Anal. Calcd for $C_{10}H_{15}F_3O$: C, 57.68; H, 7.26. Found: C, 57.52; H, 7.37.

Registry No. 1, 31555-03-0; (*E*)-2, 76480-86-9; (*Z*)-2, 76480-87-0; 3, 76480-88-1; 4, 76480-89-2; 5, 61315-75-1; 6, 76480-90-5; 7, 76480-91-6; 8, 76480-92-7; 9, 76480-93-8; 10, 76480-94-9; 11, 381-73-7; 12, 76480-95-0; (*E*)-13, 76480-96-1; (*Z*)-13, 76480-97-2; 14, 76480-98-3; 15, 372-31-6; 16, 76480-99-4; 17, 76481-00-0; 18, 76481-01-1; 19, 76481-02-2; 20, 76481-03-3; 21, 64504-53-6; 22, 76481-04-4; 23, 76481-05-5; 1-bromo-4-methylpent-3-ene, 2270-59-9; ethyl 4-hydroxy-2-butynoate, 31555-04-1; (4-methylpent-3-en-1-yl)copper, 54248-40-7; triethyl phosphonoacetate, 867-13-0.

Synthetic Route to 6-Functionalized 2-Azabicyclo[3.3.1]nonanes[1]

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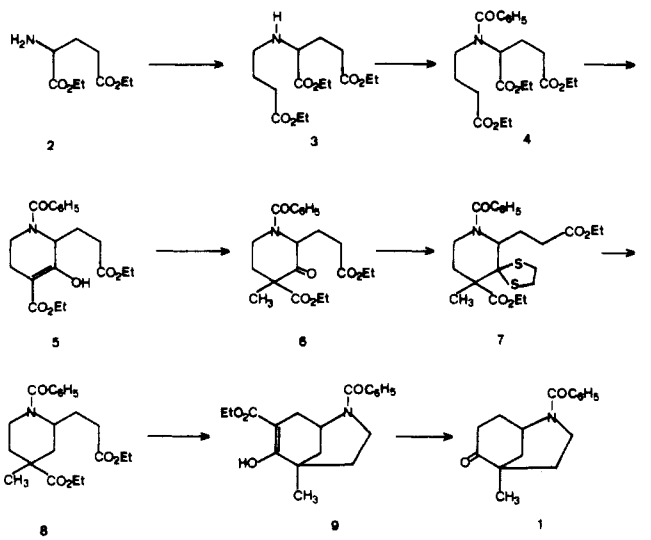
The synthesis of a 5-alkyl-2-azabicyclo[3.3.1]nonan-6-one by Dieckmann cyclization followed by decarbethoxylation from an appropriate piperidine diester, 8, is described. Monoalkylation of diethyl glutamate with ethyl 4-bromobutyrate and further benzoylation gave diethyl *N*-benzoyl-*N*-[3-(ethoxycarbonyl)propyl]glutamate (4). The ring closure of this triester by Dieckmann reaction followed by alkylation of the resulting 4-(ethoxycarbonyl)-3-piperidone 5 led to a diastereomeric mixture of 6 which was converted into the required piperidine diester 8, also in the form of a diastereomeric mixture, via the ethylene dithioketal 7 and subsequent desulfurization.

The 2-azabicyclo[3.3.1]nonane system[2] appears in numerous alkaloids (e.g., morphine, strycnine, uleine) and various synthetic compounds both of analgesic (morphinans, benzomorphans, and 5-phenylmorphans) and structural interest (2-azaadamantane). When functionalized, 2-azabicyclo[3.3.1]nonanes have been used as intermediates in the synthesis of more complex polycyclic structures,[3] especially those related to indole alkaloids[4] and to potentially active systems from a pharmacological standpoint.[5]

Our interest in the field of functionalized 2-azabicyclo[3.3.1]nonanes is focused on the possibilities they offer as intermediates in the synthesis of heteromorphans,[6] as they will allow us to adopt a new approach to such systems which, in general, have been prepared by acid-induced cyclization of 2-(heteroarylmethyl)tetrahydropyridines[7] with the limitations that this implies in some heterocyclic systems.[7e,8] In this context we intended to synthesize a

Scheme I



5-alkyl-2-azabicyclo[3.3.1]nonan-6-one, whose structural characteristics would allow the unequivocal elaboration of heteroaromatic systems fused between the 6- and 7-positions of the morphan nucleus, leading to heteromorphans[9] with a quaternary carbon atom directly attached to the aromatic ring. Such a condition is considered fundamental in synthetic analgesics[10] related to morphine.

The route we propose for the synthesis of 2-benzoyl-5-methyl-2-azabicyclo[3.3.1]nonan-6-one (1, Scheme I) implies the formation of the functionalized carbocyclic ring via Dieckmann cyclization followed by decarbethoxylation from an appropriate piperidine, 8. In turn, the polysubstituted piperidine 8, with the required methyl group for the subsequent localization of a C-5 alkyl substituent on morphan 1, can be prepared from a 4-(ethoxycarbonyl)-3-piperidone such as 5 by alkylation followed by reduction of the ketone carbonyl group. The β-keto ester 5, key intermediate of this synthetic scheme, can be obtained by

(1) This work was presented in a preliminary form at the First European Symposium on Organic Chemistry, Cologne, 1979.

(2) The 2-azabicyclo[3.3.1]nonanes are also frequently named morphans. For a review on the synthesis of such systems see J. Bosch and J. Bonjoch, *Heterocycles*, 14, 505 (1980).

(3) (a) E. L. May and J. G. Murphy, *J. Org. Chem.*, 19, 618 (1954); (b) E. L. May, *ibid.*, 23, 947 (1958); (c) H. H. Ong and E. L. May, *J. Heterocycl. Chem.*, 8, 1007 (1971); (d) H. H. Ong and E. L. May, *J. Org. Chem.*, 37, 712 (1972).

(4) L. J. Dolby and S. J. Nelson, *J. Org. Chem.*, 38, 2882 (1973).

(5) (a) J. Adachi, K. Nomura, K. Shiraki, and K. Mitsuhashi, *Chem. Pharm. Bull.*, 22, 658 (1974); (b) J. Adachi, K. Nomura, and K. Mitsuhashi, *ibid.*, 24, 85 (1976).

(6) Heteromorphans are compounds coming from isosteric substitution by an heterocyclic ring of the benzene nucleus in 6,7-benzomorphans in which the heteroaromatic ring is fused between the 6- and 7-positions of the 2-azabicyclo[3.3.1]nonane system.

(7) (a) Thienomorphans: T. A. Montzka and J. D. Matiskella, *J. Heterocycl. Chem.*, 11, 853 (1974); J. Bosch, R. Granados, and F. López, *ibid.*, 12, 651 (1975); M. Alvarez, J. Bosch, and J. Canals, *An. Quim.*, 71, 807 (1975); M. Alvarez, J. Bosch, R. Granados, and F. López, *J. Heterocycl. Chem.*, 15, 193 (1978). (b) Benzo[*b*]thienomorphans: M. Alvarez, J. Bosch, and M. Feliz, *ibid.*, 15, 1089 (1978). (c) Indolomorphans: G. C. Morrison, R. O. Waite, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.*, 32, 3691 (1967); J. Bosch and F. Boncompte, *An. Quim.*, 75, 357 (1979). (d) Pyridomorphans: D. Kishore, P. K. Khandelwal, and B. C. Joshi, *Arch. Sci.*, 27, 39 (1974). (e) Pyrrolomorphans: J. Bosch, D. Mauleón, F. Boncompte, and R. Granados, *J. Heterocycl. Chem.*, in press.

(8) Furomorphans: J. Bosch, R. Granados, and R. Llobera, *An. Quim.*, 75, 360 (1979); J. Bosch, R. Granados, R. Llobera, and D. Mauleón, *ibid.*, 75, 939 (1979).

(9) J. Bosch, J. Bonjoch, and I. Serret, *Heterocycles*, 14, 1983 (1980).

(10) N. B. Eddy and E. L. May in "Synthetic Analgesics", Part IIB, Pergamon Press, London, 1966.

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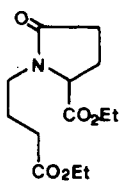
Dieckmann cyclization of a suitable triester, **4**, which is synthesized from diethyl glutamate (**2**) by alkylation with ethyl 4-bromobutyrate and further benzoylation of the resulting secondary amine.

This synthesis constitutes the first approach both to C-6-functionalized morphan systems and to 5-alkyl-2-azabicyclo[3.3.1]nonanes functionalized in the carbocyclic ring.[2]

Elaboration of the Piperidine Ring. Under the conditions required for the formation of amino triester **3** in the presence of anhydrous potassium carbonate,[11] both the starting product **2** and the resulting **3** can suffer lactamization reactions.[12] The optimum conditions we have found to minimize this secondary process are 100 °C and 80 min, operating with 0.3–0.4 mol of reagents. Otherwise, the intramolecular condensation of the amino triester **3** occurs to a certain extent (10–15% yield), affording pyrrolidine diester **10** whose structure was ascertained since it was transformed into indolizidine **11**[13] under Dieckmann reaction conditions.



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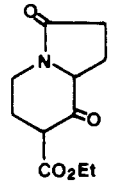

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The blocking by acylation of the secondary amino group in **3** is more advantageous than its transformation in a tertiary amine since the use of a benzoyl group as a protector group introduces simultaneously a stereochemical control element. This is a consequence of the conformational implications derived from the presence of the pseudoallylic system corresponding to the dipolar resonance form of the amide[14] in cyclic systems like those we prepare later on. The aromatic protons of benzoyl derivative **4** as well as those of all the dialkylbenzamides described in this work are equivalent in the NMR spectrum due to the lack of coplanarity between the aromatic ring and the amide carbonyl group.[15]

To our knowledge there are no precedents of Dieckmann cyclizations on triesters where, once the first cyclization is effected, the ketone carbonyl of the β-keto ester group is also included in a δ-keto ester moiety.[16] Otherwise, although Dieckmann cyclization is the usual method to obtain 4-(ethoxycarbonyl)-3-piperidones,[19] which have been used in different synthetic processes,[20] no examples exist of 3-piperidones with a C-2 carbalkoxyalkyl side chain synthesized by this procedure,[21] the compound prepared by Dieckmann cyclization more closely related to piperidine **5** being diethyl 1-benzoyl-5-oxo-2,4-piperidinedicarboxylate.[22]

In our case, the treatment of the amido triester **4** with 1 equiv of sodium ethoxide in benzene provides satisfactorily the β-keto ester **5**, which appears to be mainly enolic as cyclic β-keto esters[23] normally do, unlike acyclic ones.[24] Thus, **5** shows a strong absorption at 1660 cm^{-1} in the IR spectrum due to the enol ester. In the NMR spectrum, the signals corresponding to one enolic proton (δ 12.15) and two different ethyl ester protons were observed. Methylene and methyl protons in the β-keto ester group resonate at δ 4.22 and 1.28, downfield from side-chain ester protons (δ 4.09 and 1.22) because of the enolic character[23b] of the β-keto ester group.

In all cyclization runs with amido triester **4**, 1-benzoyl-4-(ethoxycarbonyl)-3-oxo-2-piperidinepropionic acid (**12**) was isolated as a byproduct to a greater or lesser extent depending on the strictness of the measures taken for dryness in the reaction medium. When the reaction conditions were optimized, less than 5% of acid **12** was obtained.[25] The formation of acid **12** is favored by the anchimeric assistance lent by the enolate of β-keto ester **5**[26] present in the reaction medium. Thus, the enhancement of the saponification rate by an alkoxide as a neighboring group[27] as well as the abnormally low activation energy required for the saponification of γ-keto esters[28] is well known.

Both piperidine **5** and acid **12** were treated with phenylhydrazine to isolate the corresponding pyrazolones **13** and **14**. Likewise, compounds **5** and **12** can be transformed into each other by selective saponification[26] and by esterification, respectively.

Elaboration of the Carbocyclic Ring. Alkylation of the β-keto ester **5** was achieved under kinetic control conditions with methyl iodide and potassium carbonate in acetone.[29] As a consequence of the creation of a new

(11) N. J. Leonard and W. V. Ruyle, *J. Am. Chem. Soc.*, 71, 3094 (1949).

(12) In the diethyl glutamate alkylation process with ethyl bromoacetate, lactamization of the initially formed γ-amino ester has also been described: M. E. Freed and A. R. Day, *J. Org. Chem.*, 25, 2105 (1960).

(13) A related indolizidine with a C-7 methoxycarbonyl group has been recently described: P. Yates and F. N. Maclachlan, *J. Indian Chem. Soc.*, 55, 1116 (1978).

(14) F. Johnson, *Chem. Rev.*, 68, 375 (1968).

(15) V. I. Stenberg, S. P. Singh, and V. Karain, *J. Org. Chem.*, 42, 2244 (1977).

(16) Likewise, few examples exist where a β-keto ester obtained by Dieckmann cyclization has the keto group in a γ position with respect to another ester group, although these cases are concerned with carbocyclic[17] or pentagonal heterocyclic systems.[18]

(17) (a) F. Ramirez and J. W. Sargent, *J. Am. Chem. Soc.*, 77, 6297 (1955); (b) W. S. Johnson, R. G. Christiansen, and R. E. Ireland, *ibid.*, 79, 1995 (1957).

(18) (a) B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org. Chem.*, 13, 123 (1948); (b) J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 189 (1961); (c) R. L. Augustine, Z. S. Zelawski, and D. H. Malarek, *J. Org. Chem.*, 32, 2257 (1967).

(19) (a) S. M. McElvain and J. F. Vozza, *J. Am. Chem. Soc.*, 71, 896 (1949); (b) B. M. Iselin and K. Hoffmann, *Helv. Chim. Acta*, 37, 178 (1954); (c) Z. Ozdowska, *Rocz. Chem.*, 49, 1025 (1975).

(20) (a) A. Hofmann, *Helv. Chim. Acta*, 55, 2934 (1972); (b) N. J. Lewis, K. K. Barker, R. M. Fox, Jr., and M. P. Mertes, *J. Med. Chem.*, 16, 156 (1973); (c) T. Shioiri and S. Yamada, *Tetrahedron*, 24, 4159 (1968); (d) T. Kametani, S. Huang, M. Ihara, and K. Fukumoto, *Chem. Pharm. Bull.*, 23, 2010 (1975); (e) H. G. Pars, F. E. Granchelli, R. K. Razdan, and J. K. Keller, *J. Med. Chem.*, 19, 445 (1976); (f) P. Krogsaard-Larsen, *Acta Chem. Scand., Ser B*, B31, 584 (1977); (g) Z. Ozdowska, *Pol. J. Chem.*, 52, 385 (1978).

(21) The ethyl 1-acetyl-3-oxo-2-piperidinepropionate has been prepared by a way based on the alkylation of the pyrrolidine enamine of 1-acetyl-3-piperidone which does not imply a Dieckmann cyclization: T. Masamune, H. Hayashi, M. Takasugi, and S. Fukuoka, *J. Org. Chem.*, 37, 2343 (1972).

(22) (a) F. E. King, T. J. King, and A. J. Warwick, *J. Chem. Soc.*, 3590 (1950). (b) H. C. Beyerman and P. Boekee, *Recl. Trav. Chim. Pays-Bas*, 78, 648 (1959). (c) See ref 11.

(23) (a) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, 19, 1625 (1963); (b) S. J. Rhoads, *J. Org. Chem.*, 31, 171 (1966).

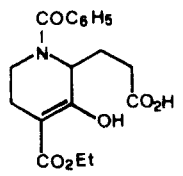
(24) J. L. Burdett and M. T. Rogers, *J. Am. Chem. Soc.*, 86, 2105 (1964).

(25) Acid **12** can be converted in just one step into methyl 1-benzoyl-4-(ethoxycarbonyl)-4-methyl-3-oxo-2-piperidinepropionate (**15**), which is synthetically equivalent to compound **6** later described. This has been carried out through alkylation of the β-keto ester group and simultaneous esterification of the propionic acid group with anhydrous potassium carbonate and methyl iodide in acetone solution.

(26) A similar reactivity has been observed in the selective saponification of the isolated ester of a dialkyl β-keto adipate [R. Richter, *Helv. Chim. Acta*, 32, 2318 (1949)] and in the formation of 3-(ethoxycarbonyl)-2-oxocyclohexaneacetic acid by selective hydrolysis of the corresponding diester (see ref 17a).

(27) U. R., Ghatak, J. Chakravarty, R. Dasgupta, and P. C. Chakraborty, *J. Chem. Soc., Perkin Trans. 1*, 2438 (1975), and reference cited therein.

(28) K. C. Kemp and M. L. Mieth, *Chem. Commun.*, 1260 (1969).



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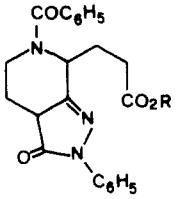


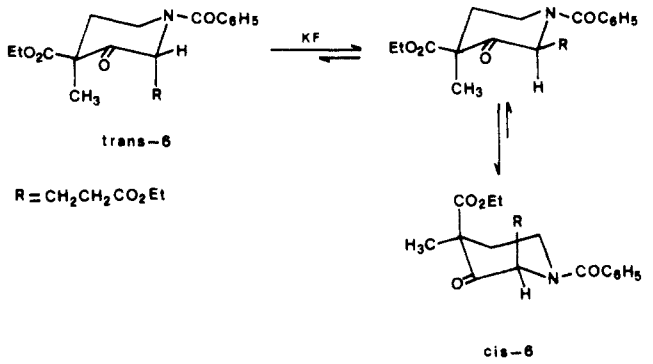
13, R = Et
14, R = H

chiral center, the main problem at this stage of the synthesis is the appearance of a diastereomeric pair and, therefore, of a possible cis or trans relationship between the C-4 ethoxycarbonyl group and the C-2 (ethoxycarbonyl)ethyl chain. Obviously, only the cis isomer is suitable for the subsequent elaboration of the morphan carbocyclic ring.

In our case a mixture of the two diastereomers of **6** was obtained in an approximate 3:2 ratio, calculated by NMR from the relative integration of singlets corresponding to the C-4 methyl groups in both isomers. The NMR spectrum of *N*-benzoylpiperidines *cis*-**6** and *trans*-**6**, which could not be separated, shows as the most characteristic common resonance the existence of a signal at δ 5.2, corresponding to the C-2 equatorial proton.[30] This value, together with the chemical shift of the C-6 protons (δ 3.4 and 4.1), indicates that the compounds *cis*-**6** and *trans*-**6** adopt a conformation where the 2-(ethoxycarbonyl)ethyl group is in an axial position. In fact, it is known that the strong steric interaction between the benzene nucleus and the substituents on carbon atoms vicinal to nitrogen in *N*,*N*-dialkylbenzamides[15] induce, in the case of *N*-benzoylpiperidines, a conformation in which the piperidine ring orientates in axial positions its largest C-2 and C-6 substituents.[31,32] This conformational behavior can be attributed to a general type of stereochemical interaction, defined as $A^{(1,3)}$ strain,[14] which recognizes steric interactions existing between substituents at the 1- and 3-positions of an allylic or pseudoallylic system. The phenomenon is confirmed by NMR spectroscopy[31] since, due to the amide carbonyl anisotropy effect,[33] signals for equatorial protons in an α position with respect to the nitrogen atom of *N*-acylpiperidines are observed at quite lower fields (δ 3.5–5.0) than those for axial (δ 2.3–3.2) ones.[31,34] These characteristics were already observed both in piperidine **5** and acid **12** (see Experimental Section).

The only signal that clearly differentiates the two epimers of **6** is the one of the methyl group at the 4-position, which appears at δ 1.30 in the major isomer and at δ 1.39 in the minor one. These chemical shifts provide the key for stereochemical assignment since in related cyclic structures an equatorial methyl group appears at higher field than an axial one.[35] Therefore the methyl signal at δ 1.30 is assigned to an equatorial methyl group and, consequently, to the cis isomer.

Scheme II



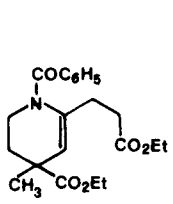
In order to obtain a larger proportion of the cis isomer, the isomeric mixture *cis*-**6** and *trans*-**6** was treated with ethanolic potassium fluoride under equilibration conditions.[36] A mixture of both diastereomers was obtained in which the cis isomer predominated (4:1).[37] This isomer is expected to be more stable than the trans isomer since a methyl group has a greater conformational preference for an equatorial position than an ethoxycarbonyl group[38] (Scheme II).

Reduction of the C-3 carbonyl group in the diastereomeric mixture **6** was carried out by thioketalization and further desulfurization with Raney nickel. Thioketal **7** was prepared by the action of ethanedithiol in presence of boron trifluoride etherate at a higher temperature than normal (80 °C).[39,40] Unfortunately, under these reaction conditions a reequilibration occurs, and an approximately equimolecular mixture of thioketals *cis*-**7** and *trans*-**7** was obtained independently of the epimeric relative ratio of the starting ketones. The greater volume of the ethoxycarbonyl group when coordinated to boron trifluoride could explain its greater conformational preference toward the equatorial position, thus promoting the reequilibration through the enol form of the ketone before thioketalization occurs.[43] However, the results may simply reflect a difference in the rate of thioketalization of the diastereomers. The loss of stereochemical control induced us to explore other reduction methods. Ketone **6** was recovered when treated with active zinc powder under modified Clemensen reduction conditions,[44] while reduction through the corresponding tosylhydrazone[45] was abandoned because of the low yield in its formation.

Reduction of the thioketal mixture **7** was carried out with W-4 Raney nickel.[46] An almost equimolecular (GLC)

(29) A. Barco, S. Benetti, and G. P. Pollini, *Synthesis*, 316 (1973).
(30) This chemical shift is similar to that observed for the C-2 equatorial proton in other 2-substituted *N*-acyl-3-piperidones: (a) R. J. Sundberg, W. V. Ligon, Jr., and L. S. Lin, *J. Org. Chem.*, **36**, 2471 (1971); (b) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron*, **27**, 4863 (1971).
(31) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).
(32) J. Quick, C. Mondello, M. Humora, and T. Brennan, *J. Org. Chem.*, **43**, 2705 (1978).
(33) W. E. Stewart and T. H. Siddall, *Chem. Rev.*, **70**, 517 (1970).
(34) H. O. House, B. A. Tefertiller, and G. G. Pitt, *J. Org. Chem.* **31**, 1073 (1966).
(35) (a) F. Johnson and N. A. Starkovsky, *Tetrahedron* Lett., 1173 (1962); (b) M. E. Kuehne, *J. Org. Chem.*, **35**, 171 (1970); (c) F. Nerdel, D. Frank, and K. Rehse, *Chem. Ber.*, **100**, 2978 (1967).
(36) (a) J. W. Scott, L. J. Durham, H. A. deJongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Lett.*, 2381 (1967). (b) See ref 30a.
(37) The same equilibrated mixture was obtained when the starting *cis*-**6** and *trans*-**6** mixture was eluted with benzene through a Merck 60 silica gel column.
(38) E. L. Eliel, H. Haubenstock, and R. V. Acharya, *J. Am. Chem. Soc.*, **83**, 2351 (1961).
(39) P. N. Rao, *J. Org. Chem.*, **36**, 2426 (1971).
(40) When the reaction was carried out at room temperature, as is usual in this type of reaction, as well as in other procedures such as dry hydrochloric acid in chloroform[41] or *p*-toluenesulfonic acid in acetic acid[42] at room temperature or at reflux, the desired result was not obtained.
(41) (a) J. D. Roberts, W. T. Moreland, Jr., and W. Frazer, *J. Am. Chem. Soc.*, **75**, 637 (1953); (b) J. R. Wiseman and W. A. Pletcher, *ibid.*, **92**, 956 (1970).
(42) R. B. Miller and R. D. Nash, *J. Org. Chem.*, **38**, 4424 (1973).
(43) In fact, the treatment of a 4:1 *cis*-**6** and *trans*-**6** mixture with boron trifluoride etherate at 80 °C overnight afforded a 3:2 mixture of these epimers.
(44) (a) S. Yamamura, M. Toda, and Y. Hirata, *Org. Synth.*, **53**, 86 (1973); (b) E. Vedejs, *Org. React.*, **22**, 401 (1975).
(45) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95**, 3662 (1973).
(46) (a) C. D. Hurd and B. Rudner, *J. Am. Chem. Soc.*, **73**, 5157 (1951); (b) G. R. Pettit and E. Van Tamelen, *Org. React.*, **12**, 356 (1962).

mixture of *cis*-8 and *trans*-8, wherefrom only the trans isomer could be isolated in a pure form, was obtained in 68% yield. As a byproduct, the enamide **16** was isolated



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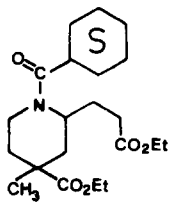

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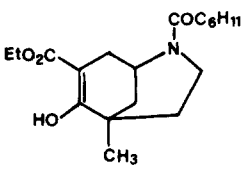

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in 4% yield.[47] The stereochemical assignment of *trans*-8 was inferred because this isomer did not afford a 2-azabicyclononane system when treated under Dieckmann cyclization conditions.

When the available enriched (2:1) *cis*-8 and *trans*-8 mixture was subjected to Dieckmann cyclization, with sodium hydride as the base in refluxing toluene, the bicyclic β-keto ester **9** was obtained in 54% yield. Occasionally *N*-(cyclohexylcarbonyl)morphan **18** was isolated in small quantities from cyclization of cyclohexylcarboxamide **17**.[49] The above yield is greater than those described in other Dieckmann condensations leading to bicyclo[3.3.1]nonane systems.[50] It suggests that the amide function[51] tends to diminish the repulsive interactions[52] between the C-3 and C-7 substituents in the flattened chair–chair conformation preferred by these systems.[53] Both IR and NMR spectra show that azabicyclo compound **9** is in its tautomeric enol form. The NMR spectrum also reveals the existence of rotamers as a consequence of the restricted rotation of the *N*-benzoyl group. This phenomenon was not observed in the precursors of **9** and probably does reflect a greater stability of the planar conformation of the amide function.[31]

Finally, β-keto ester decarbalkoxylation with sodium chloride in wet Me_2SO[54] provides in 74% yield 2-benzoyl-5-methyl-2-azabicyclo[3.3.1]nonan-6-one (**1**). Ketone **1** shows two intense absorptions at 1705 and 1620 cm^{-1} in its IR spectrum, corresponding to ketone and benzamide carbonyl groups, respectively. Once again, like in the azabicyclo systems **9** and **18**, rotamers are observed in its NMR spectrum. Thus, the C-1 methine proton appears at δ 5.25 (0.6 H) and δ 4.6 (0.4 H), while the C-3 equatorial proton, adjacent to the *N*-benzoyl group, appears at δ 4.3 (0.6 H) and δ 3.8 (0.4 H). The aromatic protons are equivalent (δ 7.40), and the quaternary methyl group appears at δ 1.10.

The presence of a C-5 quaternary carbon atom and a C-6 ketone group makes functionalized morphans **9** and **1** versatile intermediates for the subsequent elaboration of heteroaromatic rings unambiguously fused between the 6- and 7-positions of the morphan system.[9]

Experimental Section

NMR spectra were determined in $CDCl_3$ solution (except where noted) with a Perkin-Elmer R-24B (60 MHz) instrument using internal Me_4Si (δ 0) as a reference. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer. Mass spectra were obtained with a Hewlett-Packard 5930 A spectrometer. Melting points were determined on a Büchi apparatus and are uncorrected. Analytical samples were prepared by distillation on a Büchi GKR-50 Kugelrohr apparatus, unless otherwise indicated. The temperatures cited for these distillations are the maximum temperatures of the oven during the distillation. Prior to concentration, 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. The developing solvent was ether/acetone/diethylamine (95:3:2). Brine refers to a saturated aqueous sodium chloride solution. Microanalyses were performed by the Instituto de Quimica Orgánica Aplicada de Catalunya, Barcelona.

Diethyl Glutamate (2). Diethyl glutamate hydrochloride, prepared from glutamic acid (147 g, 1 mol) by a previously described procedure,[55] was dissolved in water (1 L) saturated with K_2CO_3 and the mixture extracted 10 times with Et_2O. The crude diethyl glutamate (150 g, 73%) obtained by evaporating, without heating, the dried extracts was used immediately.

Diethyl *N*-[3-(Ethoxycarbonyl)propyl]glutamate (3). A stirred mixture of **2** (66 g, 0.325 mol), ethyl 4-bromobutyrate (55 g, 0.40 mol), and anhydrous K_2CO_3 (72 g, 0.37 mol) was heated in an oil bath at 100 °C for 80 min. After the mixture cooled, 150 mL of cold water was added, the organic layer was separated, and the aqueous solution was extracted with Et_2O. The combined organic solutions were extracted with 1 N HCl. The extracts were basified with cold saturated aqueous K_2CO_3 and extracted with Et_2O. The ethereal solution was evaporated without heating to give **3** (64 g, 61%) which was used immediately in the following reaction because of its instability: NMR (CCl_4) δ 1.23 (t, 6 H, OCH_2CH_3), 1.25 (t, 3 H, $CHCO_2CH_2CH_3$), 1.0–1.5 (masked, 1 H, NH), 1.5–2.1 (m, 4 H, CH_2), 2.15–2.7 (m, 6 H, NCH_2 and CH_2CO_2Et), 3.05–3.35 (dd, J = 7, 6 Hz, 1 H, CH), 4.08 (q, 4 H, OCH_2CH_3), 4.16 (q, 2 H, $CHCO_2CH_2CH_3$); IR (NaCl) 1735 cm^{-1} (ester). The oxalate, prepared in EtOH, melted at 103–106 °C (Et_2O–EtOH). Anal. Calcd for $C_{17}H_{29}NO_{10}$: C, 50.11; H, 7.17; N, 3.44. Found: C, 50.12; H, 7.37; N, 3.49.

Diethyl *N*-Benzoyl-*N*-[3-(ethoxycarbonyl)propyl]glutamate (4). To a stirred solution of **3** (136 g, 0.43 mol) in anhydrous pyridine (250 mL) was added benzoyl chloride (60.4 g, 0.43 mol) in anhydrous pyridine (250 mL) dropwise at 0–5 °C. The mixture was stirred at room temperature overnight. The residue after filtration and evaporation was dissolved in Et_2O and washed with 1 N HCl and aqueous 5% $NaHCO_3$. The combined organic extracts were evaporated to afford **4**: 165 g (91%); bp 225–235 °C (0.1 mm); NMR δ 1.18 and 1.21 (2 t, 3 H each, OCH_2CH_3), 1.30 (t, 3 H, $CHCO_2CH_2CH_3$), 1.6–2.6 (m, 8 H, CH_2), 3.3 (deformed t, 2 H, NCH_2), 3.8–4.4 (masked, 1 H, CH), 4.00 and 4.04 (2 q, 2 H each, OCH_2CH_3), 4.15 (q, 2 H, $CHCO_2CH_2CH_3$), 7.38 (s, 5 H, C_6H_5); IR ($CHCl_3$), 1735 (ester), 1640 (benzamide) cm^{-1}. Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.70; H, 7.36; N, 3.32. Found: C, 62.68; H, 7.34; N, 3.30.

Ethyl 2-(Ethoxycarbonyl)-5-oxo-1-pyrrolidinebutyrate (10). When alkylation of **2** was carried out either under stronger

(47) Olefin formation during thioketal desulfurization is an already known process[48] which can reach a significant extent depending on the steric crowding over thioketal group and on the type of Raney nickel employed. In our case, the yield of olefin **16** increases to 19% when reduction was carried out in an acetone medium with deactivated Raney nickel.

(48) W. Reusch, "Reduction", R. L. Augustine, Ed., M. Dekker, New York, 1968, pp 196–198.

(49) Cyclohexylcarboxamide **17** would come (ca. 5% yield) from an overreduction of thioketal **7** by Raney nickel [W. Davies and Q. N. Porter, *J. Chem. Soc.*, 459 (1957)]. The hydrogenation of the benzamide aromatic ring has been also observed during enamide **16** hydrogenation in the presence of platinum oxide.

(50) (a) L. H. Sternback and S. Kaiser, *J. Am. Chem. Soc.*, 74, 2215 (1952); (b) J. P. Ferris and N. C. Miller, *ibid.*, 85, 1325 (1963).

(51) Ethyl 2-benzoyl-8-oxo-2-axabicyclo[3.3.1]nonane-7-carboxylate was also prepared in excellent yield by Dieckmann cyclization. See ref 5a.

(52) These interactions disturb the formation of the bicyclic system. When they do not exist, the cyclization occurs in good yield: J. P. Schaeffer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, 32, 1372 (1967).

(53) (a) For conformational analysis of bicyclo[3.3.1]nonanes see J. A. Peters, *Synthesis*, 321 (1979), and references cited therein. (b) For conformational analysis of 2-azabicyclo[3.3.1]nonanes see T. G. Cochran, *J. Med. Chem.*, 17, 987 (1974).

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

(55) H. F. Herbrandson and R. H. Wood, *J. Med. Chem.*, 12, 620 (1969).

conditions (time, temperature) than the above or with no quick manipulation of the amino triester **3**, after the benzoylation step lactam **10** was obtained together with the *N*-benzoyl derivative **4**. Column chromatography (SiO_2) afforded amido triester **4** (benzene/$CHCl_3$, 4:1) and lactam **10** (benzene/$CHCl_3$, 1:2): bp 160–170 °C (0.15 mm); NMR δ 1.25 and 1.30 (2 t, 3 H each, OCH_2CH_3), 1.65–2.05 (m, 2 H, $CH_2CH_2CH_2$), 2.1–2.65 (m, 6 H, CH_2 ring and CH_2CO_2Et), 3.05 and 3.60 (2 m, 1 H each, NCH_2), 3.9–4.4 (masked, 1 H, CH), 4.09 and 4.20 (2 q, 2 H each, OCH_2CH_3); IR (NaCl) 1740 (ester) and 1695 (amide) cm^{-1}; mass spectrum, *m/e* (relative intensity) 225 (24), 169 (20), 152 (44), 124 (41), 97 (100), 84 (24). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.56; H, 7.74; N, 5.16. Found: C, 58.01; H, 7.88; N, 5.53.

In the optimization attempts of the sequence leading to the amido triester **4**, **diethyl *N*-benzoylglutamate** was isolated as a white solid: mp 68–69 °C (Et_2O–petroleum ether) (lit.[56] mp 73–74 °C); NMR δ 1.20 (t, 3 H, OCH_2CH_3), 1.28 (t, 3 H, $CHCO_2CH_2CH_3$), 1.8–2.8 (m, 4 H, CH_2), 4.06 (q, 2 H, OCH_2CH_3), 4.17 (q, 2 H, $CHCO_2CH_2CH_3$), 4.80 (deformed t, 1 H, CH), 7.0 (br peak, 1 H, NH), 7.1–7.6 (m, 3 H, *m*- and *p*-ArH), 7.75–7.95 (m, 2 H, *o*-ArH); IR ($CHCl_3$) 1730 (ester) and 1665 (amide) cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.56; H, 6.84; N, 4.59.

Ethyl 1,2,3,5,6,7,8,8a-Octahydro-3,8-dioxo-7-indolizinecarboxylate (11). A solution of **10** (5.5 g, 0.02 mol) and 1.2 mL (0.02 mol) of dry EtOH in 15 mL of anhydrous benzene was added under nitrogen to 460 mg (0.02 mol) of a sodium dispersion suspended in 30 mL of benzene, and the resulting solution was refluxed for 3 h. The solvent was evaporated and the residue distributed between $CHCl_3$ and 1 N HCl. The aqueous layer was extracted with $CHCl_3$, and the combined organic extracts were evaporated to afford an oil which on chromatography (SiO_2, $CHCl_3$) gave 2.1 g (50%) of **11**: bp 210–220 °C (0.15 mm); NMR δ 1.30 (t, 3 H, OCH_2CH_3), 1.7–2.7 (m, 6 H, CH_2), 2.7–4.05 (m, 2.3 H, NCH_2 and $COCHCO_2Et$), 4.24 (q, 2 H, OCH_2CH_3), 4.05–4.45 (masked, 1 H, CH), 12.5 (s, 0.7 H, OH); IR (NaCl) 1650 cm^{-1} (enol ester and amide). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.66; N, 6.66; N, 6.22. Found: C, 58.43; H, 6.80; N, 5.92.

Ethyl 1-Benzoyl-4-(ethoxycarbonyl)-3-oxo-2-piperidinepropionate (5). A solution of **4** (86.5 g, 0.204 mol) and 11.2 mL of dry EtOH in 100 mL of anhydrous benzene was added dropwise with stirring, under nitrogen, to 4.6 g (0.2 mol) of sodium dispersion suspended in 250 mL of anhydrous benzene. The resulting solution was refluxed for 8 h. The residue after evaporation was dissolved in cold water and the nonacidic material removed with Et_2O. The ethereal extracts were evaporated and chromatographed (SiO_2) to give 5 g of **5** (9:1 benzene/$CHCl_3$) and 4 g of unreacted **4** (3:1 benzene/$CHCl_3$). The aqueous layer was acidified with 1 N HCl and extracted with $CHCl_3$. The combined organic extracts (instantaneous and intense reddish purple coloration with methanolic $FeCl_3$) were evaporated to give 52 g of an oil which solidified on standing. Crystallization from hexane/Et_2O gave 45 g (63% overall yield) of **5**: mp 80–82 °C; NMR δ 1.22 (t, 3 H, OCH_2CH_3 side chain), 1.28 (t, 3 H, OCH_2CH_3), 1.8–2.8 (m, 6 H, CH_2), 2.95 (m, 1 H, C_6H_{ax}), 3.6 (m, 1 H, C_6H_{eq}), 4.09 (q, 2 H, OCH_2CH_3 side chain), 4.22 (q, 2 H, OCH_2CH_3), 5.20 (br peak, 1 H, C_2H_{eq}), 7.35 (s, 5 H, C_6H_5), 12.30 (s, 1 H, OH); IR (KBr) 1730 (ester), 1660 (enol ester), 1620 (benzamide) cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 64.00; H, 6.66; N, 3.73. Found: C, 64.11; H, 6.71; N, 3.71.

1-Benzoyl-4-(ethoxycarbonyl)-3-oxo-2-piperidinepropionic acid (12) was obtained as a byproduct in some Dieckmann cyclizations from **4**. The combined $CHCl_3$ extracts from the acidified reaction mixture were evaporated, and the residue was chromatographed (SiO_2). On elution with benzene/$CHCl_3$ (9:1), β-keto ester **5** was separated, and with $CHCl_3$ acid **12** was isolated: mp 135–136 °C ($CHCl_3$/Et_2O); NMR δ 1.28 (t, 3 H, OCH_2CH_3), 1.9–2.8 (m, 6 H, CH_2), 3.1 (m, 1 H, C_6H_{ax}), 3.6 (m, 1 H, C_6H_{eq}), 4.23 (q, 2 H, OCH_2CH_3), 5.25 (br peak, 1 H, C_2H_{eq}), 7.45 (s, 5 H, C_6H_5), 9.85 (br peak, 1 H, COOH), 12.25 (br s, 1 H, OH); IR ($CHCl_3$) 2500–3500 (COOH), 1720 (COOH), 1665 (enol ester), 1620 (benzamide) cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.05; N, 4.03. Found: C, 62.36; H, 6.13; N, 4.08.

(56) *Beilstein, II*, 9, 186 (1949).

The same acid was obtained when a solution of aqueous 3 N KOH (50 mL) was added to **5** (100 mg, 0.26 mmol) and the mixture was kept at room temperature for 1 h. The reaction mixture was acidified with 1 N HCl and extracted with $CHCl_3$ to give 90 mg (97%) of **12**.

The acid **12** was esterified (EtOH, H_2SO_4) to yield **5** (70%).

Ethyl 6-Benzoyl-2-phenyl-3-oxo-3,3a,4,5,6,7-hexahydropyrazolo[3,4-*c*]pyridine-7-propionate (13). A mixture of **5** (2.5 g, 7 mmol) and phenylhydrazine (1.51 g, 14 mmol) in EtOH (7 mL) was heated under reflux for 140 min. Cooling afforded 1 g of crystals: mp 155–157 °C (EtOH); NMR δ 1.21 (t, 3 H, OCH_2CH_3), 2.0–3.0 (m, 6 H, CH_2), 3.5 (m, 1 H, C_5H_{ax}), 4.08 (q, 2 H, OCH_2CH_3), 3.9–4.3 (masked, 1 H, C_5H_{eq}), 5.7 (br peak, 1 H, C_7H_{eq}), 6.75–7.90 (m, 11 H, C_6H_5 and OH); IR ($CHCl_3$) 2500–3500 (OH), 1725 (ester), 1620 (benzamide) cm^{-1}. Anal. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.70; H, 6.01; N, 10.01. Found: C, 68.80; H, 5.91; N, 10.05.

6-Benzoyl-2-phenyl-3-oxo-3,3a,4,5,6,7-hexahydropyrazolo-[3,4-*c*]pyridine-7-propionic Acid (14). Phenylhydrazine (3.24 g, 0.03 mol) was added dropwise to a solution of **12** (3.47 g, 0.01 mol) in EtOH (11 mL). The resulting solution was refluxed for 140 min and evaporated, and the residue was distributed between Et_2O and aqueous 2 N NaOH. The aqueous layer was acidified and concentrated to give a solid: mp 158–160 °C (EtOH); NMR (Me_2SO-d_6) δ 2.0–4.0 (m, 8 H, CH_2), 5.5 (br peak, 1 H, C_7H_{eq}), 7.1–7.8 (m, 11 H, C_6H_5 and OH), 11.4 (br peak, 1 H, COOH); IR (KBr) 2500–3500 (OH), 1735 (COOH), 1640 (benzamide) cm^{-1}. Anal. Calcd for $C_{22}H_{21}N_3O_4 \cdot H_2O$: C, 64.54; H, 5.62; N, 10.26. Found: C, 64.36; H, 5.80; N, 10.28.

Ethyl 1-Benzoyl-4-(ethoxycarbonyl)-4-methyl-3-oxo-2-piperidinepropionate (6). A stirred mixture of **5** (15.37 g, 41 mmol), ICH_3 (58.2 g, 0.41 mol), and anhydrous K_2CO_3 (11.31 g, 82 mmol) in acetone (250 mL) was refluxed for 7 h. The inorganic materials were filtered and washed with acetone. The evaporation of the combined filtrates gave an oily residue which was dissolved in benzene and washed with H_2O and brine. Evaporation left a viscous oil (14 g, 88%), whose NMR spectrum showed it to be a 3:2 mixture of *cis*-**6** and *trans*-**6**: bp 240–250 °C (0.15 mm); NMR δ 1.23 and 1.26 (2 t, 3 H each, OCH_2CH_3), 1.30 (s, 1.8 H, CH_3(eq)), 1.39 (s, 1.2 H, CH_3(ax)), 1.5–2.9 (m, 6 H, CH_2), 2.9–3.9 (m, 2 H, NCH_2), 4.08 and 4.23 (2 q, 2 H each, OCH_2CH_3), 4.8–5.6 (br peak, 1 H, CH), 7.4 (s, 5 H, C_6H_5); IR (NaCl) 1730 (C=O), 1625 (benzamide) cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.78; N, 6.94; N, 3.59. Found: C, 64.80; H, 6.87; N, 3.52.

Methyl 1-Benzoyl-4-(ethoxycarbonyl)-4-methyl-3-oxo-2-piperidinepropionate (15). Methyl iodide (12.5 mL, 0.20 mol) was added to a solution of **12** (3.47 g, 0.01 mol) in anhydrous acetone (70 mL) containing anhydrous K_2CO_3 (5.52 g, 0.04 mol), and the solution was refluxed. Additional ICH_3 (19 mL, 0.30 mol) was added to the refluxing slurry in three portions at 2-h intervals. After the last addition, the slurry was refluxed for 2 h, cooled, and filtered. The evaporation afforded an oil which was dissolved in Et_2O and treated sequentially with 1 M aqueous K_2CO_3, brine, and water. The organic layer was evaporated to give a viscous oil: 2.4 g (64%); mixture of the cis and trans isomers (3:2 ratio); bp 235–240 °C (0.15 mm). Anal. Calcd for $C_{20}H_{25}NO_6$: C, 64.00; H, 6.66; N, 3.73. Found: C, 63.99; N, 6.78; N, 3.53.

Equilibration of the Diastereomeric Mixture of *cis*-6 and *trans*-6. A solution of the above 3:2 mixture of ketones **6** (10.58 g) and KF (30.34 g) in EtOH (1.2 L) was refluxed for 30 h. The ethanol was removed, the residue was dissolved in $CHCl_3$, and the solution was washed with water. The organic layer was evaporated to give 9.86 g (93%) of an oil whose NMR showed it to be a 4:1 mixture of *cis*-**6** and *trans*-**6**.

Ethyl 1-Benzoyl-4-(ethoxycarbonyl)-3,3-(ethylenedithio)-4-methyl-2-piperidinepropionate (7). Boron trifluoride etherate (22.6 mL, 0.18 mol) was added to a solution of the mixture of ketones **6** (14 g, 0.036 mol) in ethanedithiol (60.4 mL, 0.72 mol). The solution was stirred and heated for 8 h at 80 °C, cooled, and poured into Et_2O and H_2O, and the phases were separated. The ethereal layer was exhaustively washed with cold 2 N aqueous NaOH and brine. Evaporation yielded 13.7 g (80%) of *cis*-**7** and *trans*-**7** (1:1 mixture) as an oil: bp 240–250 °C (0.15 mm); NMR δ 1.24 (t, 3 H, OCH_2CH_3 side chain), 1.31 and 1.32 (2 t, 1.5 H each, OCH_2CH_3), 1.51 and 1.53 (2 s, 1.5 H each, CH_3), 1.6–3.0 (m, 6 H, CH_2), 3.25 (br s, 4 H, SCH_2), 3.0–3.9 (m, 2 H, NCH_2), 4.09 (q, 2

H, OCH_2CH_3 side chain), 4.19 and 4.20 (2 q, 1 H each, OCH_2CH_3), 4.6–5.2 (m, 1 H, CH), 7.40 (s, 5 H, C_6H_5); IR ($CHCl_3$) 1725 (ester), 1630 (benzamide) cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_5S_2$: C, 59.35; H, 6.66; N, 3.01; S, 13.76. Found: C, 59.03; H, 6.93; N, 3.37; S, 14.20.

Ethyl 1-Benzoyl-4-(ethoxycarbonyl)-4-methyl-2-piperidinepropionate (8). A suspension of 46.5 g (0.1 mol) of thioketals 7 and 440 g of freshly prepared W-4 Raney nickel in 2 L of EtOH was heated under reflux. After being stirred for 15 h, it was cooled, the solution filtered, and the nickel washed with EtOH. The combined filtrates were eluted through SiO_2, and the catalyst was extracted (Soxhlet) overnight with EtOH. Concentration of the combined ethanol solutions yielded an oil which was chromatographed. Elution with benzene/$CHCl_3$ (4:1) gave 1.5 g (4%) of **ethyl 1-benzoyl-4-(ethoxycarbonyl)-4-methyl-1,4,5,6-tetrahydropyridine-2-propionate (16)**: bp 220–230 °C (0.2 mm); NMR δ 1.22 and 1.25 (2 t, 3 H each, OCH_2CH_3), 1.30 (s, 3 H, CH_3), 1.5–3.0 (m, 6 H, CH_2), 3.5 (deformed t, 2 H, NCH_2), 4.03 and 4.09 (2 q, 2 H each, OCH_2CH_3), 5.20 (br s, 1 H, C=CH), 7.40 (m, 5 H, C_6H_5); IR ($CHCl_3$) 1725 (ester), 1650 (benzamide) cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.46; H, 7.55; N, 3.64. On elution with benzene/$CHCl_3$ (1:9) a *cis*-8 and *trans*-8 mixture (25 g, 67%) was obtained: bp 235–240 °C (0.15 mm); NMR δ 1.1–1.4 (m, 9 H, OCH_2CH_3 and CH_3), 1.5–2.8 (m, 8 H, CH_2), 3.25 (m, 1 H, C_6H_{ax}), 3.6 (m, 1 H, C_6H_{eq}), 3.9–4.3 (m, 4 H, OCH_2CH_3), 4.5 (m, 1 H, C_2H_{eq}), 7.3 (s, 5 H, C_6H_5); IR ($CHCl_3$) 1720 (ester), 1615 (benzamide) cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.20; H, 7.73; N, 3.73. Found: C, 67.29; H, 7.93; N, 3.58. When the mixture was allowed to stand, *trans*-8 crystallized from the more polar fractions: mp 74–75 °C (hexane–Et_2O); NMR δ 1.22 and 1.23 (2 t, 3 H each, OCH_2CH_3), 1.28 (s, 3 H, CH_3(ax)), 4.04 and 4.11 (2 q, 2 H each, OCH_2CH_3); IR (KBr) 1735 (ester), 1615 (benzamide) cm^{-1}. Anal. Calcd for $C_{21}H_{29}NO_5$: C, 67.20; H, 7.73; N, 3.73. Found: C, 67.16; H, 7.74; N, 3.68.

Ethyl 2-Benzoyl-5-methyl-6-oxo-2-azabicyclo[3.3.1]nonane-7-carboxylate (9). A sodium hydride oil dispersion (55%, 2.4 g, 55 mmol) was suspended in anhydrous toluene (80 mL) under nitrogen and a 2:1 *cis*-8 and *trans*-8 mixture (6.94 g, 18.5 mmol) in anhydrous toluene (80 mL) containing a few drops of EtOH was added dropwise with stirring at room temperature. The resulting mixture was refluxed with vigorous stirring for 8 h. After evaporation the residue was dissolved in 1 N HCl and extracted with $CHCl_3$. The combined organic extracts were evaporated to give an oil which on chromatography (SiO_2, 2:1 benzene/$CHCl_3$) gave 2.2 g (54% based on *cis*-8) of 9: bp 220–230 °C (0.4 mm); NMR δ 1.20 (s, 3 H, CH_3), 1.30 (t, 3 H, OCH_2CH_3), 1.65 (br peak, 4 H, 4- and 9-CH_2), 2.45 (br peak, 2 H, 8-CH_2), 2.9–3.9 (m, 2 H, 3-CH_2), 4.20 (q, 2 H, OCH_2CH_3), 4.0–4.4 (masked, 0.6 H, C_1H), 5.15 (br peak, 0.4 H, C_1H), 7.30 (s, 5 H, C_6H_5), 12.3 (s, 1 H, OH); IR ($CHCl_3$) 1650 (enol ester), 1615 (benzamide) cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.01; H, 7.17; N, 4.15. **Ethyl 2-(cyclohexylcarbonyl)-5-methyl-6-oxo-2-azabicyclo[3.3.1]nonane-7-carboxylate (18)** was obtained as a byproduct in the above Dieckmann cyclization when the crude desulfurization mixture was used without further purification. Compound 18 was isolated as a colorless oil from chromatography (SiO_2, 9:1 benzene/$CHCl_3$): NMR δ 1.20 (s, 3 H, CH_3), 1.30 (t, 3 H, OCH_2CH_3), 1.4–3.0 (m, 17 H, COC_6H_{11} and CH_2), 2.9–3.9 (m, 2 H, 3-CH_2), 4.20 (q, 2 H, OCH_2CH_3), 4.0–4.4 (masked, 0.6 H, C_1H), 5.05 (br peak, 0.4 H, C_1H), 12.3 (s, 1 H, OH); mass spectrum, *m/e* (relative intensity) 335 (3), 263 (4), 207 (80), 96 (100), 83 (86).

2-Benzoyl-5-methyl-2-azabicyclo[3.3.1]nonan-6-one (1). Sodium chloride (410 mg, 7 mmol), water (360 mg, 20 mmol), and Me_2SO (5 mL) were added to 9 (2.1 g, 6.38 mmol), and the heterogeneous reaction mixture was heated to 155–160 °C for 3 h. The mixture was extracted with Et_2O, and the ethereal extracts were washed exhaustively with brine. After the organic layer had been dried and concentrated, the residual oil was chromatographed on silica gel with a benzene–$CHCl_3$ (1:9) eluent to separate 1.25 g (76%) of 1: bp 220–230 °C (0.6 mm); NMR δ 1.10 (s, 3 H, CH_3), 1.5–2.3 (m, 6 H, CH_2), 2.4 (m, 2 H, $COCH_2$), 3.2 (m, 1 H, C_3H_{ax}), 3.8 (br peak, 0.4 H, C_3H_{eq}), 4.3 (br, 0.6 H, C_3H_{eq}), 4.6 (br, 0.4 H, C_1H), 5.25 (br, 0.6 H, C_1H), 7.4 (s, 5 H, C_6H_5); IR (NaCl) 1705 (ketone), 1625 (benzamide) cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.87; H, 7.38; N, 5.40. Found: C, 74.68; H, 7.70; N, 5.44.

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Registry No. 1, 76359-07-4; 2, 16450-41-2; 3, 76359-08-5; 3 oxalate, 76359-09-6; 4, 75274-00-9; 5, 76359-10-9; *cis*-6, 76359-11-0; *trans*-6, 76359-12-1; *cis*-7, 76359-13-2; *trans*-7, 76419-57-3; *cis*-8, 76359-14-3; *trans*-8, 76359-15-4; 9, 76359-16-5; 10, 76359-17-6; 11, 76359-18-7; 12, 76359-19-8; 13, 75144-74-0; 14, 76359-20-1; *cis*-15, 76359-21-2; *trans*-15, 76359-22-3; 16, 76359-23-4; 18, 76359-24-5; ethyl 4-bromobutyrate, 2969-81-5; benzoyl chloride, 98-88-4; diethyl *N*-benzoylglutamate, 42807-47-6; phenylhydrazine, 100-63-0; ICH_3, 74-88-4; ethanedithiol, 540-63-6.

Selective Preparation. 30.[1] A Convenient Preparation of 5,13-Di-*tert*-butyl-8,16-disubstituted-[2.2]metacyclophanes and Their Trans-*tert*-butylation and Halogenation Reactions

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The preparation of 5,13-di-*tert*-butyl-8,16-disubtituted-[2.2]metacyclophanes (**16a–k**) from the corresponding 4-substituted-*tert*-butylbenzenes was described. The $AlCl_3$–CH_3NO_2-catalyzed trans-*tert*-butylation of 5,13-di-*tert*-butyl-8,16-dimethyl[2.2]metacyclophane (**16b**) in benzene afforded 8,16-dimethyl[2.2]metacyclophane (**28a**) in good yield. However, the similar reaction of diethyl derivative **16c** gave only a complex mixture of products. Treatment of **16b** and **28a** with NBS in CCl_4 afforded the corresponding dibromides **38** and **39** in 86% and 95% yields, respectively. The bromination of **16b** and **16c** with bromine in CCl_4 afforded the corresponding *anti*-10b,10c-dialkyl-4,5,9,10-tetrabromo-2,7-di-*tert*-butyl-10b,10c-dihydropyrenes **41a** and **41b** in good yields, respectively. However, it was also found that the bromination of **16b** and **16c** in the presence of Fe powder in the same solvent afforded 4,5,9,10-tetrabromo-2,7-di-*tert*-butylpyrene (**40**) in good yield in all cases. On the other hand, the bromination of **28a** with bromine in the presence of Fe powder gave 2,7-dimethyl-3,6,8,11-tetrabromo-4,5,9,10-tetrahydropyrene (**42**). The reaction pathway of the bromination of **16** is discussed.

Although Boekelheide and his co-workers[2-11] have reported the synthesis of interesting 8-mono- and 8,16-di-substituted-[2.2]metacyclophanes in low total yields from simple starting compounds, their preparative routes seem

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