Studies in the 7-Azabicyclo[2.2.1]heptane System. I. Pseudo-4-norcocaine[1]

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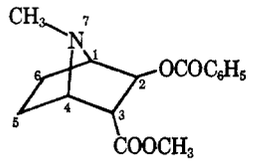
N-Benzylpyrrole and acetylenedicarboxylic acid afforded a Diels–Alder adduct, 2,3-dicarboxy-7-benzyl-7-azabicyclo[2.2.1]hepta-2,5-diene. This was reduced, and the product was treated with benzyl chloroformate followed by acetic anhydride to give 7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane-2,3-di-*endo*-dicarboxylic acid anhydride. Sequential treatment of the anhydride with methanol, thionyl chloride, and dimethyl cadmium followed by 1*N* acid work-up yielded 2-*exo*-acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane. Baeyer–Villiger oxidation of the ketone followed by base hydrolysis provided 2-*exo*-hydroxy-3-*endo*-carboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane. Esterification of this with diazomethane and then with benzoyl chloride gave 2-*exo*-benzoyloxy-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane which was subjected to hydrogenolysis and reductive methylation to obtain pseudo-4-norcocaine, 2-*exo*-benzoyloxy-3-*endo*-carbomethoxy-7-methyl-7-azabicyclo[2.2.1]heptane. Structural and stereochemical assignments for these compounds and for products of the novel reactions characteristic of the new 7-azabicyclo[2.2.1]heptane system have been made on the basis of nmr data.

The proposition that conformationally rigid and representative pharmacophores may selectively or uniquely affect the adaptability of the undoubtedly different receptors involved in the several biological responses induced by conformationally mobile analogs has led to these studies on the chemistry of the novel 7-azabicyclo[2.2.1]heptane system, a rigid and versatile superstructure of potential biological importance.

This report details the first exploitation of the novel Diels–Alder reaction of pyrroles. It deals generally with the chemistry of the new 7-azabicyclo[2.2.1]-heptane system and specifically with the stereoselective synthesis of pseudo-4-norcocaine, 2-*exo*-benzoyloxy-3-*endo*-carbomethoxy-7-methyl-7-azabicyclo[2.2.1]heptane (**1**).



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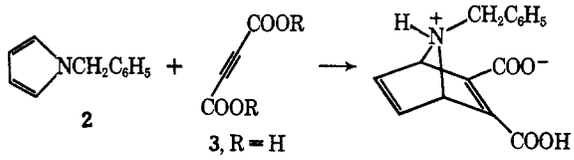
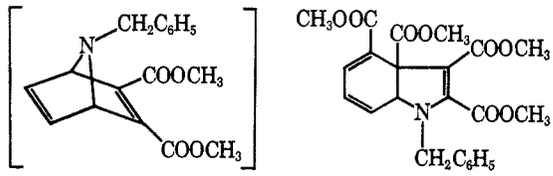
Diels–Alder adducts of pyrroles had been widely sought but were unknown[3] until Mandell and Blanchard[4] reported the synthesis, in about 9% yield, of 2,3-dicarboxy-7-benzyl-7-azabicyclo[2.2.1]hepta-2,5-diene (**4**) from N-benzylpyrrole (**2**) and acetylenedicarboxylic acid (**3**). Classically, the Michael-type addition products are isolated.[3,4] Using dienophile **5**, Acheson and Vernon[5] obtained 2,3,3a,4-tetracarbomethoxy-1-benzyl-3a,7a-dihydroindole (**7**) but no Diels–Alder adduct. It was proposed[5] that 2,3-dicarbomethoxy-7-benzyl-7-azabicyclo[2.2.1]hepta-2,5-diene (**6**), a Diels–Alder adduct, is a transient intermediate which adds a second mole of dienophile. The isolation of 2,3-dicarboxy-7-carbomethoxy-7-azabicyclo[2.2.1]hepta-2,5-diene (**8**), albeit in only 2.7% yield,[6] suggests that isolability of **4** is not necessarily the result of zwitterion[7] precipitation in the ether solution and augurs well for the intermediacy of **6**.[6]

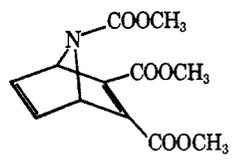
In these laboratories several modifications of these reactions were directed at improving the yield of adduct. Very slow addition (1–2 days) of **3** to **2** at high dilution afforded slightly lower yield of **4**. However, extending



2 **3**, R = H; **5**, R = CH_3 **4**



6 **7**



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the usual[3] reflux time to 6 days doubled the yield (18%). At lower temperatures, even after weeks, the yield was poor, and in a higher boiling solvent, diglyme, no Diels–Alder adduct was isolable. Using acetic or trifluoroacetic acid in ether, **2** and **5** failed to afford **6**, although with acetic acid **7** was obtained. Methyl iodide also failed to trap **6**. As the rate of addition of a second mole of **5** to **6** may be more rapid than quaternization, this is not taken as evidence against intermediacy of **6**. These results have suggested other modifications now in progress and have also led to obvious speculation on the behavior of 2- and 2,5-disubstituted pyrroles which are currently under investigation as Diels–Alder participants.

(1) (a) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p N060. (b) This investigation was supported by Research Grant NB-03593 from the Institute of Neurological Diseases and Blindness, U. S. Public Health Service.

(2) (a) Abstracted from the Ph.D. Thesis of A. S., Columbia University, 1968; recipient of an Iranian Government Scholarship, 1963–1967. (b) Author to whom inquiries should be addressed.

(3) M. C. Kloetzel in "Organic Reactions," R. Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p 38; A. Wasserman, "Diels-Alder Reactions," Elsevier Publishing Co., New York, N. Y., 1965, p 11.

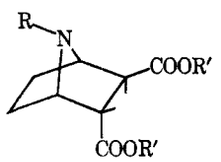
(4) (a) L. Mandell and W. A. Blanchard, *J. Amer. Chem. Soc.*, **79**, 2343 (1957); (b) L. Mandell and W. A. Blanchard, *ibid.*, **79**, 6198 (1957).

(5) R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1148 (1962).

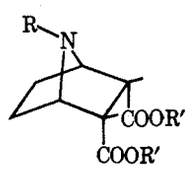
(6) R. M. Acheson and J. M. Vernon, *ibid.*, 1008 (1963).

(7) L. Mandell, J. U. Piper, and C. E. Pesterfield, *J. Org. Chem.*, **28**, 574 (1963).

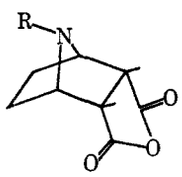
Although Mandell and Blanchard[4] reduced the adduct (**4**) and observed an uptake of 3 mol of hydrogen, the product (*cf.* **9**, **10**) was not isolated. When the reduction was carried out in these laboratories using aqueous sodium carbonate and palladium, the diastereoisomeric mixture of amino acids (**9**, **10**) could not be separated by fractional crystallization. Treatment with benzyl chloroformate (CBZ chloride) gave a mixture of CBZ diacids (**11**, **12**) which could not be efficiently separated to provide high yields of pure *cis* and *trans* isomers. However, treatment of the mixture with acetic anhydride afforded a pure cyclic (*cf.* **14**) anhydride assigned the structure of 7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane-2,3-di-*endo*-dicarboxylic acid anhydride (**13**) on the basis of the more probable mode of hydrogenation (*exo*) and the nmr spectrum which shows a two-hydrogen multiplet centered at 3.7 ppm for hydrogens at C-2 and C-3.



9, R = R′ = H
11, R = CBZ; R′ = H
14, R = CBZ; R′ = CH_3CO
20, R = Ts; R′ = H
33, R = CBZ; R′ = CH_3
34, R = Ts; R′ = CH_3



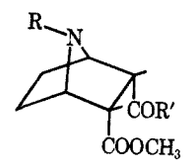
10, R = R′ = H
12, R = CBZ; R′ = H
21, R = Ts; R′ = H



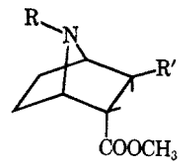
13, R = CBZ
22, R = Ts

If these hydrogens were di-*endo*, the angle between them and the bridgehead hydrogens would be close to 80°, and this would result in a coupling constant close to 0 Hz.[8] A singlet would result, since the hydrogens at C-2 and C-3 are chemically equivalent. Assignment of the *endo*-anhydride structure (**13**) is also corroborated by the nmr spectrum of 2,3-di-*endo*-dicarboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**12**) obtained by hydrolysis of **13**. The diacid exhibits a two-hydrogen, broad, poorly resolved multiplet centered at 3.3 ppm. The splitting into multiplets (**12**, **13**) arises because of coupling of the C-2 and C-3 hydrogens with the bridgehead and *exo* hydrogens at C-6 and C-5, respectively.[8]

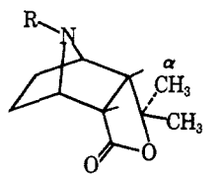
Methanolysis of the anhydride afforded the acid ester (**15**). Sequential treatment of **15** with thionyl chloride and dimethyl cadmium followed by decomposition of the reaction mixture with aqueous ammonium chloride and chromatography of the neutral product on acid-washed alumina afforded an oil assigned the keto ester structure, **16**. Decomposition of a second reaction mixture with 1*N* hydrochloric acid, followed by the same work-up, gave a solid, apparently



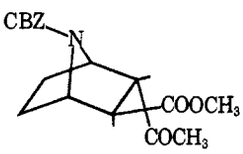
15, R = CBZ; R′ = OH
16, R = CBZ; R′ = CH_3
23, R = Ts; R′ = CH_3



17, R = CBZ; R′ = CH_3CO
19, R = CBZ; R′ = CH_3COO
24, R = Ts; R′ = CH_3CO
27, R = Ts; R′ = CH_3COO



25, R = CBZ
26, R = Ts



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epimeric keto ester assigned the structure of 2-*exo*-acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**17**) on the following bases.

First, if **16** and **17** are epimeric, it is more likely that the ketone function rather than the ester function would have epimerized in the 1*N* acid work-up.

Second, the nmr spectrum of the solid shows a one-hydrogen doublet centered at 2.98 ppm for the hydrogen at C-2 with $J_{2,3}$ = 5 Hz.[8] Decoupling shows that the hydrogen at C-2, now a singlet, is coupled only with the hydrogen at C-3. The latter appears as a broad multiplet centered at 3.59 ppm and is partly obscured by the three-hydrogen singlet of the methyl ester. As both hydrogens at C-2 and C-3 do not appear as multiplets or as doublets, this clearly rules out *cis* configurations for the solid obtained in the 1*N* acid work-up. This does not rule out the alternative stereochemistry (**18**). Obviously, **18** could arise from epimerization of the ester rather than the ketone. As this would afford a multiplet for the hydrogen at C-2 and a doublet for the hydrogen at C-3, it was necessary to unequivocally assign the chemical shifts. This was done by proceeding one step further along the preselected sequence to **1**. Baeyer–Villiger oxidation of **17** afforded a diester assigned the structure of 2-*exo*-acetoxy-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**19**) in which the hydrogen at C-2 appeared as a doublet centered at 5.05 ppm. The chemical shift establishes the relationship of this signal to the hydrogen at C-2. The splitting pattern establishes the fact that the hydrogen at C-2 is *endo*. As the Baeyer–Villiger oxidation is known to proceed with retention of configuration,[9] the solid precursor must have the *endo*-carbomethoxy-*exo*-acetyl stereochemistry as in **17**.

Third, that the oil assigned the structure **16** is epimeric to **17** was confirmed by the following sequence of reactions in which analogs of both solid epimeric keto esters could be obtained in pure form.

The crude mixture of reduced acids (**9**, **10**) was converted into a mixture of N-*p*-toluenesulfonyl (N = Ts) analogs (**20**, **21**) which was treated with acetic anhydride to give a cyclic anhydride assigned, by analogy, the structure **22**. Sequential treatment of this anhydride with methanol, thionyl chloride, and

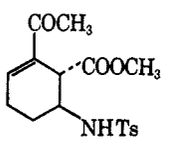
(8) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); (b) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); (c) K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal, and H. G. Welsh, *J. Amer. Chem. Soc.*, **89**, 2401 (1967).

(9) J. A. Berson and S. Suzuki, *ibid.*, **81**, 4088 (1959).

dimethylcadmium followed by decomposition of the reaction mixture with aqueous ammonium chloride afforded a crystalline product assigned the structure **23**. The nmr spectrum shows a two-hydrogen multiplet centered at 3.47 ppm for the hydrogens at C-2 and C-3. This is consistent with the di-*endo*-stereochemistry. Treatment of **23** with hydrobromic acid in acetic acid afforded a solid, epimeric keto ester assigned the structure **24**, 2-*exo*-acetyl-3-*endo*-carbomethoxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane. The nmr spectrum of **24** shows a one-hydrogen multiplet centered at 3.61 ppm for the *exo*-hydrogen at C-3 and a one-hydrogen doublet centered at 2.97 ppm for the *endo*-hydrogen at C-2. Finally, **16** and **17** were converted into **24**. After hydrogenolysis of **17**, the crude product was treated with *p*-toluenesulfonyl chloride in pyridine to afford **24**. The same sequence for **16** was followed by epimerization to give **24**.

In the reaction of dimethylcadmium with the acyl halide obtained from **15**, a liquid by-product was isolated and was assigned the structure of 2-*endo*-(1′-[1′-hydroxy-1′-methyl]ethyl)-3-*endo*-carboxy-7-carboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane γ-lactone (**25**) on the basis of its nmr and ir spectra. This was converted into the corresponding solid, sulfonamide analog (**26**) by hydrogenolysis and treatment of the crude amino lactone with *p*-toluenesulfonyl chloride. Incomplete reaction of the Grignard reagent with cadmium chloride undoubtedly led to the conversion of **16** into **25**. The nmr spectrum of **26** shows a one-hydrogen two-doublet pattern centered at 3.67 ppm for the *exo* hydrogen at C-3 and a one hydrogen two-doublet pattern centered at 3.02 ppm for the *exo* hydrogen at C-2. The assignments of $J_{1,2}$ = 4.0 Hz and $J_{3,4}$ = 7.0 Hz are consistent with angular deviations expected from relief of nonbonded interactions between the α-methyl and the ethylene bridge. Such relief is brought about by puckering of the five-membered ring to place the carbon bearing the two methyl groups above the plane of the other elements of the γ-lactone. This distortion enlarges the $H_1C_1C_2$–$H_2C_2C_1$ dihedral angle and decreases the $H_3C_3C_4$–$H_4C_4C_3$ dihedral angle. These data establish the di-*endo* stereochemistry for **26** since the di-*exo* isomer would exhibit doublets for both hydrogens at C-2 and C-3. This also confirms the stereochemical assignments for **22**–**24**.

The neutral fraction from the Baeyer–Villiger reaction afforded only 20% yield of **19** based on unrecovered (75%) starting material. The nmr spectrum of the neutral fraction obtained from **24** indicated a mixture of 30% **27** and 70% **24**. The latter oxidation appears more fruitful, but acid-catalyzed epimerization of **23** to give **24** also afforded about 70% *trans*-4-(*p*-toluenesulfonylamido)-3-carbomethoxy-2-acetylcyclohex-1-ene (**28**). Thus, use of the sulfonamide blocking group in reaction sequences leading to **1** have been abandoned. The ir spectrum of **28** exhibits a band at 1670 cm^{-1} (α,β-unsaturated ketone, C=O) which is shifted to 1714 cm^{-1} after reduction of **28** over palladium. The nmr spectrum of **28** shows no absorption for bridgehead hydrogens at 4–5 ppm but has a one-hydrogen triplet centered at 7.15 ppm (H—C=C—C=O) which disappeared after reduction of **28** over palladium.



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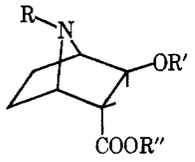
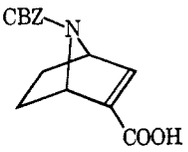


29, R = CBZ; R′ = R″ = H
31, R = CBZ; R′ = H; R″ = CH_3
32, R = CBZ; R′ = C_6H_5CO; R″ = CH_3



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Base hydrolysis of **19** afforded 2-*exo*-hydroxy-3-*endo*-carboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**29**) and 2-carboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]hept-2-ene (**30**). The ir spectra of **29** and **30** exhibit absorptions at 1725 (acid, C=O) and 1673 cm^{-1} (α,β-unsaturated acid, C=O), respectively. The nmr spectrum of **29** shows a one-hydrogen doublet centered at 4.21 ppm for the proton at C-2 with $J_{2,3}$ = 2.5 Hz and a one-hydrogen two-doublet pattern centered at 2.88 ppm with $J_{3,4}$ = 5 Hz for the hydrogen at C-3. In the nmr spectrum of **30** there is a one-hydrogen doublet centered at 7.15 ppm for the hydrogen at C-3 with $J_{3,4}$ = 2.5 Hz. Both the chemical shift and the splitting are similar for norbornene-2-carboxylic acid.[10]

Following esterification of **29** with diazomethane, the crude methyl ester (**31**) which exhibited a three-hydrogen singlet at 3.69 ppm ($COOCH_3$) was benzoylated to give 2-*exo*-benzoyloxy-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**32**). The nmr spectrum of **32** shows a one-hydrogen doublet centered at 5.32 ppm for the *endo* hydrogen at C-2 and a one-hydrogen multiplet centered at 3.31 ppm for the *exo* hydrogen at C-3. The benzylic hydrogen which appeared as a singlet in all spectra to this point now appear as two signals at 5.06 and 5.15 ppm. This may be due to the anisotropic effect of the phenyl group of the benzoate ester on these hydrogens. A similar effect has also been observed by Whitlock.[11] This also lends support to the *exo* assignment for the benzoate moiety. The nmr splitting pattern (d, m) observed for the hydrogens at C-2 and C-3 also confirms this stereochemical assignment. The diester (**32**) was hydrogenolyzed to give the amino diester which was not isolated but was immediately converted into the N-methyl analog, pseudo-4-norcocaine (**1**), by treatment with formalin followed by platinum oxide reduction. The product was an oil which was characterized as the hydrochloride salt. The nmr spectra of the oil and the salt clearly establish their structure and stereochemistry according to the considerations applied to earlier spectral data.

Attention was now drawn to studies on the mixed *trans* anhydride (**14**) as a potential precursor for **1**. Hydrolysis of **14** afforded an impure acid (**11**) which resisted all attempts at crystallization. Hydrogenolysis of **11** afforded a solid amino acid, 2,3-*trans*-dicarboxy-7-azabicyclo[2.2.1]heptane (**9**), from which pure, solid

(10) R. A. Finnegan and R. S. McNees, *J. Org. Chem.*, **29**, 3234(1964).
(11) H. W. Whitlockand G. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3600 (1967).

11 was obtained upon treatment with benzyl chloroformate. These and the dimethyl ester (33) obtained upon treatment of 11 with diazomethane, as well as the N-*p*-toluenesulfonyl analogs (20, 34) prepared from 9 all exhibit a doublet for the hydrogen at C-2 and a multiplet for the hydrogen at C-3 thus confirming these stereochemical assignments.

Experimental Section[12]

1-Benzylpyrrole (2).—This was prepared in 52% yield, bp 79–81° (0.7 mm), according to the method described by Josey, *et al.*,[13] bp 123–125° (12 mm).

2,3-Dicarboxy-7-benzyl-7-azabicyclo[2.2.1]hepta-2,5-diene (4).—A solution of 1-benzylpyrrole (1446 g, 9.20 mol), anhydrous acetylenedicarboxylic acid (1049 g, 9.20 mol), prepared from the monopotassium salt, and 5 l. of dry ether was allowed to reflux for 2 days. The precipitate was harvested, and the filtrate was allowed to reflux for 4 days. The process was continued until the filtrate failed to afford additional quantities of solid. The combined yellow solids were washed with hot acetone until the filtrate was colorless. The light yellow residue (4) weighed 462 g (18.5%): mp 210–212° (lit.[4b] mp 210–212°), and mp 212–214° after crystallization from water.

7-Carbobenzyloxy-7-azabicyclo[2.2.1]heptane-2,3-di-*endo*-dicarboxylic Acid Anhydride (13).—A solution of 39 g (144 mmol) of 4 in 200 ml of 10% aqueous sodium carbonate was reduced (3.0 g 10% Pd–C, 28°, 60 psig) until uptake of hydrogen had stopped (100 psig calculated, 96 psig absorbed). After removal of catalyst, the filtrate was treated with 30 g of solid sodium carbonate and 34.1 g (0.2 mol) of benzyl chloroformate and was stirred overnight. The excess benzyl chloroformate was removed by extraction with ether. The aqueous phase was acidified (HCl), and the oil which separated was extracted with ether. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from benzene to give 34 g of a mixture of diacids (9, 10) which was treated with 50 ml of acetic anhydride at 110° for 2 hr. The excess acetic anhydride and acetic acid were removed under reduced pressure, and the residue was crystallized from chloroform–ether to give 14.1 g (32.5%) of 13: mp 171–173°; ir ($HCCl_3$), 1710 (carbobenzyloxy, C=O), 1820, 1780 cm^{-1} (anhydride, C=O); nmr (CH_2Cl_2), δ 7.45 (s, 5, C_6H_5), 5.13 (s, 2, CH_2–Ph), 4.8–4.6 (m 2, bridgehead), 3.78–3.62 (m, 2, CH-*exo*-C=O-*endo*), 2.15–1.52 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.61; H, 4.83; N, 4.46.

The residual oil obtained from evaporation of the mother liquor contained the mixed anhydrides (*cf.* 14): ir ($HCCl_3$), 1825 cm^{-1} (anhydride, C=O).

2,3-*trans*-Dicarboxy-7-azabicyclo[2.2.1]heptane (9).—The residual oil (20 g) containing the mixed anhydrides obtained in the preceding experiment was dissolved in 100 ml of acetone and 20 ml of water. The solution was allowed to reflux for 3 hr and was evaporated to give an oil. This was dissolved in 100 ml of methanol and was hydrogenated (2.0 g 10% Pd–C, 28°, 50 psig) for 48 hr during which time crystals appeared in the reaction vessel. The solid was removed by filtration. After the solid was boiled in hot water, the mixturew as refiltered. The aqueous filtrate was evaporated, and the residue was crystallized from water–ethanol to afford 4.20 g (15.7% based on 4) of 9: mp 279–280°.

Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.99; N, 7.57. Found: C, 51.71; H, 5.93; N, 7.68.

The assignment of stereochemistry is based on the nmr spectra of the compounds described in the following experiments.

2,3-*trans*-Dicarboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (11).—To 3.70 g (20.0 mmol) of 9 was added 100 ml of 5% sodium carbonate solution and 4.3 g (25 mmol) of benzyl chloroformate. After stirring overnight, the excess benzyl chloroformate was removed by extraction with ether. The aqueous phase was acidified (HCl) and was extracted with ether. The ether was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from benzene–petroleum ether (bp 30–60°) to give 5.75 g (90%) of 11: mp 162–164°; nmr ($DCCl_3$), δ 7.38 (s, 5, C_6H_5), 5.1 (s, 2, CH_2–Ph), 4.82–4.55 (m, 2, bridgehead), 3.62 (broad t, 1, $J_{2,3} = J_{3,4} = 5$ Hz, CH-*exo*-C=O-*endo*), 3.08 (d, 1, CH-*endo*-C=O-*exo*), 1.97–1.58 ppm (m, 4, CH_2CH_2).

2,3-*trans*-Dicarbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1] heptane (33).—An ethereal solution of 495 mg (1.55 mmol) of 11 was treated with a slight excess of ethereal diazomethane. The excess diazomethane was decomposed with 1 drop of acetic acid. The ethereal solution was washed with aqueous sodium bicarbonate solution, dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ether–petroleum ether and afforded 485 mg (90%) of 33: mp 97–98°; nmr ($DCCl_3$), δ 7.38 (s, 5, C_6H_5), 5.1 (s, 2, CH_2–Ph), 4.78–4.55 (m, 2, bridgehead), 3.71 (s, 3, O-CH_3), 3.68 (s, 3, OCH_3), 3.60 (m, 1, CH-*exo*-COOMe-*endo*), 3.09 (d, 1, $J_{2,3} = 5$ Hz, CH-*endo*-COOMe-*exo*), 2.00–1.42 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.23; H, 6.10; N, 4.03. Found: C, 61.90; H, 6.27; N, 3.96.

2,3-Di-*endo*-dicarboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]-heptane (12).—A solution of 301 mg (1.0 mmol) of 13 in 5 ml of acetone and 2 ml of water was allowed to reflux for 3 hr. The solvent was removed, and the residue was crystallized from ether–petroleum ether to give 287 mg (90%) of 12: mp 151–153°; nmr (CD_3COCD_3), δ 7.38 (s, 5, C_6H_5), 5.16 (s, 2, CH_2–Ph), 4.58–4.34 (m, 2, bridgehead), 3.39–3.20 (broad t, 2, CH-*exo*-C=O-*endo*), 2.20–1.05 ppm (m, 4, CH_2CH_2).

2-*exo*-Acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (17).—A mixture of 135.5 g (0.45 mol) of 13 and 300 ml of methanol was allowed to reflux for 3 hr. Excess methanol was removed under reduced pressure. The resulting half-ester (15) [nmr ($DCCl_3$), δ 7.18 (s, 5, C_6H_5), 5.02 (s, 2, CH_2–Ph), 4.50–4.30 (broad m, 2, bridgehead), 3.54 (s, 3, $COOCH_3$), 3.25–3.10 (broad m, 2, CHCOOMe, CHCOO–), 2.20–1.40 ppm (m, 4, CH_2CH_2)] was converted into the acyl halide by treatment with 100 ml of thionyl chloride and 200 ml of benzene at 60° for 3 hr. The benzene and thionyl chloride were removed under reduced pressure to give the acid chloride: ir ($HCCl_3$), 1795 cm^{-1} (acyl halide, C=O); nmr ($DCCl_3$), δ 7.34 (s, 5, C_6H_5), 5.17 (s, 2, CH_2–Ph), 4.75–4.40 (m, 2, bridgehead), 3.71 (s, 3, $COOCH_3$), 3.70–3.10 (m, 2, CHCOOMe, CHCOCl) 2.30–1.20 ppm (m, 4, CH_2CH_2).

Dimethylcadmium reagent was prepared by slowly adding a solution of 190 g (2.0 mol) of methyl bromide in 800 ml of anhydrous ether to 42.5 g (1.75 g-atoms) of magnesium in 400 ml of anhydrous ether. After the Grignard reagent had formed, 157.6 g (0.86 mol) of anhydrous cadmium chloride was added with cooling. The mixture was allowed to stir for 2 hr at room temperature or until the Michler ketone test proved negative. The ether was evaporated, and the residue was resuspended in 1500 ml of dry benzene.

The dimethylcadmium reagent was cooled (10°), and the acid chloride in 250 ml of dry benzene was slowly added. After 2 hr of stirring at room temperature, the reaction mixture was cooled (10°) and was decomposed with 500 ml of 1 *N* acid (HCl). The organic layer was separated, and the aqueous layer was extracted with ether. The extract was washed with aqueous sodium bicarbonate and water and was finally dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on acid-washed alumina using 25% ether–petroleum ether as the eluent to give 103.6 g (69.5%) of 17: mp 78–79°; nmr (CCl_4), δ 7.22 (s, 5, C_6H_5), 4.95 (s, 2, CH_2–Ph), 4.60–4.40 (m, 2, bridgehead), 3.68 (s, 3, OCH_3), 3.59 (m, 1, CH-*exo*-COOMe-*endo*), 2.98 (d, 1, $J_{2,3} = 5$ Hz, CH-*endo*-COMe-*exo*), 2.18 (s, 3, $COCH_3$), 1.90–1.35 ppm (m, 4, CH_2CH_2),

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.35; H, 6.49; N, 4.48.

When saturated ammonium chloride solution was used for decomposition of the reaction mixture, the above work-up afforded an oil. On the basis of subsequent studies in the N-*p*-toluenesulfonamide series, this oil is believed to be the epimeric 2-*endo*-acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo-[2.2.1]heptane (16).

(12) All melting points were determined with a Thomas–Hoover Unimelt apparatus and are uncorrected. Samples were placed in the bath 10° below the reported melting point and heated at a rate of 2°/min. Elemental analyses were performed by Dr. Weiler and Dr. Strauss, Oxford, England, or by Schwartzkopf Analytical Laboratories, New York, N. Y. Infrared spectra were recorded on a Perkin-Elmer Model 421 double-gratin gspectrophotometer. Cited frequencies are believed accurate to within ±5 cm^{-1}. The nmr spectra were obtained using a Varian Model A-60A spectrometer. Unless otherwise designated, samples were run as 15% w/v solution with tetramethylsilane as an internal reference standard.

(13) A. D. Josey, R. J. Tuite, and H. R. Snyder, *J. Amer. Chem. Soc.*, **82**, 1597 (1960).

2-*endo*-[1′-(1′-Hydroxy-1′-methyl)ethyl]-3-*endo*-carboxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane γ-Lactone (26).—In an earlier attempt to prepare **17**, the Michler ketone test was not undertaken. Continued elution of the chromatographic column with ether–petroleum ether afforded 3 g of an impure oil: ir ($HCCl_3$), 1760 (γ-lactone, C=O), 1700 cm^{-1} (carbobenzyloxy, C=O); nmr ($DCCl_3$), δ 7.28 (s, 5, C_6H_5), 5.05 (s, 2, CH_2–Ph), 4.6–4.18 (m, 2, bridgehead), 3.8–2.0 (complex, 2, CH–C=O, CH–C–O), 1.92–1.72 (m, 4, CH_2CH_2), 1.47 (s, 3, C–CH_3), 1.28 ppm (s, 3, C–CH_3). The spectrum is indicative of the addition of residual methyl magnesium bromide to the ketone (**17**) to form a *t*-alkoxide which cyclized with the ester group to form the lactone (**25**). After hydrogenolysis (0.1 g 10% Pd–C, 29°, 1 atm, methanol, 48 hr) the catalyst was removed, and the filtrate was evaporated to give a residue which was dissolved in dilute aqueous acid (HCl). After extraction with ether, the aqueous was made basic (Na_2CO_3) and was reextracted with chloroform. The chloroformic extract was dried (Na_2SO_4), filtered, and evaporated to give a residue which was dissolved in 10 ml of pyridine and treated with 2.2 g of *p*-toluenesulfonyl chloride. The reaction mixture was stirred overnight, acidified (HCl), and extracted with ether. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ethanol to give 2.9 g of **26**: mp 145–147°; ir ($HCCl_3$), 1755 (γ-lactone, C=O), 1150 cm^{-1} (N–SO_2); nmr ($DCCl_3$), δ 7.98–7.25 (m, 4, C_6H_4), 4.51–4.27 (m, 2, bridgehead), 3.02 (2 d, 1, $J_{1,2}$ = 4.0 Hz, CH-*exo*-C–O-*endo*), 3.67 (2 d, 1, $J_{3,4}$ = 7.0 Hz, $J_{2,3}$ = 10 Hz, CH-*exo*-C=O-*endo*), 2.42 (s, 3, CH_3–Ph), 2.02–1.78 (m, 4, CH_2CH_2), 1.51 (s, 3, C–CH_3), 1.36 ppm (s, 3, C–CH_3).

Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18. Found: C, 60.59; H, 6.48; N, 4.26.

7-(*p*-Toluenesulfonyl)-7-azabicyclo[2.2.1]heptane-2,3-di-*endo*-dicarboxylic Acid Anhydride (22).—To 27.1 g (100 mmol) of **4** was added 150 ml of 10% sodium carbonate solution. Reduction (4.0 g, 10% Pd–C, 30°, 50 psig) was continued until uptake of hydrogen stopped. After removal of the catalyst, the filtrate was treated with 22.9 g (120 mmol) of *p*-toluenesulfonyl chloride and stirred overnight. The excess *p*-toluenesulfonyl chloride was extracted with ether. The aqueous layer was acidified (HCl) and extracted with ether. The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was treated with 30 ml of acetic anhydride at 110° for 2 hr. The excess acetic anhydride was removed under reduced pressure. The residue was crystallized from chloroform to give 10.93 g (34%) of **22**: mp 232–233°; ir (Nujol mull), 1860, 1780 cm^{-1} (anhydride, C=O).

Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.07; H, 4.71; N, 4.36. Found: C, 55.81; H, 4.48; N, 4.47.

2-*endo*-Acetyl-3-*endo*-carbomethoxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (23).—A mixture of 3.21 g (10 mmol) of **22** and 50 ml of methanol was allowed to reflux for 3 hr. The methanol was evaporated. The resulting half-ester [ir ($HCCl_3$), 1732 cm^{-1} (ester, C=O); nmr (CCl_4), δ 3.61 ppm (s, 3, COO-CH_3)] was converted into the acid chloride [ir ($HCCl_3$), 1790 cm^{-1} (acyl halide, C=O)] by treatment with 5 ml of thionyl chloride and 50 ml of dry benzene at 60° for 2 hr. The benzene and thionyl chloride were removed under reduced pressure.

The dimethylcadmium reagent was prepared by permitting 0.97 g (40 mg-atoms) of magnesium to react with 4.75 g (50 mmol) of methyl bromide in anhydrous ether followed by addition of 3.67 g (20 mmol) of anhydrous cadmium chloride at 5°. The mixture was stirred at room temperature for 2 hr. The ether was evaporated, and the solid was resuspended in 100 ml of dry benzene.

A solution of the acyl halide in dry benzene was added to the cooled dimethylcadmium reagent and stirred for 2 hr. The reaction mixture was decomposed at 0° with 100 ml of saturated ammonium chloride. The aqueous layer was extracted with ether. The extract was washed with aqueous sodium bicarbonate, dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ether–petroleum ether to give 1.41 g (40%) of **23**: mp 103–104°; nmr ($DCCl_3$), δ 7.94–7.20 (m, 4, C_6H_4), 4.52–4.21 (m, 2, bridgehead), 3.64 (s, 3, OCH_3), 3.60–3.47 (m, 2, CH-*exo*-COOMe-*endo*, CH-*exo*-COMe-*endo*), 2.43 (s, 3, CH_3–Ph), 2.11 (s, 3, CH_3—C=O), 1.91–1.58 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.95; H, 5.82; N, 4.32.

Isomerization of 2-*endo*-Acetyl-3-*endo*-carbomethoxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (23) to 2-*exo*-Acetyl-3-*endo*-carbomethoxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (24) and *trans*-4-(*p*-Toluenesulfonamido)-3-carbomethoxy-2-acetylcyclohex-1-ene (28).—To a solution of 300 mg (0.85 mmol) of **23** in 6 ml of acetic acid was added 0.6 ml of 48% hydrobromic acid. After 2 hr at room temperature, 15 ml of water was added. The solution was neutralized ($NaHCO_3$) and was extracted with chloroform. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from chloroform–ether to afford 197 mg (66%) of **28**: mp 177–178°; ir ($HCCl_3$), 1670 (α,β-unsaturated ketone, C=O), 1735 cm^{-1} (ester, C=O); nmr (CD_3COCD_3), δ 7.15 (t, 1, CH=C—COMe), 5.0–4.0 absent (bridgehead), 3.58 (s, 3, $COOCH_3$), 2.48 (s, 3, CH_3–Ph), 2.37 ppm (s, 3, $COCH_3$).

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 58.03; H, 5.90; N, 4.02.

Reduction of **28** (0.1 g 10% Pd–C, 22°, 1 atm, methanol) resulted in the uptake of about 1 equiv of hydrogen. After removal of catalyst and solvent, a crystalline solid was obtained. The broad melting range and the nmr spectrum are consistent with the expected mixture of diastereoisomers: ir (C_6H_6), 1714 (ketone, C=O), 1735 cm^{-1} (ester, C=O); nmr ($CDCl_3$), δ 7.15 absent (CH=C—C=O), 5.0–4.0 absent (bridgehead), 3.58 and 3.42 (s and s, 3, $COOCH_3$), 2.42 (s, 3, CH_3–Ph), 2.28 ppm (s, 3, $COCH_3$), with notable broadening of the latter two bands compared with those in **28**. The ir shift in the ketonic absorption supports an α,β-unsaturated ketone assignment for **28**. The geometry of the olefin (**28**) is inferred on the basis of the geometry existing in the azabicyclo precursor.

The chloroform–ether mother liquor from which **28** was obtained was evaporated. The residue was crystallized from ether–petroleum ether to afford 30 mg (10%) of **24**: mp 107–108°; nmr ($DCCl_3$), δ 7.98–7.22 (m, 4, C_6H_4), 4.62–4.32 (m, 2, bridgehead), 3.69 (s, 3, OCH_3), 3.68–3.5 (m, 1, CH-*exo*-COOMe-*endo*), 2.97 (d, 1, $J_{2,3}$ = 5 Hz, CH-*endo*-COMe-*exo*), 2.42 (s, 3, CH_3–Ph), 2.12 (s, 3, CH_3—C=O), 2.1–1.43 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{17}H_{21}NO_5S$: C, 58.10; H, 6.02; N, 3.99. Found: C, 57.77; H, 6.17; N, 4.01.

Conversion of 2-*exo*-Acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (17) and 2-*endo*-Acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxyl-7-azabicyclo[2.2.1]heptane (16) into 2-*exo*-acetyl-3-*endo*-carbomethoxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (24).—A solution of 7.0 g (21 mmol) of **17** was hydrogenated (0.2 g, 10% Pd–C, 20°, 50 psig, methanol, 48 hr). The catalyst was removed, and the filtrate was evaporated under reduced pressure. The residue was dissolved in water, acidified (HCl), and extracted with ether. The aqueous layer was made basic (Na_2CO_3) and was extracted three times with chloroform. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in 25 ml of pyridine, and 4.19 g (22 mmol) of *p*-toluenesulfonyl chloride was added. The mixture was stirred overnight, added to aqueous acid (HCl), and extracted with ether. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ether–petroleum ether and was recrystallized from ethanol to give 7.0 g (95%) of **24**: mp 107–108°.

In like manner, the oil assigned the structure **16** was converted into **24**. This was identical in all physical respects with that prepared from **17**. During the process the ketone function apparently epimerized from *endo* to *exo*.

Baeyer–Villiger Oxidation of 2-*exo*-Acetyl-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (17).—To a solution of 48.4 g (0.146 mol) of **17** in 700 ml of methylene chloride was added 284 g (2.0 mol) of anhydrous disodium hydrogen phosphate. Peroxytrifluoroacetic acid prepared from 19.83 ml (0.73 mol) of 90% hydrogen peroxide, 185.4 g (0.883 mol) of trifluoroacetic anhydride, and 200 ml of methylene chloride was slowly added to the ketone mixture with stirring and cooling in an ice bath. Stirring was continued at room temperature for 24 hr. The mixture was cooled in an ice bath, and 500 ml of cold water was added. The organic layer was separated, and the aqueous phase was extracted twice with more dichloromethane. The combined extract was washed twice with 15% aqueous sodium carbonate, once with 10% hydrochloric acid, and once with 10% aqueous sodium bisulfite. The combined organic extract was dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on Florasil using 5% ether–petroleum ether as the eluent. Two fractions were separated. The first fraction contained 7 g of an oil, 2-*exo*-acetoxy-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**19**): nmr ($DCCl_3$), δ 7.33 (s, 5, C_6H_5), 5.13 (s, 2, CH_2-Ph), 5.05

(d, 1, $J_{2,3}$ = 2.8 Hz, CH-*endo*-OCOMe-*exo*), 4.76–4.33 (m, 2, bridgehead), 3.71 (s, 3, OCH_3), 3.06 (2 d, 1, $J_{3,4}$ = 5 Hz, CH-*exo*-COOMe-*endo*), 1.90 (s, 3, $OCOCH_3$), 1.78–1.36 ppm (m, 4, CH_2CH_2). The second fraction contained 12 g (25%, 36.5 mmol) of starting material (**17**).

The oil (**19**) was dissolved in 20 ml of methanol and 5 ml of water containing 1 drop of phenolphthalein. The solution was allowed to reflux gently while a 4% aqueous sodium hydroxide was added at a rate sufficient to maintain the solution basic to the indicator. After completion of the hydrolysis, the solvents were removed under reduced pressure. The residue was dissolved in 35 ml of water. The solution was acidified (HCl) and extracted with ether. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ether–petroleum ether to give 2.3 g (7.9 mmol, 5.4%) of 2-*exo*-hydroxy-3-*endo*-carboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**29**): mp 137–139°; ir (KBr), 3445 (OH), 1725 (acid, C=O), 1675 cm^{-1} (carbobenzyloxy, C=O); nmr (CD_3COCD_3), δ 7.38 (s, 5, C_6H_5), 5.10 (s, 2, CH_2–Ph), 4.65–4.11 (m, 2, bridgehead), 4.21 (d, 1, $J_{2,3}$ = 2.5 Hz, CH-*endo*-O-*exo*), 2.99–2.77 (2 d, 1, $J_{3,4}$ = 5 Hz, CH-*exo*-C=O-*endo*), 2.18–1.4 ppm (m, 5, CH_2CH_2 and OH).

Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.84; H, 5.88; N, 4.81. Found: C, 61.96; H, 6.31; N, 4.92.

The ether–petroleum ether mother liquor, from which **29** was obtained, was evaporated, and the residue was crystallized from benzene–petroleum ether and was recrystallized from ether–petroleum ether to afford 1.2 g (2.9%, 4.1 mmol) of 2-carboxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]hept-2-ene (**30**): mp 116–117°; ir (KBr) 1708 (carbobenzyloxy, C=O), 1673 cm^{-1} (α,β-unsaturated acid, C=O); nmr ($DCCl_3$), δ 7.37 (s, 5, C_6H_5), 7.15 (d, 1, $J_{3,4}$ = 2.5 Hz, HC=C—C=O), 5.11 (s, 2, CH_2–Ph), 5.15–4.98 (m, 2, bridgehead), 2.15–1.10 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.94; H, 5.53; N, 5.13. Found: C, 65.80; H, 5.41; N, 5.15.

2-*exo*-Benzoyloxy-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (32).—To 1.25 g (4.3 mmol) of **29** in 200 ml of ether was added a slight excess of an ethereal solution of diazomethane. After 15 min the excess diazomethane was decomposed with a few drops of acetic acid. The ether was washed with aqueous sodium bicarbonate, dried (Na_2SO_4), filtered, and evaporated to give an oil, 2-*exo*-hydroxy-3-*endo*-carbomethoxy-7-carbobenzyloxy-7-azabicyclo[2.2.1]heptane (**31**): nmr ($DCCl_3$), δ 3.69 ppm (s, 3, $COOCH_3$). This crude oil was dissolved in 20 ml of pyridine and 0.62 g (4.4 mmol) of benzoyl chloride was added. The mixture was stirred at room temperature for 24 hr, cooled (0°), acidified (HCl), and extracted with ether. The extract was washed with sodium bicarbonate solution, dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ether–petroleum ether to give 1.23 g (70%) of **32**: mp 100–101°; nmr ($DCCl_3$), δ 8.12–7.37 (m, 5, C_6H_5—C=O), 7.23 (s, 5, C_6H_5), 5.32 (d, 1, $J_{2,3}$ = 2.6 Hz, CH-*endo*-OCOPh-*exo*), 5.15 and 5.06 (s and s, 2, CH_2–Ph), 4.88–4.50 (m, 2, bridgehead), 3.74 (s, 3, OCH_3), 3.4–3.17 (m, 1, CH-*exo*-COOMe-*endo*), 2.12–1.46 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{23}H_{23}NO_6$: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.25; H, 5.78; N, 3.58.

2-*exo*-Benzoyloxy-3-*endo*-carbomethoxy-7-methyl-7-azabicyclo[2.2.1]heptane Hydrochloride, Pseudo-4-norcocaine Hydrochloride (1 HCl).—Hydrogenolysis of 0.63 g (1.3 mmol) of **32** (0.1 g 10% Pd–C, 20°, 1 atm, methanol, 48 hr) was followed by removal of catalyst and evaporation of the filtrate. The residue was dissolved in 10 ml of water, made alkaline (Na_2CO_3), and extracted five times with 20 ml of chloroform. The combined extract was dried (Na_2SO_4), filtered, and evaporated. The residue was dissolved in 10 ml of methanol and 0.3 ml of formalin (37% aqueous formaldehyde) was added. The solution was stirred for 7 hr. The mixture was hydrogenated (0.1 g PtO_2, 20°, 1 atm, 24 hr), and the catalyst was removed. The filtrate was evaporated to give an oil (**1**): nmr ($DCCl_3$), δ 8.18–7.29 (m, 5, C_6H_5), 5.2 (d, 1, $J_{2,3}$ = 3 Hz, CH-*endo*-OCOPh-*exo*), 3.7 (s, 3, OCH_3), 3.67–3.15 (m, 3, bridgehead and CH-*exo*-COOMe-*endo*), 2.33 (s, 3, N–CH_3), 2.05–1.2 ppm (m, 4, CH_2CH_2). This oil was dissolved in anhydrous ether, and the solution was treated with dry hydrochloric acid. The precipitate was collected and was crystallized from acetone–ether to afford 0.26 g (62%) of **1** HCl: mp 169–171°; nmr (D_2O, TMS as external standard), δ 8.1–7.40 (m, 5, C_6H_5), 5.31 (d, 1, $J_{2,3}$ = 3 Hz, CH-*endo*-OCOPh-*exo*), 4.60–4.26 (m, 2, bridgehead), 3.77 (s, 3, OCH_3), 3.77–3.50 (m, 1, CH-*exo*-COOMe-*endo*), 3.10 and 2.87 (s, and s, 3, N–CH_3), 2.22–1.66 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{16}H_{20}NO_4Cl$: C, 58.98; H, 6.19; N, 4.27. Found: C, 58.71; H, 6.39; N, 4.59.

2,3-*trans*-Dicarboxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (20).—To a solution of 9.26 g (50 mmol) of **9** in 200 ml of 5% aqueous sodium hydroxide was added 13.9 g (73 mmol) of *p*-toluenesulfonyl chloride. After stirring overnight the excess *p*-toluenesulfonyl chloride was extracted with ether. The aqueous was acidified (HCl) and was extracted with ether. The extract was dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ethyl acetate–petroleum ether to afford 15.44 g (91%) of **20**: mp 225–226°; nmr (CD_3COCD_3–$CDCl_3$), δ 7.91–7.21 (m, 4, C_6H_4), 4.68–4.32 (m, 2, bridgehead), 3.74–3.50 (broad t, $J_{2,3}$ = $J_{3,4}$ = 5 Hz, CH-*exo*-COO-*endo*), 3.0 (d, 1, CH-*endo*-COO-*exo*), 2.42 (s, 3, CH_3–Ph), 2.25–1.65 ppm (m, 4, CH_2CH_2).

Anal. Calcd for $C_{15}H_{17}NO_6S$: C, 53.08; H, 5.05; N, 4.13. Found: C, 53.10; H, 5.27; N, 4.27.

2,3-*trans*-Dicarbomethoxy-7-(*p*-toluenesulfonyl)-7-azabicyclo[2.2.1]heptane (34).—To 13.57 g (40 mmol) of **20** in ether was added a slight excess of an ethereal solution of diazomethane. After 10 min the excess diazomethane was decomposed with acetic acid. The ether was washed with aqueous sodium bicarbonate, dried (Na_2SO_4), filtered, and evaporated. The residue was crystallized from ether–petroleum ether to give 13.5 g (92%) of **34**: mp 98–100°; nmr ($CDCl_3$), δ 7.81–7.16 (m, 4, C_6H_4), 4.59–4.39 (m, 2, bridgehead), 3.70 (s, 3, OCH_3), 3.61 (s, 3, OCH_3), 3.55 (m, 1, CH-*exo*-COOMe-*endo*), 3.0 (d, 1, $J_{2,3}$ = 5 Hz, CH-*endo*-COOMe-*exo*), 2.14 (s, 3, CH_3–Ph), 2.1–1.41 ppm (m, 4, CH_2CH_2).

Registry No.—**1**, 17037-61-5; **1** HCl, 17037-62-6; **9**, 17037-63-7; **11**, 17037-64-8; **12**, 17037-40-0; **13**, 17037-41-1; **15**, 17037-42-2; **15** acid chloride, 17037-58-0; **17**, 17037-43-3; **19**, 17037-44-4; **20**, 17037-45-5; **22**, 17037-46-6; **23**, 17037-47-7; **23** half-ester, 17037-59-1; **23** acid chloride, 17037-60-4; **24**, 17037-48-8; **25**, 17037-49-9; **26**, 17037-50-2; **28**, 17037-51-3; **29**, 17037-52-4; **30** 17037-53-5; **31**, 17037-54-1; **32**, 17037-55-7; **33**, 17037-56-8; **34**, 17037-57-9.