tricyclic system **22**. Alternative synthetic routes based on the Bischler–Napieralski cyclization of *N*-phenethyl-δ-hydroxy amide **5** or *N*-phenethylpiperidine-2,4-dione ethylene ketal **15** failed. The reluctance of the tertiary phenethyl amides **11** and **15** to give cyclized products under Bischler–Napieralski conditions contrary to the behavior of the secondary phenethyl amides **5** and **18** is discussed.

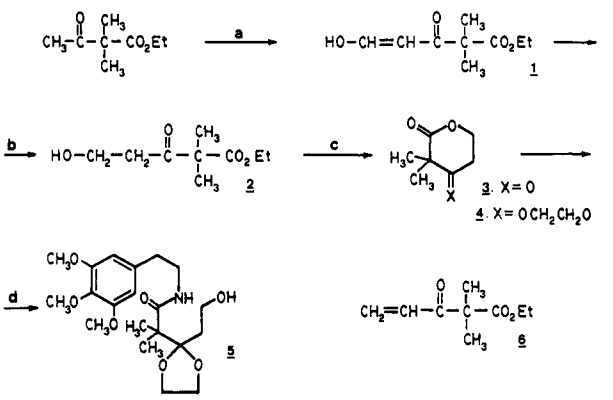
Although attention to the benzo[a]quinolizidin-2-one ring system[2] was initially focused on its application as an intermediate in the synthesis of emetine and other related ipecac alkaloids,[3] the Brossi findings[3a] about the reserpine-like activity of some 3-alkyl derivatives suggested that members with other substitution in ring C might be worthy of study. In this context, a number of 1-, 3-, and 4-alkyl-substituted, as well as 4,4-dialkyl-substituted, benzo[a]quinolizidin-2-ones have been prepared[2,4] for synthetic or/and pharmacological purposes, but to our knowledge only one unsuccessful attempt to synthesize a 1,1-dimethyl derivative by an intramolecular Mannich-type cyclization of an appropriate 3,4-dihydroisoquinolinium salt has been made.[5] Hence, the synthesis of this system by other methods seemed of interest.

In this paper we report the first synthesis of a 1,1-dimethylbenzo[a]quinolizidin-2-one system and the full details of our different synthetic approaches. As a synthetic goal we chose a derivative possessing three methoxy groups on the aromatic ring,[6] because of its similarity to several 2-(3,4,5-trimethoxyphenyl)-4-piperidinones prepared by us in previous work.[7] Initially, we planned the synthesis by Bischler–Napieralski[8] cyclization of hydroxy amide **5**, which was expected to be readily accessible through condensation of mescaline and lactone **4**, as shown in Scheme I. This methodology [two ring closures in *N*-(arylethyl)-δ-hydroxy amides] has been successfully applied to the synthesis of the benzo[a]quinolizidine ring system,[9] but no reports have been made of its extension to the 2-oxo series.

Lactone **4**, the key compound in this route, was prepared as follows. Ethyl 2,2-dimethylacetoacetate was allowed to react with sodium and ethyl formate according to the procedure developed for the diethyl analogue[10] to give the hydroxymethylene derivative **1** which, without further purification, was converted (44% overall yield) into the hydroxy ester **2** by hydrogenation over Raney nickel catalyst. Cyclization to lactone **3** was initially effected by heating it in the presence of *p*-toluenesulfonic acid in benzene solution. Under these conditions, the desired compound **3** was isolated in low yield (29%), the enone **6** being the main product (40%). However, when lactonization of **2** was carried out in the presence of ethylene glycol, simultaneous cyclization and ketalization occurred to give lactone **4** in 62% yield.

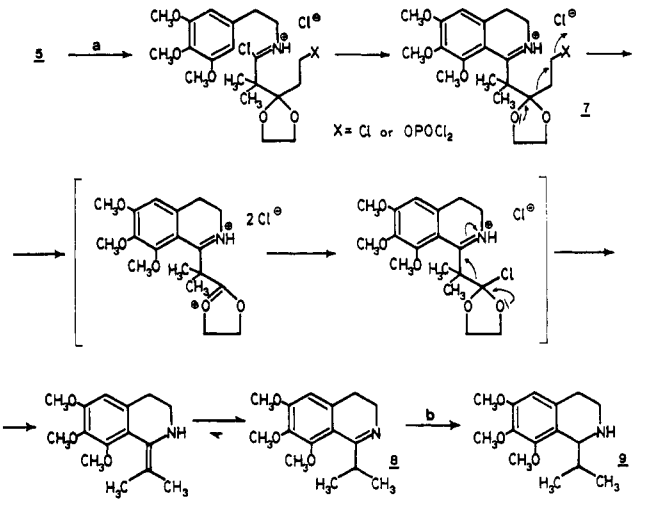
Aminolysis[11] of **4** with mescaline produced the expected hydroxy amide **5** in good yield. Nevertheless, Bischler–Napieralski cyclodehydration of **5** followed by sodium borohydride reduction, under the conditions described for

Scheme I



Reagents: a. HCO_2Et, Na, Et_2O; b. H_2, Ra-Ni; c. p-TsOH, C_6H_6, reflux or p-TsOH, C_6H_6, $(CH_2OH)_2$, reflux; d. mescaline, 40–50 °C.

Scheme II



Reagents: a. $POCl_3$, toluene, reflux; b. $NaBH_4$, MeOH

(1) This work was presented in a preliminary form at the 18th Reunión Bienal de la Real Sociedad Española de Fisica y Quimica, Burgos, Spain, 1980.

(2) For a recent review on the benzo[a]quinolizine ring system with pertinent references, see: Popp, F. D.; Watts, R. F. *Heterocycles* **1977**, *6*, 1189.

† University of Valencia.

‡ University of Barcelona.

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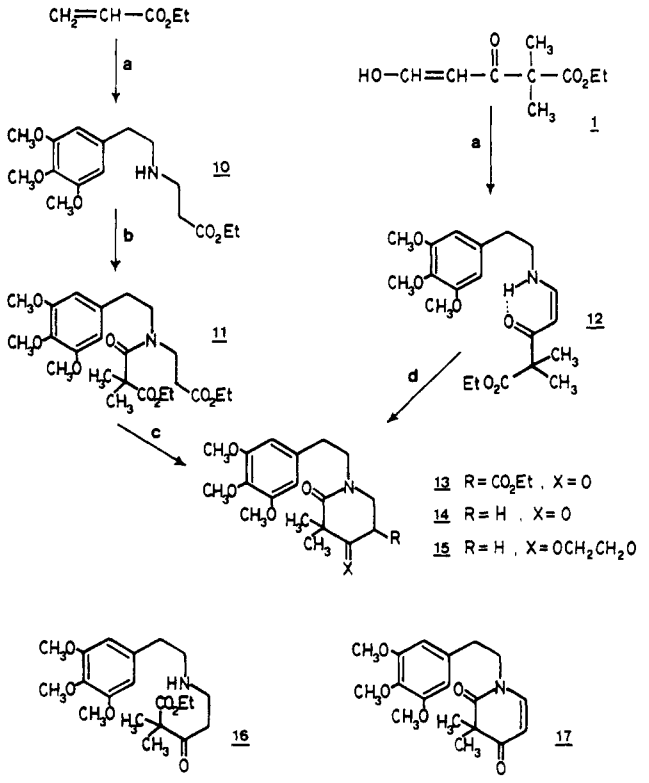
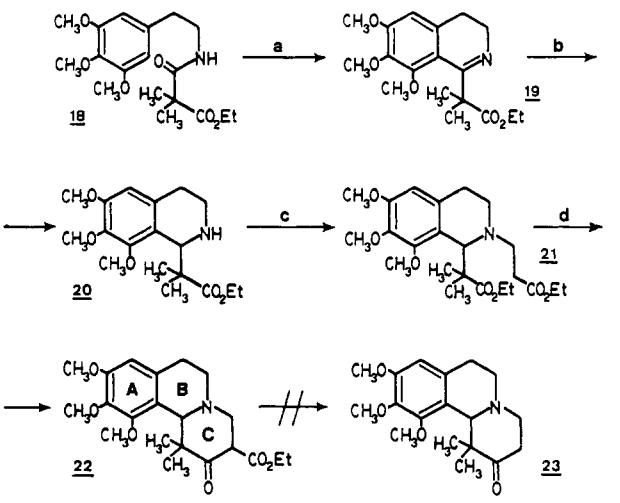
Scheme III



Reagents: a. mescaline, EtOH; b. $ClCOC(CH_3)_2CO_2Et$, $CHCl_3$, Na_2CO_3, H_2O; c. NaH, C_6H_6, reflux; d. H_2, EtOH, HCl.

cyclization of related δ-hydroxy amides,[9,11c,12] led (64% yield) to the unexpected tetrahydroisoquinoline **9**.[13] When

Scheme IV



Reagents: a. $POCl_3$, toluene, reflux; b. $NaBH_3CN$, glacial AcOH; c. $CH_2=CH-CO_2Et$, EtOH, r. t.; d. NaH, C_6H_6, reflux.

the reduction step was omitted, the product was the dihydroisoquinoline **8**, which was converted into **9** by sodium borohydride reduction, thus indicating that the cleavage process occurs during the cyclization step. Formation of dihydroisoquinoline **8** can be explained by two heterolytic fragmentations[14] from a cyclized intermediate, **7**, as shown in Scheme II.

Since some *N*-phenethyl-4,4-(ethylenedioxy)-2-piperidinones have been successfully converted[15] into benzo[*a*]quinolizidin-2-ones by Bischler–Napieralski cyclization, we turned our attention to the ketal **15**, in which the piperidine ring is already performed, as the precursor of the desired 1,1-dimethylbenzo[*a*]quinolizidin-2-one system. We prepared this ketal in 73% yield from piperidinedione **14** which, in turn, was obtained as outlined in Scheme III by two separate synthetic pathways.

First, **14** was synthesized in four steps by Michael addition of mescaline to ethyl acrylate followed by condensation of the resulting amino ester **10** with ethyl 2-(chloroformyl)-2-methylpropionate, Dieckmann ring closure of the amido diester **11**, and, finally, acid-catalyzed decarbethoxylation of the resulting β-keto ester **13**. The overall yield of this sequence was 32%.

A second approach to **14** started with the condensation of hydroxymethylene ketone **1** and mescaline, which was found to give good yields (79%) of enaminone **12**.[16,17] Catalytic hydrogenation of **12** in ethanolic HCl caused simultaneous reduction of the carbon–carbon double bond and ring closure to give **14** in 58% yield.[18] Enaminone **12** was also converted into piperidinedione **14** by heating it in the presence of an ethanolic solution of sodium eth-

(3) (a) Brossi, A.; Lindlar, H.; Walter, M.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 119. (b) Openshaw, H. T.; Wittaker, N. *J. Chem. Soc.* **1963**, 1449. (c) Szántay, C.; Toke, L.; Kolonits, P. *J. Org. Chem.* **1966**, *31*, 1447. See also the references cited therein.

(4) For more recent syntheses, see: (a) Szabo, L.; Honty, K.; Töke, L.; Toth, I.; Szántay, C. *Chem. Ber.* **1972**, *105*, 3215. (b) Szántay, C.; Szentirmay, E.; Szabo, L. *Tetrahedron Lett.* **1974**, *3725*. (c) Buzas, A.; Cavier, R.; Cossais, F.; Finet, J.-P.; Jacquet, J.-P.; Lavielle, G.; Platzer, N. *Helv. Chim. Acta* **1977**, *60*, 2122. (d) Shono, T.; Sasaki, M.; Nagami, N.; Hamaguchi, H. *Tetrahedron Lett.* **1982**, *23*, 97. See also the references cited therein.

(5) Szántay, C.; Rohaly, J. *Chem. Ber.* **1965**, *98*, 557.

(6) There are few examples of the synthesis of trimethoxybenzo[*a*]-quinolizidin-2-ones: (a) See ref 3a. (b) Sugiura, M.; Takao, N.; Iwasa, K.; Sasaki, Y. *Chem. Pharm. Bull.* **1978**, *26*, 1901. (c) Sugiura, M.; Takao, N.; Iwasa, K.; Sasaki, Y. *Ibid.* **1979**, *27*, 3144.

(7) (a) Bosch, J.; Domingo, A.; López, F.; Rubiralta, M. *J. Heterocycl. Chem.* **1980**, *17*, 241. (b) Bosch, J.; Rubiralta, M.; Domingo, A.; Sistaré, J. *Ibid.* **1981**, *18*, 47. (c) Bosch, J.; Rubiralta, M.; Moral, M. *Heterocycles* **1982**, *19*, 473. (d) Bosch, J.; Rubiralta, M. *An. Quim.* **1983**, *79C*, 27.

(8) For a review on the Bischler–Napieralski reaction, see: Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

(9) (a) Zymalkowski, F.; Schmidt, F. *Arch. Pharm.* **1967**, *300*, 229. (b) Zymalkowski, F.; Meise, W. *Heterocycles* **1978**, *9*, 1474. (c) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 457.

(10) (a) Benary, E.; Meyer, H.; Charisius, K. *Chem. Ber.* **1926**, *59*, 108. (b) Schnider, O. *Festschr. Emil Barell* **1936**, 195; *Chem. Abstr.* **1937**, *31*, 2607. (c) Tsukita, K. *J. Pharm. Soc. Jpn.* **1949**, *69*, 194; *Chem. Abstr.* **1950**, *44*, 1506*h*.

(11) (a) Cromwell, N. H.; Cook, K. E. *J. Am. Chem. Soc.* **1958**, *80*, 4573. (b) Jones, J. B.; Young, J. M. *Can. J. Chem.* **1966**, *44*, 1059. (c) Nakagawa, M.; Kiuchi, M.; Obi, M.; Tonozuka, M.; Kobayashi, K.; Hino, T.; Ban, Y. *Chem. Pharm. Bull.* **1975**, *23*, 304.

(12) (a) Meise, W.; Zymalkowski, F. *Tetrahedron Lett.* **1969**, 1475. (b) Meise, W.; Muller, H. L. *Synthesis* **1976**, 719. (c) Meise, W.; Pfisterer, H. *Arch. Pharm.* **1977**, *310*, 495, 501.

(13) As described for other 1-isopropyl-1,2,3,4-tetrahydroisoquinolines, **9** shows a characteristic magnetic nonequivalence of the two isopropyl methyl groups in the NMR spectrum, either as the free base or as the hydrochloride: Kajtar, M.; Radics, L. *Chem. Commun.* **1967**, 784.

(14) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.

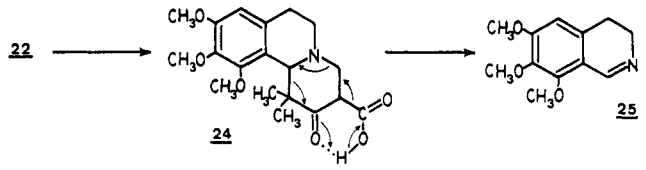
(15) (a) Itoh, N.; Sugasawa, S. *Tetrahedron* **1959**, *6*, 16. (b) Itoh, N.; Sugasawa, S. *J. Org. Chem.* **1959**, *24*, 2042. (c) Osbond, J. M. *J. Chem. Soc.* **1961**, 4711.

(16) For a review on the chemistry of enaminones, see: Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

(17) We assumed that this compound adopts a cis-s-cis conformation (see Scheme III) as shown by the coupling constants in the NMR spectrum (see Experimental Section).

(18) When enaminone **12** was hydrogenated in the presence of glacial acetic acid, amino keto ester **16** was obtained in 77% yield. However, lactamization of this amino ester by heating it in vacuo or in high-boiling solvents, with or without basic catalysts, proceeded in low yields.

Scheme V



oxide followed by palladium-catalyzed hydrogenation of the resulting tetrahydropyridinedione **17**. The low yield (33%) in the cyclization step in comparison with those reported in closely related cyclizations of N-unsubstituted enaminones[10b,c] can be attributed to the lack of stabilization of **17** as amide ion.

In spite of the successful precedents[15] of similar Bischler–Napieralski cyclizations, lactam ketal **15** was recovered unchanged after being heated in the presence of phosphorus oxychloride. This result will be discussed later.

Since the final formation of ring B by cyclization either from hydroxy amide **5** or from amido ketal **15** was not suitable for the preparation of the desired benzo[a]-quinolizidin-2-one system, we pursued a new approach in which the key step was piperidine ring formation by Dieckmann cyclization[19] of an appropriately substituted tetrahydroisoquinoline diester **21**.

The synthesis of **21** was initially planned by Bischler–Napieralski cyclization of amido diester **11**. This cyclization failed,[20] so we next directed our efforts toward the reaction sequence depicted in Scheme IV. Condensation of mescaline and ethyl 2-(chloroformyl)-2-methylpropionate gave amido ester **18** which was subjected to Bischler–Napieralski cyclization to give the expected dihydroisoquinoline **19** in high yield. Although sodium borohydride reduction of **19** has proved to be ineffective,[21] tetrahydroisoquinoline **20** was obtained in 94% yield after prolonged treatment of **19** with sodium cyanoborohydride in glacial acetic acid.[22] Michael addition of **20** to ethyl acrylate followed by Dieckmann cyclization of the resulting amino diester **21** gave (37% overall yield) the expected β-keto ester **22** as a mixture of keto–enol tautomers, as shown by its spectroscopic data and a positive $FeCl_3$–MeOH test.

With the preparation of β-keto ester **22** we have established the first successful route for the synthesis of the 1,1-dimethylbenzo[a]quinolizidin-2-one system. However, attempts to obtain ketone **23** by decarbethoxylation of **22** under a variety of conditions[23] led to dihydroisoquinoline **25** in yields higher than 70%. Formation of **25** under these conditions[26] can be rationalized by successive or simultaneous retro-Michael and retro-Mannich processes from the intermediate β-keto acid **24**, as illustrated in Scheme V. This result could be correlated with the reported failure in the condensation between 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride and isopropyl vinyl ketone.[5]

Finally, it is worth commenting upon the different behavior under Bischler–Napieralski conditions of the four phenethyl amides prepared in this work. As discussed above, secondary phenethyl amides **5** and **18** react normally (in spite of the fragmentation observed for **5**) to give dihydroisoquinoline systems, while the tertiary analogues **11** and **15** do not cyclize under similar experimental conditions. However, in general, no significant differences can be observed between the reactivity of secondary and tertiary amides under Bischler–Napieralski conditions. Our results can be explained on the basis of the accepted mechanism for this reaction in which, for a secondary amide, an equilibrium between the initially formed imidoyl chloride and the corresponding nitrilium salt has been claimed.[27] Obviously, from tertiary amides this equilibrium cannot be established, and cyclization occurs by direct nucleophilic displacement of the halogen atom by the arene carbon. The simultaneous presence of two methyl groups α to the amide carbonyl group as well as a methoxy group ortho to the cyclization position accounts for the different behavior of our secondary and tertiary amides in the Bischler–Napieralski reaction. The nucleophilic attack of the arene carbon atom upon the planar nitrilium ion coming from our secondary phenethyl amides can be normally effected, while the approximation of the aromatic nucleus to the sp^2-hybridized carbon atom of the intermediate imidoyl chloride arising from our tertiary phenethyl amides appears to be highly hindered.

Experimental Section

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. NMR spectra were measured on a Perkin-Elmer R-24B (60 MHz) instrument with internal Me_4Si (δ 0) as a reference. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Prior to evaporation under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 63–200 μm), and the spots were located with UV light or iodoplatinate reagent. All elution solutions were prepared by volume. All microdistillations were made on a Büchi GKR-50 Kugelrohr apparatus. Microanalyses were performed by Instituto de Quimica Bio-Orgânica, Barcelona.

Ethyl 5-Hydroxy-2,2-dimethyl-3-oxopentanoate (2). Sodium metal (11.4 g, 0.49 mol), cut into small pieces, was added at 0–5 °C to a stirred solution of ethyl 2,2-dimethylacetoacetate[28] (78.1 g, 0.49 mol and ethyl formate (54.9 g, 0.74 mol) in anhydrous Et_2O (1 L). After addition of absolute EtOH (3 mL), the mixture was stirred at 0 °C for 6 h, and the resulting suspension was allowed to stand overnight at room temperature. Absolute EtOH (15 mL) was added, and stirring was renewed for 1 h. The reaction mixture was quenched with H_2O (100 mL), the ethereal layer was separated, and the aqueous one was washed with Et_2O. The combined ethereal solutions were extracted with H_2O and discarded while the combined aqueous phases were acidified with 10% HCl solution and extracted with Et_2O. The ethereal extracts were washed with saturated NaCl solution (15 mL), dried, and evaporated to give 61.5 g (67%) of enol 1: NMR (CCl_4) δ 1.24 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.34 (s, 6 H, CH_3), 4.11 (q, J = 7

(19) By a similar ring closure we have recently synthesized 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidinone (see ref 7a).

(20) Amido diester **11** was recovered when it was refluxed in the presence of phosphorus oxychloride either in toluene solution or without solvent. The same result was obtained by using phosphorus pentachloride in carbon tetrachloride solution for 72 h at room temperature.

(21) The failure of this reaction can be attributed to the existence of a small concentration of protonated dihydroisoquinoline in methanol solution and to a slow attack of the hydride ion due to the steric hindrance caused by the two methyl groups. When the reduction was effected in the presence of a stoichiometric amount of hydrogen chloride, in order to increase the concentration of the iminium salt in the equilibrium, a 4:1 mixture of di- and tetrahydroisoquinolines **19** and **20**, respectively, was obtained.

(22) Gribble, G. W.; Heald, P. W. *Synthesis* **1975**, 650.

(23) By the action of boiling 10% AcOH or HCl, by heating at 150 °C in wet Me_2SO in the presence of lithium or sodium chloride,[24] or by refluxing with ethanolic barium hydroxide.[25]

(24) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957. (b) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(25) Grieco, P. A.; Noguez, J. A.; Masaki, Y. *J. Org. Chem.* **1977**, *42*, 495.

(26) Formation of a dihydroisoquinoline as the main product has been reported in the decarbethoxylation of some ethyl 1-alkyl-6,7-dimethoxy-2-oxobenzo[a]quinolizidine-3-carboxylates: Kawanishi, M. *Chem. Pharm. Bull.* **1962**, *10*, 185.

(27) (a) Fodor, G.; Gal, J.; Phillips, B. A. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 919. (b) Fodor, G.; Nabugandi, S. *Tetrahedron* **1980**, *21*, *36*, 1279. (c) Nabugandi, S.; Fodor, G. *J. Heterocycl. Chem.* **1980**, *17*, 1457.

(28) *Beilstein, 4th ed.* **1921**, *3*, 695.

Hz, 2 H, OCH_2), 5.46 (d, J = 5.2 Hz, 1 H, COCH=), 7.50 (d, J = 5.2 Hz, 1 H, =CHOH). A solution of 1 (14.3 g, 76.8 mmol) in absolute EtOH (100 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of freshly prepared Raney nickel[29] (1.5 g). When hydrogen absorption ceased, the solution was filtered, and the catalyst was washed with EtOH (50 mL). Evaporation of the combined EtOH solutions gave an oil (13.3 g) which was distilled to yield 9.3 g (65%) of pure hydroxy ester **2** as a colorless liquid: bp 60–68 °C (0.25 mm); IR (neat) 3550–3400 (OH), 1710 (CO) cm^{-1}; NMR (CCl_4) δ 1.24 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.28 (s, 6 H, CH_3), 2.60 (t, J = 5.7 Hz, 2 H, $COCH_2$), 2.76 (s, 1 H, OH), 3.71 (t, J = 5.7 Hz, 2 H, CH_2OH), 4.13 (q, J = 7 Hz, 2 H, OCH_2CH_3). Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.56. Found: C, 57.62; H, 8.92.

2,2-Dimethyl-3-oxo-5-pentanolide (3). A solution of **2** (9.3 g, 49.4 mmol) and *p*-TsOH monohydrate (1 g) in 1.5 L of anhydrous toluene was refluxed for 3 h with removal of water by a Dean–Stark trap. After cooling, the mixture was washed with 15% Na_2CO_3 solution and dried. The evaporation afforded an oil which on fractional distillation gave 2.0 g (24%) of **ethyl 2,2-dimethyl-3-oxo-4-pentenoate (6)**: bp 140–150 °C (14 mm); NMR (CCl_4) δ 1.21 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.33 (s, 6 H, CH_3), 4.12 (q, J = 7 Hz, 2 H, OCH_2), 5.61 (dd, J_{cis} = 4 Hz, J_{trans} = 8.5 Hz, 1 H, =CH), 6.30 (d, J = 4 Hz, 1 H, =CH, trans), 6.37 (d, J = 8.5 Hz, 1 H, =CH, cis). Lactone **3** (1.33 g, 19%) distilled at 200–210 °C (14 mm): NMR (CCl_4) δ 1.35 (s, 6 H, CH_3), 2.71 (t, J = 6 Hz, 2 H, $COCH_2$), 4.46 (t, J = 6, 2 H, OCH_2). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.27; H, 7.01.

3,3-(Ethylenedioxy)-2,2-dimethyl-5-pentanolide (4). A solution of **2** (2 g, 10.6 mmole, ethylene glycol (2 g, 32 mmol), and *p*-TsOH monohydrate (0.5 g) in 500 mL of anhydrous benzene was refluxed for 4 h in a flask fitted with a Dean–Stark water separator. After cooling, the mixture was washed with 1 N NaOH solution and then with H_2O. The solvent was dried and evaporated, and the oily residue (2.1 g) was distilled to give 0.25 g (14%) of enone **6** and 1.3 g (62%) of lactone **4** as a colorless liquid: bp 130–135 °C (0.2 mm); IR (neat) 1730 cm^{-1} (CO); NMR (CCl_4) δ 1.21 (s, 6 H, CH_3), 1.97 (t, J = 6.2 Hz, 2 H, $COCH_2$), 3.95 (s, 4 H, OCH_2CH_2O), 4.20 (t, J = 6.2 Hz, 2 H, $COOCH_2$). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.08; H, 7.71.

***N*-(3,4,5-Trimethoxyphenethyl)-3,3-(ethylenedioxy)-5-hydroxy-2,2-dimethylpentanamide (5).** A mixture of mescaline[30] (4.5 g, 21.3 mmol) and lactone **4** (3.8 g, 20 mmol) was stirred at 40–50 °C for 6 days, after which it was chromatographed. On elution with $CHCl_3$ starting lactone (1.3 g) was recovered while elution with 97:3 $CHCl_3$–MeOH gave 4.6 g (86% based on unrecovered lactone) of amide **5** as a syrup: IR ($CHCl_3$) 3550 (OH), 3400 (NH), 1660 (CO) cm^{-1}; NMR (CCl_4) δ 1.04 (s, 6 H, CH_3), 1.74 (t, J = 6.3 Hz, 2 H, CH_2), 2.37 (br s, 1 H, OH), 2.63 (t, J = 6.2 Hz, 2 H, $ArCH_2$), 3.30 (t, J = 6.2 Hz, 2 H, NCH_2), 3.40 (t, J = 6.3 Hz, 2 H, CH_2OH), 3.63 (s, 3 H, *p*-OCH_3), 3.73 (s, 6 H, *m*-OCH_3), 3.91 (s, 4 H, OCH_2CH_2O), 6.26 (s, 2 H, Ar H), 6.40 (m, 1 H, NH). Anal. Calcd for $C_{20}H_{31}NO_7$: C, 60.43; H, 7.86; N, 3.52. Found: C, 60.29; H, 7.71; N, 3.64.

Bischler–Napieralski Cyclization of Hydroxy Amide 5. A solution of **5** (1.58 g, 3.97 mmol) and $POCl_3$ (6.09 g, 39.7 mmol) in 6 mL of anhydrous toluene was refluxed under N_2 for 2 h. After evaporation of the solvent the residue was digested with hot hexane and dissolved in absolute MeOH (40 mL). To this ice-cooled solution was added $NaBH_4$ (2.5 g, 66 mmol) in small portions, and the resulting mixture was refluxed for 30 min. The solvent was evaporated, and the residue was heated with 2 N HCl (60 mL) for 10 min. The solution was basified with saturated Na_2CO_3 solution and extracted with Et_2O. The ethereal extracts were dried and evaporated to give 0.67 g (64%) of tetrahydroisoquinoline **9**: IR ($CHCl_3$) 3320 cm^{-1} (NH); NMR (CCl_4) δ 0.69 and 0.95 (2 d, J = 7 Hz, 3 H each, CH_3), 1.2–1.6 (m, 1 H, $CHCH_3$), 1.83 (s, 1 H, NH), 2.1–3.3 (complex signal, 4 H, CH_2), 3.69, 3.73, and 3.79 (3 s, 3 H each, OCH_3), 3.7–4.0 (masked signal, 1 H, NCH), 6.11 (s, 1 H, Ar H). For the hydrochloride: mp 220–221 °C (acetone–EtOH); IR ($CHCl_3$) 3400 cm^{-1} (NH); NMR ($CDCl_3$) δ 0.99 and 1.22 (2 d, J = 7 Hz, 3 H each, CH_3), 1.4–1.8 (m, 1 H, $CHCH_3$), 2.2–3.4 (complex signal, 4 H, CH_2), 3.76 and 3.89 (2 s, 6 H and 3 H, respectively, OCH_3), 4.55 (br s, 1 H, NCH), 6.38 (s, 1 H, Ar H), 8.70 and 10.40 (2 br s, 1 H each, NH_2). Anal. Calcd for $C_{15}H_{24}ClNO_3$: C, 59.69; H, 8.01; N, 4.64; Cl, 11.74. Found: C, 59.69; H, 8.20; N, 4.87; Cl, 11.71.

In another run, the oily residue after evaporation of toluene was distributed between 0.5 N NaOH solution (25 mL) and $CHCl_3$ (25 mL). The organic layer was separated, and the aqueous one was extracted with $CHCl_3$. The combined organic extracts were dried and evaporated to give 0.72 (69%) of dihydroisoquinoline **8**: IR (neat) 1615 cm^{-1} (C=N); NMR (CCl_4) δ 1.05 (d, J = 7 Hz, 6 H, CH_3), 2.32 (t, J = 7 Hz, 2 H, Ar CH_2), 3.38 (t, J = 7 Hz, 2 H, NCH_2), 3.1–3.7 (masked signal, 1 H, CH), 3.73 and 3.81 (2 s, 3 H and 6 H, respectively, OCH_3), 6.38 (s, 1 H, Ar H). For the hydrochloride: mp 153–154 °C (acetone); IR (KBr) 1640 cm^{-1} (C=N). Anal. Calcd for $C_{15}H_{22}ClNO_3 \cdot 1.5H_2O$: C, 55.12; H, 7.71; N, 4.28; Cl, 10.84. Found: C, 55.36; H, 7.54; N, 4.30; Cl, 10.85.

Ethyl 3-[(3,4,5-Trimethoxyphenethyl)amino]propionate (10). A solution of mescaline[30] (4.5 g, 21.3 mmol) and ethyl acrylate (2.4 g, 24 mmol) in EtOH (6 mL) was stirred at room temperature for 16 h. The solvent and excess ethyl acrylate were removed by evaporation in vacuo to give 6.7 g (98%) of amino ester **10**: IR (neat) 3320 (NH), 1730 (CO) cm^{-1}; NMR (CCl_4) δ 1.19 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.24 (s, 1 H, NH), 2.33 (t, 2 H, CH_2CO), 2.4–2.9 (complex signal, 6 H, NCH_2 and Ar CH_2), 3.66 (s, 3 H, *p*-OCH_3), 3.71 (s, 6 H, *m*-OCH_3), 3.98 (q, J = 7 Hz, 2 H, OCH_2), 6.25 (s, 2 H, Ar H). For the hydrochloride, mp 146–147 °C (acetone). Anal. Calcd for $C_{16}H_{26}ClNO_5$: C, 55.24; H, 7.53; N, 4.02; Cl, 10.19. Found: C, 55.31; H, 7.59; N, 4.03; Cl, 10.48.

Ethyl *N*-[2-(Ethoxycarbonyl)ethyl]-*N*-(3,4,5-trimethoxyphenethyl)-2,2-dimethylmalonamate (11). A solution of ethyl 2-(chloroformyl)-2-methylpropionate[31] (3.6 g, 20.2 mmol) in $CHCl_3$ (100 mL) was added dropwise to a well-stirred mixture of amino ester **10** (6.3 g, 20.2 mmol), $Na_2CO_3 \cdot 10H_2O$ (4.0 g, 14 mmol), $CHCl_3$ (50 mL), and H_2O (50 mL). After the mixture was stirred at room temperature for 4 h, the organic layer was decanted, washed successively with 10% HCl and saturated $NaHCO_3$ solutions, and dried. Evaporation of the solvent gave 7.3 g (80%) of crude amide **11**: IR (neat) 1720 (CO ester), 1640 (CO amide) cm^{-1}; NMR (CCl_4) δ 1.22 (t, J = 7 Hz, 6 H, OCH_2CH_3), 1.33 (s, 6 H, CH_3), 2.3–2.8 (complex signal, 4 H, CH_2CO and $ArCH_2$), 3.2–3.7 (complex signal, 4 H, NCH_2), 3.63 (s, 3 H, *p*-OCH_3), 3.74 (s, 6 H, *m*-OCH_3), 4.03 and 4.10 (2 q, J = 7 Hz, 2 H each, OCH_2), 6.23 (s, 2 H, Ar H). An analytical sample was purified by distillation; bp 240–250 °C (0.3 mm). Anal. Calcd for $C_{23}H_{35}NO_8$: C, 60.91; H, 7.77; N, 3.08. Found: C, 61.30; H, 7.88; N, 3.25.

Ethyl (*Z*)-2,2-Dimethyl-3-oxo-5-[(3,4,5-trimethoxyphenethyl)amino]-4-pentenoate (12). A solution of 1 (2.40 g, 12.9 mmol) and mescaline[30] (2.72 g, 12.9 mmol) in absolute EtOH (50 mL) was stirred at room temperature for 24 h. The solvent was removed, and the residue was taken up in Et_2O. The ethereal solution was successively washed with 10% HCl solution, 10% Na_2CO_3 solution, and H_2O. Evaporation of the solvent gave 3.86 g (79%) of crude enaminone **12** as a syrup: IR ($CHCl_3$) 1720 (CO ester), 1635 (CO enone) cm^{-1}; NMR (CCl_4) δ 1.20 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.26 (s, 6 H, CH_3), 2.68 (t, J = 6.5 Hz, 2 H, Ar CH_2), 3.33 (apparent q, J = 6.5 Hz, 2 H, NCH_2), 3.65 (s, 3 H, *p*-OCH_3), 3.73 (s, 6 H, *m*-OCH_3), 4.02 (q, J = 7 Hz, 2 H, OCH_2), 4.77 (d, J = 7.5 Hz, 1 H, COCH=), 6.20 (s, 2 H, Ar H), 6.43 (dd, $J_{CH=CH}$ = 7.5 Hz, J_{CH-NH} = 12.5 Hz, 1 H, =CHN), 9.5–9.9 (br s, 1 H, NH). A sample was purified by SiO_2 column chromatography ($CHCl_3$ as the eluent). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.17; H, 7.93; N, 3.85.

3,3-Dimethyl-1-(3,4,5-trimethoxyphenethyl)piperidine-2,4-dione (14). Method A. From Amido Diester 11. A solution of diester **11** (1.0 g, 2.22 mmol) in anhydrous benzene (20 mL) containing a few drops of absolute EtOH was added dropwise under N_2 to a suspension of paraffin-free sodium hydride (0.13 g, 5.55 mmol, 55% in mineral oil; washed three times with 20 mL of benzene) in anhydrous benzene (20 mL). The resulting mixture was refluxed for 4 h. After the mixture cooled, 0.4 mL of 50% AcOH solution was added. The mixture was filtered, dried over anhydrous K_2CO_3, and evaporated to give 0.57 g (63%) of crude

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keto ester **13** (positive $FeCl_3$/MeOH test), which was dissolved in 10% HCl solution (15 mL) and refluxed for 6 h. The mixture was cooled and extracted with Et_2O. Evaporation of the dried extracts followed by SiO_2 column chromatography of the residue ($CHCl_3$ as eluent) afforded 0.30 g (64%) of pieridinedione **14** as a colorless viscous oil: bp 225–230 °C (0.15 mm); IR ($CHCl_3$) 1715 (CO), 1635 (CO amide) cm^{-1}; NMR (CCl_4) δ 1.19 (s, 6 H, CH_3), 2.43 (t, J = 6.2 Hz, 2 H, $COCH_2$), 2.72 (t, J = 7 Hz, 2 H, Ar CH_2), 3.22 (t, J = 6.2 Hz, 2 H, NCH_2 endocyclic), 3.59 (t, J = 7 Hz, 2 H, NCH_2 exocyclic), 3.64 (s, 3 H, p-OCH_3), 3.77 (s, 6 H, m-OCH_3), 6.32 (s, 2 H, Ar H). Anal. Calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.17. Found: C, 64.29; H, 7.51; N, 4.00.

Method B. From Enaminone 12. A solution of enaminone **12** (2.37 g, 6.25 mmol) in absolute EtOH (70 mL) containing 30 drops of concentrated HCl was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (0.36 g). When hydrogen absorption ceased, the catalyst was filtered off, and the solution was evaporated. The residue was distributed between 10% NaOH solution and Et_2O. The organic layer was separated, the aqueous one was extracted with Et_2O, and the combined ethereal extracts were dried. Evaporation of the solvent followed by SiO_2 column chromatography of the oily residue ($CHCl_3$ as eluent) afforded 1.22 g (58%) of pure piperidinedione **14**. When hydrogenation of enaminone **12** (3.86 g, 10.2 mmol) was carried out in EtOH solution (80 mL) containing 20 drops of glacial AcOH with 1.2 g of Pd/C as a catalyst and the resulting mixture was worked up in the usual way, 3.01 g (77%) of crude amino keto ester **16** was obtained: IR ($CHCl_3$) 1730 (CO ester), 1710 (CO ketone) cm^{-1}; NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.37 (s, 6 H, CH_3), 2.6–3.1 (complex signal, 8 H, CH_2), 3.38 (br s, 1 H, NH), 3.75 (s, 3 H, p-OCH_3), 3.79 (s, 6 H, m-OCH_3), 4.14 (q, J = 7 Hz, 2 H, OCH_2), 6.38 (s, 2 H, Ar H).

Alternatively, a mixture of enaminone **12** (3.22 g, 8.5 mmol), sodium ethoxide (0.58 g, 8.5 mmol), and EtOH (20 mL) was refluxed for 30 min. The resultant dark solution was concentrated, acidified with 5% HCl solution, and extracted with Et_2O. The ethereal extracts were dried and evaporated to give 3.0 g of a dark brown resinous oil which was chromatographed. On elution with 97:3 $CHCl_3$–MeOH, pure enamido ketone **17** (0.95 g, 33%) was obtained: NMR (CCl_4) δ 1.29 (s, 6 H, CH_3), 2.74 (t, 2 H, ArCH_2), 3.6–3.9 (masked t, 2 H, NCH_2), 3.68 (s, 3 H, p-OCH_3), 3.78 (s, 6 H, m-OCH_3), 5.18 (d, J = 7.5 Hz, 1 H, COCH=), 6.24 (s, 2 H, Ar H), 6.79 (d, J = 7.5 Hz, 1 H, NCH=). A solution of **17** (0.95 g, 2.84 mmol) in absolute EtOH (30 mL) was hydrogenated at room temperature and atmospheric pressure in the presence of 10% Pd/C (0.3 g). When the absorption ceased, the catalyst was filtered off, and the solution was evaporated to give 0.86 g (90%) of pure piperidinedione **14**.

4,4-(Ethylenedioxy)-3,3-dimethyl-1-(3,4,5-trimethoxyphenethyl)-2-piperidinone (15). A stirred mixture of piperidinedione **14** (0.18 g, 0.53 mmol), anhydrous benzene (50 mL), ethylene glycol (0.16 g, 2.65 mmol), and p-TsOH (40 mg) was refluxed for 24 h with removal of water by a Dean–Stark trap. After cooling, the solution was washed with 10% NaOH solution and H_2O. Evaporation of the dried organic solvent gave 0.15 g (73%) of ketal **15** as a colorless viscous oil: bp 230–235 °C (0.1 mm); IR (neat) 1634 cm^{-1} (CO); NMR (CCl_4) δ 1.09 (s, 6 H, CH_3), 1.76 (t, J = 6.5 Hz, 2 H, $OCCH_2$), 2.63 (t, J = 7 Hz, 2 H, Ar CH_2), 2.99 (t, J = 6.5 Hz, 2 H, NCH_2 endocyclic), 3.37 (t, J = 7 Hz, 2 H, NCH_2 exocyclic), 3.61 (s, 3 H, p-OCH_3), 3.72 (s, 6 H, m-OCH_3), 3.83 (s, 4 H, OCH_2CH_2O), 6.27 (s, 2 H, Ar H). Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.36; H, 7.59; N, 3.76.

Ethyl *N*-(3,4,5-Trimethoxyphenethyl)-2,2-dimethylmalonamate (18). A solution of ethyl 2-(chloroformyl)-2-methylpropionate[31] (3.87 g, 22 mmol) in $CHCl_3$ (50 mL) was added dropwise over a 1-h period to a vigorously stirred mixture of mescaline[30] (4.58 g, 22 mmol), $Na_2CO_3 \cdot 10H_2O$ (4.28 g, 15 mmol), $CHCl_3$ (50 mL), and H_2O (50 mL). The mixture was stirred at room temperature for 4 h, after which it was worked up as above for compound **11** to give 7.25 g (95%) of amide **18**: IR (neat) 3360 (NH), 1725 (CO ester), 1650 (CO amide) cm^{-1}; NMR (CCl_4) δ 1.17 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.30 (s, 6 H, CH_3), 2.62 (t, J = 7 Hz, 2 H, Ar CH_2), 3.34 (apparent q, J = 7 Hz, 2 H, NCH_2), 3.63 (s, 3 H, p-OCH_3), 3.71 (s, 6 H, m-OCH_3), 4.01 (q, J = 7 Hz, 2 H, OCH_2), 6.28 (s, 2 H, Ar H), 6.52 (t, J = 7 Hz, 1 H, NH). An analytical sample was prepared by filtration through an SiO_2 column ($CHCl_3$ as the eluent). Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.69; N, 3.96. Found: C, 60.87; H, 7.80; N, 3.95.

Ethyl 6,7,8-Trimethoxy-α,α-dimethyl-3,4-dihydroisoquinoline-1-acetate (19). A solution of amide **18** (7.25 g, 20.5 mmol) and $POCl_3$ (30 g, 196 mmol) in anhydrous toluene (30 mL) was refluxed for 4 h. The residue after evaporation was dissolved in 20% HCl solution and washed with Et_2O. The aqueous solution was cooled to 0 °C, basified with 50% NaOH solution, and extracted with Et_2O. The combined ethereal extracts were dried and evaporated to give 5.97 g (87%) of dihydroisoquinoline **19**: bp 230–240 °C (0.6 mm); IR (neat) 1725 (CO), 1605 (C=N) cm^{-1}; NMR (CCl_4) δ 1.16 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.29 (s, 6 H, CH_3), 2.33 (t, J = 7 Hz, 2 H, Ar CH_2), 3.45 (t, J = 7 Hz, 2 H, NCH_2), 3.66, 3.74, and 3.79 (3 s, 3 H each, OCH_3), 4.02 (q, J = 7 Hz, 2 H, OCH_2), 6.36 (s, 1 H, Ar H). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.17. Found: C, 64.49; H, 7.52; N, 4.10.

Ethyl 6,7,8-Trimethoxy-α,α-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-acetate (20). To a stirred solution of dihydroisoquinoline **19** (5.62 g, 16.7 mmol) in glacial AcOH (40 mL) was added $NaBH_3CN$ (2.08 g, 33.4 mmol) portionwise under N_2. The mixture was stirred at room temperature for 3 h, at 50 °C for 1 h, and at room temperature overnight. The solution was poured into H_2O, made alkaline with 50% NaOH solution, and extracted with Et_2O. The ethereal extracts were dried and evaporated to give 5.30 g (94%) of pure amino ester **20** as a colorless viscous oil: IR (neat) 3380 (NH), 1725 (CO) cm^{-1}; NMR (CCl_4) δ 0.97 (s, 6 H, CH_3), 1.25 (t, J = 7 Hz, 3 H, OCH_2CH_3), 1.9–3.3 (complex signal, 4 H, CH_2), 3.73 and 3.79 (2 s, 6 H and 3 H, respectively, OCH_3), 3.80 (masked signal, 1 H, NH), 4.06 (q, J = 7 Hz, 2 H, OCH_2), 4.63 (s, 1 H, CH), 6.27 (s, 1 H, Ar H). For the hydrochloride: mp 162–164 °C (acetone–Et_2O); IR (KBr) 1712 cm^{-1} (CO). Anal. Calcd for $C_{18}H_{28}ClNO_5$: C, 57.82; H, 7.54; N, 3.77; Cl, 9.55. Found: C, 57.84; H, 7.56; N, 3.85; Cl, 9.58.

Ethyl 2-[2-(Ethoxycarbonyl)ethyl]-6,7,8-trimethoxy-α,α-dimethyl-1,2,3,4-tetrahydroisoquinoline-1-acetate (21). A solution of **20** (1.89 g, 5.6 mmol) and ethyl acrylate (2.8 g, 28 mmol) in absolute EtOH (25 mL) was stirred at room temperature for 48 h. The solvent and the excess of reagent were removed, and the oily residue was chromatographed. On elution with 3:7 benzene–$CHCl_3$, pure amino diester **21** (2.14 g, 87%) was obtained: IR ($CHCl_3$) 1718 cm^{-1} (CO); NMR (CCl_4) δ 0.97 and 1.00 (2 s, 3 H each, CH_3), 1.21 and 1.24 (2 t, J = 7 Hz, 3 H each, OCH_2CH_3), 2.2–3.1 (complex signal, 8 H, CH_2), 3.71 and 3.75 (2 s, 3 H and 6 H, respectively, OCH_3), 4.03 (q, J = 7 Hz, 4 H, OCH_2), 4.19 (s, 1 H, CH), 6.26 (s, 1 H, Ar H). Anal. Calcd for $C_{23}H_{35}NO_7$: C, 63.14; H, 8.06; N, 3.20. Found: C, 63.01; H, 8.05; N, 3.20.

Ethyl 9,10,11-Trimethoxy-1,1-dimethyl-2-oxo-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine-3-carboxylate (22). A solution of diester **21** (2.14 g, 4.9 mmol) in anhydrous benzene (40 mL) was added dropwise under N_2 to a suspension of paraffin-free sodium hydride (0.29 g, 12.2 mmol, 55% in mineral oil; washed three times with 20 mL of benzene) in anhydrous benzene (40 mL). After the addition of a few drops of absolute EtOH, the mixture was refluxed for 4 h, cooled, and worked up as above for compound **13** to give an oil which was chromatographed. On elution with 3:7 benzene–$CHCl_3$, pure keto ester **22** (0.88 g, 43%) was obtained: IR ($CHCl_3$) 1730–1700 (CO ester and ketone, keto form), 1650 (CO ester, enol form) cm^{-1}; NMR (CCl_4) δ 0.68 and 1.00 (2 s, 0.45 H each, CH_3 keto form), 0.87 and 1.19 (2 s, 2.55 H each, CH_3 enol form), 1.30 (t, J = 7 Hz, 3 H, OCH_2CH_3 keto and enol form), 2.3–3.2 (complex signal, 4.30 H, $arCH_2CH_2N$ keto and enol form, and NCH_2CH keto form), 3.44 (s, 1.70 H, NCH_2C= enol form), 3.73 (s, 9 H, OCH_3), 3.82 (s, 1 H, NCH), 4.17 (q, J = 7 Hz, 2 H, OCH_2), 6.27 (s, 1 H, Ar H), 12.30 (s, 0.85 H, OH). Anal. Calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.46; N, 3.57. Found: C, 64.60; H, 7.68; N, 3.49.

6,7,8-Trimethoxy-3,4-dihydroisoquinoline (25).[32] **Run 1.** A solution of keto ester **22** (0.40 g, 1.02 mmol) in 10% aqueous HCl (50 mL) was refluxed for 3 h, cooled, basified with solid Na_2CO_3, and extracted with Et_2O. The organic extracts were dried and evaporated to give 0.16 g (71%) of **25**. For the hydrochloride: mp 215–217 °C (Et_2O–acetone); IR ($CHCl_3$) 3380 cm^{-1} (NH); NMR

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($CDCl_3$) δ 3.05 (br t, 2 H, Ar CH_2), 3.79, 3.97, and 4.05 (3 s, 3 H each, OCH_3), 3.7-4.3 (masked signal, 2 H, NCH_2), 6.57 (s, 1 H, Ar H), 8.81 (d, J = 8 Hz, 1 H, =CH).

Run 2. Keto ester **22** (0.12 g, 0.30 mmol) was combined with LiCl (0.02 g, 0.47 mmol), H_2O (0.2 g, 11.1 mmol), and Me_2SO (2 mL). The mixture was heated at 100 °C for 4 h. After the usual workup[24] 50 mg (80%) of **25** was obtained.

Run 3. A mixture of **22** (0.21 g, 0.53 mmol), $Ba(OH)_2 \cdot 8H_2O$ (0.42 g, 1.40 mmol), EtOH (3 mL), and H_2O (4 mL) was refluxed for 14 h. The solvent was removed, and the residue was taken up in cold 6 N HCl (10 mL). The solution was washed with Et_2O, basified with cold 2 N NaOH solution, and extracted with Et_2O. Evaporation of the dried extracts gave 85 mg (70%) of **25**.

Registry No. **1**, 84752-50-1; **2**, 84752-35-2; **3**, 84752-36-3; **4**, 84752-37-4; **5**, 84752-38-5; **6**, 79314-67-3; **8**, 84752-39-6; **8**·HCl, 84752-52-3; **9**, 84774-87-8; **9**·HCl, 84752-51-2; **10**, 84752-40-9; **10**·HCl, 84752-54-5; **11**, 84752-41-0; **12**, 84774-88-9; **13**, 84752-53-4; **14**, 84752-42-1; **15**, 84752-44-3; **17**, 84752-43-2; **18**, 84752-45-4; **19**, 84752-46-5; **20**, 84752-47-6; **20**·HCl, 84786-78-7; **21**, 84752-48-7; **22**, 84752-49-8; **25**, 13338-60-8; **25**·HCl, 84786-79-8; ethyl 2,2-dimethylacetoacetate, 597-04-6; mescaline, 54-04-6; ethyl 2-(chloroformyl)-2-methylpropionate, 64244-87-7; ethyl chloride, 75-00-3; ethyl acrylate, 140-88-5.

Photooxidation of Some Triaza- and Tetraazabenzopentalenes

Angelo Albini, Gian Franco Bettinetti,* and Giovanna Minoli

Istituto di Chimica Organica dell'Università, 27100 Pavia, Italy

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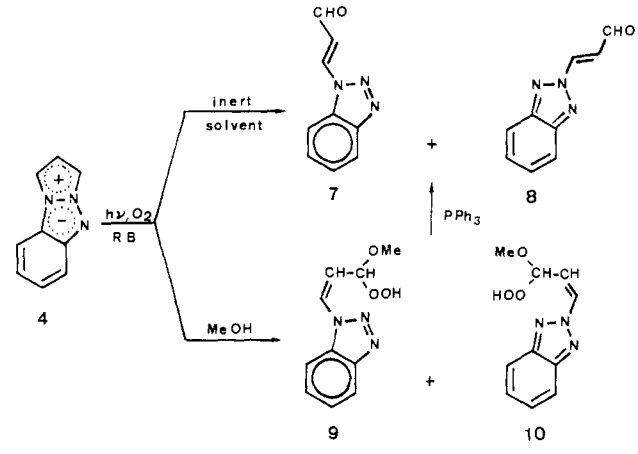
The dye-sensitized photooxidation of some tri- and tetraazabenzopentalenes is reported. The pyrazolobenzotriazole **4** is converted to a mixture of 3-(1-benzotriazolyl)- and 3-(2-benzotriazolyl)propenals (**7** and **8**) in inert solvents, while in methanol the corresponding methoxy hydroperoxides **9** and **10** are formed. The products from 1,2,3-triazolo[1,2-*a*]benzotriazole (**5**) are the diazabutadiene derivative **11** and *cis,cis*-mucononitrile; it is suggested that these arise from the intermediate 2-benzotriazolyl nitrene. These reactions of **4** and **5** are rationalized by assuming the formation of intermediate carbonyl oxides. 1,2,3-Triazolo[2,1-*a*]benzotriazole (**6**) does not react under these conditions. The rates of reaction of azapentalenes **1a**, **2**, **4**, and **5** with singlet oxygen have been determined.

Information on the question of the intermediates involved in the addition of singlet oxygen to organic substrates can in principle be obtained by study of reactions of dipolar substrates. Although singlet oxygen should add to 1,3 dipoles in the same way as to dienes, on the basis of similarities between their MO correlation diagrams,[1] the former processes are poorly documented. Diazo derivatives,[1-5] nitrones,[6] sulfur and pyridinium ylides,[7] and azomethinimines[8] have been shown to undergo photooxidation. However, in every case the photoreaction results in fragmentation, providing only indirect understanding of the primary addition step. Some heterocyclic betaines, namely, sydnones and related compounds,[9-13] have also been studied, and here too the reactions resulted in extensive fragmentation.

Scheme I



Another class of stable heterocyclic betaines that can be considered in studies of addition of singlet oxygen is the azapentalene mesoionic betaines, which have not been extensively investigated despite the relatively easy accessibility of several members.[14] We have previously shown that some triazapentalene derivatives such as 5*H*-pyrazolo[1′,2′:1,2]1,2,3-triazolo[5,4-*a*]phenazin-4-ium inner salts (**1a,b**)[15] and 1,3-dimethylpyrazolo[1,2-*a*]benzotriazole

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