Table I

reagent	thiocyanate	solvent	temp, °C	sulfide	% yield
$CF_3(CF_2)_3MgI$	$C_6H_5CH_2SCN$	diethyl ether	−15	$C_6H_5CH_2S(CF_2)_3CF_3$	50
$CF_3(CF_2)_3Cu$	$C_6H_5CH_2SCN$	dimethyl sulfoxide	100	$C_6H_5CH_2S(CF_2)_3CF_3$	25
$(CF_3)_2CFK$	$C_6H_5CH_2SCN$	sulfolane	100	$C_6H_5CH_2SCF(CF_3)_2$	37
$(CF_3)_2CFK$	CH_3SCN	sulfolane	100	$CH_3SCF(CF_3)_2$	51
$(CF_3)_2CFK$	C_6H_5SCN	sulfolane	100	$C_6H_5SCF(CF_3)_2$	56
$(CF_3)_2CFK$	p-$NO_2C_6H_4SCN$	sulfolane	100	p-$NO_2C_6H_4SCF(CF_3)_2$	57
$CF_3(CF_2)_3MgI$	p-ClC_6H_4SCN	diethyl ether	−15	p-$ClC_6H_4S(CF_2)_3CF_3$	45
CF_3CFClK	$C_6H_5CH_2SCN$	sulfolane	100	$C_6H_5CH_2SCFClCF_3$	50

a mixture of 7.3 g (100 mmol) of methyl thiocyanate, 15 g (100 mmol) of perfluoropropene, 12 g of potassium fluoride, 1 g of cesium fluoride, and 100 mL of sulfolane. Because of the low boiling point of methyl perfluoroisopropyl sulfide, bp 53–55 °C, the contents of the autoclave were distilled directly to afford 11.2 g of the sulfide (51.8 mmol): yield 51%; ^{19}F NMR ϕ 70.5 (CF_3, d), 155 (CF, sept, $^3J_{FF}$ = 4.5 Hz); ^1H NMR δ 2.5.

Reaction of Perfluoropropene with Potassium Fluoride and Phenyl Thiocyanate. The phenyl thiocyanate was prepared from diphenyl disulfide according to the method described by Harpp et al.[10] Starting from 13.5 g of the cyanate (100 mmol), 15 g of perfluoropropene (100 mmol), 12 g of potassium fluoride, 1 g of cesium fluoride, and 75 mL of sulfolane, 15.6 g of phenyl perfluoroisopropyl sulfide was isolated (56 mmol): yield 56%; m/e 278 (M^+); bp 67–69 °C (20 mm); ^{19}F NMR ϕ 73 (CF_3, d), 155.5 (CF, sept, $^3J_{FF}$ = 7.5 Hz); ^1H NMR δ 7.15 (m). Anal. Calcd for $C_9H_5F_7S$: C, 38.86; H, 1.81; F, 47.81. Found: C, 38.79; H, 1.83; F, 46.35.

Reaction of Perfluoropropene with Potassium Fluoride and *p*-Nitrophenyl Thiocyanate. Starting from 3.4 g (18.8 mmol) of p-nitrophenyl thiocyanate,[10] 5 g of perfluoropropene, 2 g of potassium fluoride, 0.2 g of cesium fluoride, and 20 mL of sulfolane, 3.5 g (10.8 mmol) of p-nitrophenyl perfluoroisopropyl sulfide was isolated: yield 57%; bp 120 °C (3 mm); m/e 323–325 (M^+); ^{19}F NMR ϕ 72.5 (CF_3), 150 (CF); ^1H NMR δ 7.9 (CH, d, $^3J_{HH}$ = 8 Hz), 8.25 (CH, d). Anal. Calcd for $C_9H_4F_7NO_2S$: C, 33.43; H, 1.23; F, 41.17. Found: C, 33.36; H, 1.23; F, 41.69.

Reaction of Perfluorobutylmagnesium Bromide with *p*-Chlorophenyl Thiocyanate. The Grignard reagent was prepared from 5.4 g (50 mmol) of ethyl bromide, 1.4 g of Mg, 50 mL of diethyl ether, and 13.8 g (40 mmol) of perfluorobutyl iodide. To this solution kept at −15 °C was added a solution of 6.5 g (40 mmol) of p-chlorophenyl thiocyanate[10] in 20 mL of diethyl ether. Hydrolysis was carried out with dilute hydrochloric acid at 0 °C. After workup as above, 6.7 g (18 mmol) of p-chlorophenyl perfluorobutyl sulfide was isolated: yield 45%; bp 70–75 °C (1 mm); m/e 376–378 (M^+); ^{19}F NMR ϕ 82.9 (CF_3), 89 (CF_2S), 122 and 127.4 (CF_2CF_2); ^1H NMR δ 7.41 and 7.58 ($^3J_{HH}$ = 9 Hz). Anal. Calcd for $C_{10}H_4ClF_9S$: C, 35.08; H, 1.60; F, 45.40. Found: C, 34.92; H, 1.62; F, 45.10.

Reaction of Chlorotrifluoroethylene with Potassium Fluoride and Benzyl Thiocyanate. Starting from 12 g (100 mmol) of chlorotrifluoroethylene, 15 g (100 mmol) of benzyl thiocyanate, 12 g of potassium fluoride, 1 g of cesium fluoride, and 75 mL of tetramethylenesulfone, 13 g (50 mmol) of benzyl 1-chloro tetrafluoroethyl sulfide was isolated: bp 75–80 °C (1 mm); Yield 50%; m/e 258–260 (M^+); ^{19}F NMR ϕ 76.3 (CF_3, d), 95 (CF, 9, $^3J_{FF}$ = 8 Hz); ^1H NMR δ 7.15 (phenyl, s), 4.1 (CH_2, s). Anal. Calcd for $C_9H_7ClF_4S$: C, 41.77; H, 2.7; F, 29.4. Found: C, 41.87; H, 2.76; F, 29.41.

Chlorinolysis of Benzyl Perfluoroisopropyl Sulfide. Benzyl perfluoroisopropyl sulfide (4.5 g, 15.4 mmol) was dissolved in 10 mL of tetrachloroethane. Chlorine was bubbled into this solution until the formation of a persistent yellow color over it. The evolved gas was led to a condenser surrounded by a mixture of dry ice and carbon tetrachloride where part of the perfluoroisopropylsulfenyl chloride was trapped. The remaining chloride was distilled from the reaction mixture under a nitrogen atmosphere: yield 2.7 g (11.4 mmol, 77%); bp 52 °C; mass spectrum, m/e 236–238 (M^+), 217–219 ($(M - F)^+$), 201 ($(M - Cl)^+$), 167–169 ($(M - CF_3)^+$); ^{19}F NMR ϕ 78.3 (CF_3, d), 163 (CF, sept, $^3J_{FF}$ = 6 Hz). Benzyl chloride was separated from the residue and identified by comparison with an authentic sample.

Chlorinolysis of Benzyl 1-Chlorotetrafluoroethyl Sulfide. The sulfide 5.2 g (20 mmol) was dissolved in 10 mL of tetrachloroethane. Chlorine was bubbled into this solution. After 0.5 h, the solution was distilled under reduced pressure, and the fraction boiling in the range 30–50 °C (15 mm) was collected. It contained (1-chlorotetrafluoroethyl)sulfenyl chloride and a small amount of tetrachloroethane (insoluble). The sulfenyl chloride was separated and purified by redistillation: 1.6 g (39%); bp 95–97 °C; ^{19}F NMR ϕ 90.6 (CF_3, d), 124.3 (CFCl, q, $^3J_{FF}$ = 9 Hz). Anal. Calcd for $C_2Cl_2F_4S$: C, 11.82. Found: C, 12.12.

Registry No. 4 (R = $CH_2C_6H_5$), 3012-37-1; 4 (R = CH_3), 556-64-9; 4 (R = C_6H_5), 5285-87-0; 4 (R = p-$NO_2C_6H_4$), 2137-92-0; 4 (R = p-ClC_6H_4), 3226-37-7; 5 (R = $CH_2C_6H_5$; R_F = $(CF_2)_3CF_3$), 76665-91-3; 5 (R = $CH_2C_6H_5$; R_F = $CF(CF_3)_2$), 68409-03-0; 5 (R= CH_3; R_F = $CF(CF_3)_2$), 34968-41-7; 5 (R = C_6H_5; R_F = $CF(CF_3)_2$), 65799-63-5; 5 (R = p-$NO_2C_6H_4$; R_F = $CF(CF_3)_2$), 76665-92-4; 5 (R = p-ClC_6H_4; R_F = $(CF_2)_3CF_3$), 76665-93-5; 5 (R = $CH_2C_6H_5$; R_F = $CFClCF_3$), 76684-17-8; 8 (R_F = $CF(CF_3)_2$, 51031-50-6; 8 (R_F = $CFClCF_3$), 57160-01-7; perfluorobutyl iodide, 423-39-2; perfluoropropene, 116-15-4; chlorotrifluoroethylene, 79-38-9.

(10) Harpp, D. N.; Friedlander, B. T.; Smith, R. A. *Synthesis* **1979**, 181.

(11) Reaction of organic thiocyanates with carbanions generated from chloroform in aqueous medium leads to trichloromethyl sulfides. Makosza, M.; Fedorynski, M. *Synthesis* **1974**, 274.

Cycloaddition Reactions of Indenes. 4. 1:2 Adducts from 1-(1*H*-Inden-2- and -3-yl)pyrrolidines with Dimethyl Acetylenedicarboxylate[1]

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Discussion

1-(1*H*-Inden-3-yl)pyrrolidine[3] (**1a**) in 1:2 molar ratio reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing benzene to give a 1:2 adduct (**4**, 25%; Scheme I) as a white crystalline solid. The product is different in type from the previously described[1b] 1:2 adducts (**7** formed via intermediate 1:1 adducts (**6**) from 3-substituted indenes (**5**, Scheme II). Its NMR spectrum (in $CDCl_3$) shows four aromatic protons and no vinyl protons. In addition, there are a methylene doublet at δ 2.98 and a methine triplet at δ 4.33 which appear to be coupled (J = 3.5 Hz). No other aliphatic protons are present except those in the

(1) (a) Paper 1: Noland, W. E.; Landucci, L. L.; Kameswaran, V. *J. Org. Chem.* **1980**, *45*, 3456–3461. (b) Paper 2: Noland, W. E.; Kameswaran, V.; Landucci, L. L. *Ibid.* **1980**, *45*, 4564–4572. (c) Paper 3: Noland, W. E.; Kameswaran, V. *Ibid.* **1981**, *46*, 1318.

(2) Taken in part from the Ph.D. thesis of Venkataraman Kameswaran, University of Minnesota, Minneapolis, MN, June 1971; *Diss. Abstr. B.* **1972**, *32*, 6918–6919.

(3) Bergmann, E. D.; Hoffmann, E. *J. Org. Chem.* **1961**, *26*, 3555–3556.

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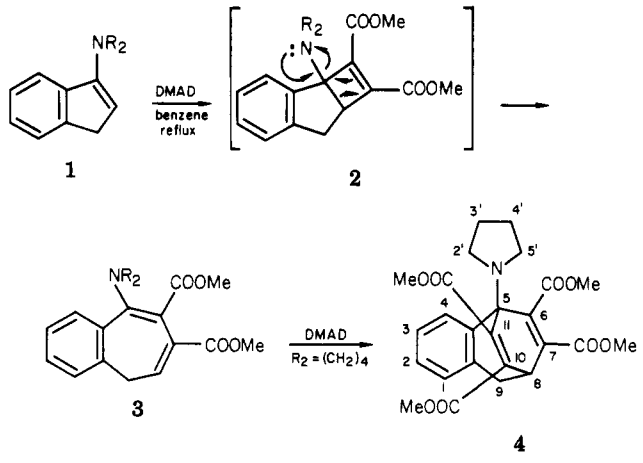
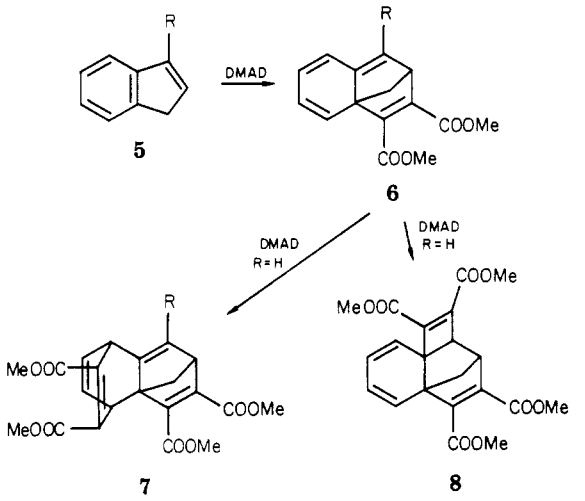
Scheme I

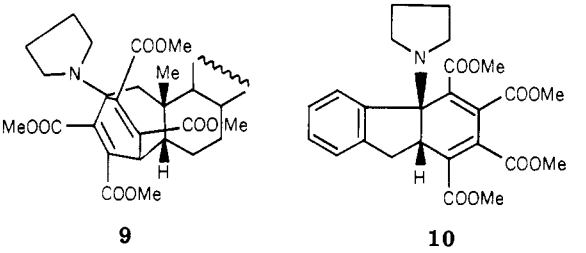


a, $R_2 = (CH_2)_4$; b, $R_2 = (CH_3)_2$

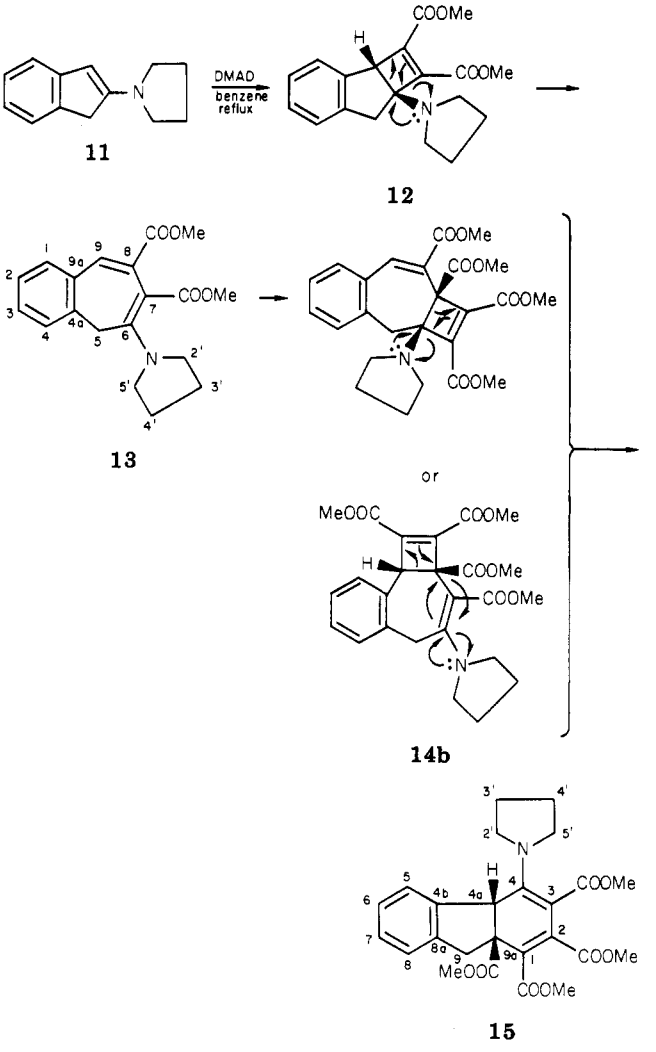
Scheme II



Scheme III



Scheme IV



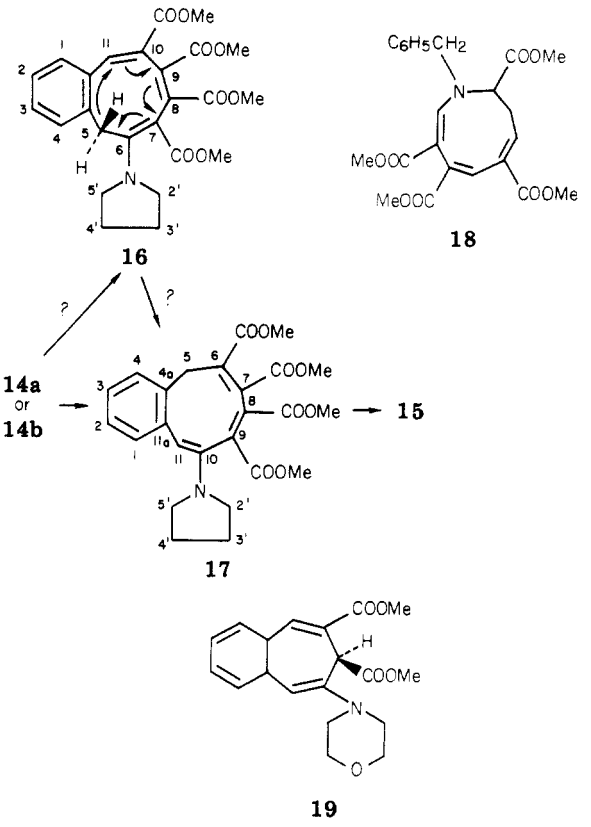
pyrrolidine ring multiplets and the 12 ester methyl protons, which appear as two singlets, at δ 3.67 and 3.75, indicating a symmetrical structure. The UV spectrum (in 95% C_2H_5OH) contains only rising end absorption with a diffuse shoulder at 240 nm (log ϵ 3.89), indicating that the pyrrolidine nitrogen is not conjugated with the ester groups and is, therefore, probably at a bridgehead. The ^{13}C NMR spectrum of the 1:2 adduct (see Experimental Section) contains 17 peaks of relative intensity ≥10% and includes at least eight pairs of superimposed peaks which account for 16 carbons. The four pyrrolidine methylene carbons (α and β) appear as a pair of triplets, the four ester methyl carbons appear as a pair of quartets, and the four vinyl and four carbonyl carbons appear as two pairs of singlets. These observations appear consistent with the symmetrical structure 4, which would be formed from 1 by a [$_\pi$2 + $_\pi$2] cycloaddition to form a 1:1 cyclobutene adduct (**2a**). Thermal ring enlargement of **2a** would then give a benzocycloheptatriene (benzotropilidene) intermediate (**3a**) containing a 1,3-diene system which could then undergo a Diels–Alder [$_\pi$4 + $_\pi$2] cycloaddition to give the 1:2 adduct **4**. Good analogy for the postulated formation of **2a** and **3a** lies in the work of Berchtold and Uhlig,[4] Brannock and co-workers,[5] and Doyle,[6] who reported that enamines of cyclic ketones react with DMAD to form intermediate cyclobutene adducts which rearrange under the conditions of the reaction (refluxing toluene,[4] benzene,[6] or at lower temperatures[5]) with expansion of the carbocyclic ring by two carbon atoms. Doyle[6] has applied this reaction to *N,N*-dimethyl-1*H*-inden-3-amine (**1b**) with DMAD in benzene at room temperature, which gave the cyclobutene adduct (**2b**) in quantitative yield. Ring enlargement of **2b** in refluxing benzene gave the corresponding benzocycloheptatriene (**3b**) in 90% yield.[6] A Diels-Alder structure similar to **4** has been proposed[7] for the 1:2 adduct (**9**, Scheme III) from the Δ^2-pyrrolidine enamine of coprostan-3-one and DMAD, based on the observation of no olefinic protons and an "unsplit proton" at δ 3.98 in the NMR spectrum, though the number of ester methyl peaks

(4) Berchtold, G. A.; Uhlig, G. F. *J. Org. Chem.* **1963**, *28*, 1459–1462.
(5) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1464–1468.
(6) Doyle, T. W. *Can. J. Chem.* **1970**, *48*, 1633–1638.
(7) Bose, A. K.; Mina, G.; Manhas, M. S.; Rzucidlo, E. *Tetrahedron Lett.* **1963**, 1467–1471.

was not reported. An unsymmetrical structure (**10**) could be derived for the 1:2 adduct from **1a** and DMAD (and, correspondingly, for **9**), but it appears to be ruled out by the symmetry of the NMR spectra and limited conjugation in the UV spectrum of **4**.

The corresponding reaction of 1-(1*H*-inden-2-yl)-pyrrolidine[8] (**11**) in 1:2 molar ratio with DMAD in refluxing benzene also gave a 1:2 adduct (**15**, 45%; Scheme IV) as a yellow crystalline solid quite different in type from **4** and also different in type from the previously described[1b] 1:2 adducts (**8**) formed via intermediate 1:1 adducts (**6**) from 3-unsubstituted 1*H*-indenes. The same 1:2 adduct (**15**) was also obtained, in 69% yield, from the reaction of the 1:1 adduct **13**[4] (similar in structure to **3**) with DMAD in a 1:1 molar ratio in refluxing benzene. The second addition of DMAD to **13**, however, is different from the second [$_\pi4$ + $_\pi2$] cycloaddition to **3**. Following the analogy for [$_\pi2$ + $_\pi2$] cycloadditions of enamines,[4-6] three possible structures, **15**, **16**, or **17**, were considered for the 1:2 adduct. The IR spectrum shows a strong band at 1535 cm^{-1} and the UV spectra (as well as the yellow color of the adduct) show a high degree of conjugation, with the longest wavelength band at 391 nm (see Experimental Section). By comparison, the 1:1 adduct **13**[4] also has a strong band in the IR at 1530 cm^{-1} and a somewhat less but still strongly conjugated UV spectrum (362 nm), and the 1:1 adduct **3b**[6] has a band in the IR at 1580 cm^{-1} and a UV spectrum (349) nm) still showing considerable conjugation. This indicates that the pyrrolidine nitrogen of the adduct cannot be at a bridgehead, as in **4**, but must be part of a long conjugated system and could be compatible with the three structures. While both **16** and **17** appear highly conjugated, Dreiding models show that the triene system in both structures would not be coplanar and that the central double bond is twisted way out of plane. For example, the conjugated azacyclononatriene system, tetramethyl 1-benzyl-2,3-dihydro-1*H*-azonine-2,5,7,8-tetracarboxylate (**18**), another ring enlargement product of DMAD in which the enamine nitrogen is part of the ring system, has a UV spectrum consisting only of a band at 274 nm (log ϵ 4.13).[9] Thus, no significant conjugation of the enamine with the benzene ring would be expected in **16**, while **17** might be stabilized by direct conjugation of the enamine with the benzene ring, as is observed at 375 nm in the 1:1 adduct[4] (**19**) from 1-(1*H*-inden-2-yl)morpholine and DMAD (Scheme V). Structure **15** has an almost planar 1,3-cyclohexadiene system in conjugation with the enamine and could be compatible with the UV spectrum observed. The ^{1}H NMR spectrum (in $CDCl_3$) of the 1:2 adduct shows four aromatic protons and four separate ester methyl singlets, indicative of an unsymmetrical structure. Also, it has a one-proton singlet at δ 4.45 which, if it is a vinyl and not a methine proton, would have to be of the high-field type found on the β-carbon of enamines, expected to appear at δ 4–5.[10] This contrasts with the position of the one-proton singlet at δ 7.58 in **13**,[4] a model compound for **16**. Thus, structure **16** is ruled out. There are two additional aliphatic protons, assumed to be methylene, besides the eight from the pyrrolidine, included in the downfield aliphatic (α-pyrrolidine) multiplet at δ 2.90–4.13. The ^{13}C NMR

Scheme V



spectrum of the 1:2 adduct, unlike **4**, clearly shows an unsymmetrical structure. Furthermore, it shows four vinyl carbons, two less than would be expected for either structure **16** or **17**. Other significant features include the fact that the methine carbon (the 4a-CH of **15**) is present in the aliphatic region at δ 47.3 as a doublet of doublets with $^1J_{CH}$ = 135.5 and $^3J_{C_{4a}H_5}$ = 4.0 Hz, and the aliphatic quaternary carbon (the 9a-C of **15**) is present at δ 54.8 as a doublet of triplets with $^2J_{C_{9a}H_{4a}}$ = 5.0 and $^2J_{C_{9a}H_9}$ = 2.3 Hz. A quaternary C_3-carbon doublet ($^3J_{C_3H}$ = 2.7 Hz) at δ 96.8 (relative intensity 7%) is clearly indicative of a β-vinyl carbon of an enamine and is also observed in the ^{13}C NMR spectrum of **13**, which has a peak at δ 97.3 (34%) assigned to the C-7 vinyl carbon. All the signals in the ^{13}C NMR spectrum of the 1:2 adduct can plausibly be assigned to carbons in structure **15** (see Experimental Section).

The 1:1 adduct **13** has been reported previously by Berchtold and Uhlig[4] as the end product, in 78% yield, of the reaction of **11** and DMAD in a 1:1 molar ratio in refluxing toluene. This shows that the first addition is faster than the second. In our case, with a 1:2 molar ratio of the reactants in refluxing benzene, the 1:1 adduct **13** appears to be an intermediate, as shown in Scheme IV, since both **11** (45%) and **13** (69%) give the same 1:2 adduct **15**. The failure of **13** to undergo [$_\pi4$ + $_\pi2$] cycloaddition across its 1,3-diene system, as did **3** (going to **4**), is possibly due to better conjugation in **13** than in **3**. The potential for either [$_\pi4$ + $_\pi2$] (CCl_4, 100 °C) or [$_\pi2$ + $_\pi2$] cycloaddition and ring enlargement (CH_3CN, 25 °C) or Michael addition (CH_3OH, 25 °C) by DMAD to an endocyclic enamine in a 2,3-dihydro-1*H*-azepine system has been shown by Eberbach and Carré[9] to depend on the polarity of the solvent used. The second addition to **13** could proceed by [$_\pi2$ + $_\pi2$] cycloaddition of DMAD either to the enamine double bond (giving **14a**) or to its less sterically hindered vinylogous extension (giving **14b**). A 1,5-hydrogen shift suprafacial on the [$_\sigma2_s$ + $_\sigma2_s$ + $_\pi2_s$] system of **14a** (or on the [$_\sigma2_s$ + $_\pi2_s$

(8) (a) Blomquist, A. T.; Moriconi, E. J. *J. Org. Chem.* **1961**, *26*, 3761–3769. (b) Schroth, W.; Fischer, G. W. *Chem. Ber.* **1969**, *102*, 575–589. (c) Edlund, U. *Acta Chem. Scand.* **1972**, *26*, 2972.

(9) Eberbach, W.; Carré, J. C. *Tetrahedron Lett.* **1980**, *21*, 1145–1148.

(10) (a) Gurowitz, W. D.; Joseph, M. A. *J. Org. Chem.* **1967**, *32*, 3289–3292. (b) Malhotra, S. K. In "Enamines: Synthesis, Structure, and Reactions"; Cook, A. G., Ed.; Marcel Dekker: New York, 1969; pp 46–47. (c) Dyke, S. F. "The Chemistry of Enamines"; Cambridge University Press: London, England, 1973; p 11.

+ $_{\sigma}2_{s}$] system of **14b**) could give **17**[11] by a sterically and energetically favorable ring-expansion reaction, which can also be considered as a modified ene reaction. This reaction would be mechanistically different from the ring expansion postulated during the formation of 1:1 adducts from enamines and DMAD. Thermally allowed transannular [$_{\pi}6_{s}$] electrocyclic ring closure of **17** could then give the thermodynamically more stable 9,9a-dihydro-4a*H*-fluorene **15**, which could release whatever additional energy is necessary to make the overall reaction go.

Experimental Section

Melting points were determined on a calibrated Mel-Temp melting-point apparatus. Ultraviolet spectra (UV) were determined on a Beckman DK-2A, Bausch and Lomb 505, or Varian Associates Cary 17D spectrophotometer. Infrared spectra (IR) were determined on a Perkin-Elmer Model 257 or Unicam SP-200 spectrophotometer. Nuclear magnetic resonance spectra (NMR) were determined, using tetramethylsilane as an internal standard, on Varian Associates spectrometers, using for ^{1}H a Model T-60 at the University of Minnesota and for ^{13}C Model CFT-20 or FT-80A at the American Cyanamid Company, Agricultural Research Division, Princeton, NJ. Low-resolution electron-impact mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6D spectrometer by Mr. Adrian S. Swanson and his associates. Elemental microanalyses were performed by Henry V. Isaacson under the supervision of Professor C. F. Koelsch at the University of Minnesota.

1-(1*H*-Inden-3-yl)pyrrolidine (1a) was prepared from the condensation of 2,3-dihydro-1*H*-inden-1-one and pyrrolidine as described by Bergmann and Hoffmann[3] in 48% yield as a pale yellow liquid: bp 140 °C (2 mm) [lit.[3] 35%; bp 142–144 °C (2 mm)]; NMR (CCl_4) δ 1.45–2.02 (m, 3.6 H, 3-, 4-CH_2), 2.02–3.02 (cm, 1.0 H, 1′-CH_2) overlapping 3.01–3.51 (m, 5.4 H, 2-, 5-CH_2), 4.88 (t, $J_{2',1'}$ = 2 Hz, 0.8 H, 2′-H), 6.82–7.35 (m, 3.1 H, 5′-, 6′-, 7′-H), 7.35-7.75 (m, 1.1 H, 4′-H). As has been noted,[3] the product is very unstable and was used immediately.

Reaction of 1-(1*H*-Inden-3-yl)pyrrolidine (1a) with DMAD. Tetramethyl 8,9-Dihydro-5-(1-pyrrolidinyl)-5,8-etheno-5*H*-benzocycloheptadiene-6,7,10,11-tetracarboxylate (4). A solution of **1a** (0.925 g, 4.99 mmol) and DMAD (1.42 g, 9.99 mmol) in benzene (10 mL) was stirred at room temperature for 0.5 h and then refluxed for 4 h. The benzene was removed in a rotating evaporator. The residual dark brown oil was dissolved in methanol (5 mL) and the solution allowed to evaporate slowly, causing separation of a pale yellow solid (0.60 g, 25%), mp 164-167 °C. Crystallization from methanol gave white crystals: mp 167 °C; UV (95% C_2H_5OH) rising end absorption, λ (log ϵ) 240 nm (diffuse sh, 3.89); IR (Nujol) 1738 (s), 1730 (s) (C=O), 1661 (mw), 1633 (m) (C=C) cm^{-1}; NMR (13% w/v in $CDCl_3$) δ 1.60–1.93 (m, 4.0 H, 3′-, 4′-CH_2), 2.98 (d, $J_{9,8}$ = 3.5 Hz, 1.8 H, 9-CH_2), 3.23–3.47 (m, 4.2 H, 2′-, 5′-CH_2), 3.67 (s, 5.8 H, 7-, 10-$COOCH_3$), 3.75 (s, 6.4 H, 6-, 11-$COOCH_3$), 4.33 (t, $J_{8,9}$ = 3.5 Hz, 0.9 H, 8-H), 6.77–7.40 (m, 3.1 H, 1-, 2-, 3-H), 7.70–7.93 (m, 0.8 H, 4-H); ^{13}C NMR ($CDCl_3$, CFT-20, 20 MHz, proton decoupled, multiplicities obtained from off-resonance decoupled spectrum) δ (relative peak heights, multiplicity) 25.4 (74, t, pyrrolidine 3′- and 4′-CH_2), 31.4 (33, t, 9-CH_2), 34.0 (40, d, 8-CH), 49.3 (70, t, pyrrolidine 2′- and 5′-CH_2), 51.7 (11, noise?), 52.1 (98, q, 7- and 10-$COOCH_3$), 52.4 (100, q, 6- and 11-$COOCH_3$), 70.4 (23, s, 5-C), 75.75, 77.34, 78.97 (t, 16, 13, 17, $CDCl_3$), 125.1 (38), 127.8 (51), 127.9 (48), 132.4 (45) (Ar CH, probably 1, 2, 3, 4), 129.9 (74), 133.3 (49) (Ar C, probably 9a, 4a), 138.0 (36, 7- and 10-C), 151.2 (56, 6- and 11-C), 164.0 (47, 7- and 10-$COOCH_3$), 167.3 (61, 6- and 11-$COOCH_3$); mass spectrum (50 eV, 300 °C; relative intensity >17, M* indicates ^{13}C peak), *m/e* 469 (34, M), 438 (22, M - OCH_3), 411 (30, M - $COOCH_2$ or M* - $COOCH_3$), 410 (100, M - $COOCH_3$), 378 (44, M - $HCOOCH_3$ - OCH_3), 366 (22, M - CH_3OH - C_4H_9N), 350 (22, M - $COOCH_3$ - $HCOOCH_3$), 309 (22, M - $COOCH_3$ - OCH_3 - C_4H_8N), 70 (28, C_4H_8N).

Anal. Calcd for $C_{25}H_{27}NO_8$ (mol wt 469.50): C, 63.96; H, 5.80; N, 2.99. Found: C, 64.04; H, 5.94; N, 2.94.

1-(1*H*-Inden-2-yl)pyrrolidine (11) was prepared from the condensation of 2,3-dihydro-1*H*-inden-2-one[12] (0.99 g, 7.49 mmol) and pyrrolidine (2.14 g, 30.1 mmol) as described by Blomquist and Moriconi.[8a] The benzene and excess pyrrolidine were removed by distillation at atmospheric pressure and the dark residue was used directly in the next step.

^{13}C NMR Spectrum of Dimethyl 6-(1-Pyrrolidinyl)-5*H*-benzocycloheptatriene-7,8-dicarboxylate (13). ^{13}C NMR ($CDCl_3$, CFT-20, 20 MHz, proton decoupled, multiplicities obtained from off-resonance decoupled spectrum) δ (relative peak heights, multiplicity) 25.3 (100, t, pyrrolidine 3′- and 4′-CH_2), 38.1 (47, t, 5-CH_2), 51.2 (76, q, 7-$COOCH_3$), 51.8 (100, t, pyrrolidine 2′- and 5′-CH_2), 52.1 (76, q, 8-$COOCH_3$), 75.89, 77.50, 79.10 (t, 22, 29, 22, $CDCl_3$), 97.3 (34, s, 7-C), 126.5 (52, d), 127.5 (57, d), 128.6 (66, d), 128.7 (77, d) (Ar CH, probably 1, 4, 3, 2), 128.8 (76, d, 9-CH), 134.1 (61, s, 4a-C), 135.0 (50, s, 9a-C), 136.2 (54, s, 8-C), 149.3 (46, s, 6-C), 167.6 (36, s, $COOCH_3$), 170.4 (34, s, $COOCH_3$).

Reaction of 1-(1*H*-Inden-2-yl)pyrrolidine (11) with DMAD. Tetramethyl 9,9a-Dihydro-4-(1-pyrrolidinyl)-4a*H*-fluorene-1,2,3,9a-tetracarboxylate (15). A solution of the crude, dark residue of **11** and DMAD (2.13 g, 15.0 mmol) in benzene (20 mL) was refluxed for 8 h. The benzene was removed in a rotating evaporator and the residual dark red oil was crystallized from methanol, giving a yellow crystalline solid (1.60 g, 45%), mp 140–143 °C. Two recrystallizations from methanol gave yellow crystals: mp 143.5–144 °C; UV (95% C_2H_5OH) λ_{max} (log ϵ) 263 nm (4.12), 317 (3.99), 387 (4.11); UV (CH_3OH)[13] λ_{max} (log ϵ) 261 nm (4.14), 319 (4.09), 391 (4.11); UV ($CHCl_3$)[14] 265 nm (4.14), 319 (4.01), 391 (4.12); IR (halocarbon oil–Nujol) 1729 (s), 1710 (ms, C=O), 1535 (s, aromatic) cm^{-1}; IR (KBr) 1723 (s), 1709 (sh, ms, C=O), 1534 (s, conjugated enamine) cm^{-1}; NMR (16% w/v in $CDCl_3$) δ 1.70–2.10 (m, 3.9 H, pyrrolidine 3′-, 4′-CH_2), 2.90–4.13 (cm with strong peaks at 3.23 and 3.38, $w_{1/2}$ = 3 and 4 Hz, respectively, pyrrolidine 2′-, 5′-CH_2 and one more CH_2) overlapping 3.55, 3.58, 3.64, 3.80 (4 s, 4 $COOCH_3$, total 17.9 H), 4.45 (s, 0.8 H, CH), 6.95–7.30 (m, 3.7 H, 3 aromatic H), 7.83–8.06 (m, 0.7 H, 1 aromatic H); ^{13}C NMR ($CDCl_3$, FT-80A, 20 MHz, proton decoupled and coupled) δ (relative peak heights, multiplicity) 25.5 (62, t, $^{1}J_{CH}$ = 133.2 Hz, pyrrolidine 3′- and 4′-CH_2), 39.3 (28, t, $^{1}J_{CH}$ = 134.3 Hz, 9-CH_2), 47.3 (37, dd, $^{1}J_{CH}$ = 135.5, $^{3}J_{C_{4a}H_5}$ = 4.0 Hz, 4a-CH), 50.8 (39, q, $^{1}J_{CH}$ = 146.0 Hz, 9a-$COOCH_3$), 51.7 (42, q, $^{1}J_{CH}$ = 146.6 Hz, 3-$COOCH_3$), 52.3 (100, t, $^{1}J_{CH}$ = 143.1 Hz, pyrrolidine 2′- and 5′-CH_2), 52.6 (57, 2 q, $^{1}J_{CH}$ = 147.6, 1- and 2-$COOCH_3$), 54.8 (29, dt, $^{2}J_{C_{9a}H_{4a}}$ = 5.0, $^{2}J_{C_{9a}H_9}$ = 2.3 Hz, 9a-C), 75.98, 77.58, 79.19 (t, $CDCl_3$), 96.8 (7, d, $^{3}J_{C_3H_{4a}}$ = 2.7 Hz, 3-C), 124.5 (55, 2d with further coupling $^{1}J_{CH}$ = 162.0 Hz, $^{3}J_{CH}$ = 6.0 Hz, 6- and 7-CH, superimposed on s, 2-C), 127.1 (43, d with further coupling, $^{1}J_{CH}$ = 159.0 Hz, $^{3}J_{C_5H_7}$ = 8 Hz, $^{3}J_{C_5H_{4a}}$ = 4 Hz, 5-CH), 127.9 (38, d with further coupling, $^{1}J_{CH}$ = 159.2 Hz, $^{3}J_{C_8H_6}$ = 7.5 Hz, 8-CH), 133.7 (6, s with fine splitting, 1-C), 138.1 (15, s with fine splitting, 8a-C), 145.1 (30, s with fine splitting, 4b-C), 152.4 (21, d, $^{2}J_{C_4H_{4a}}$ = 6.1 Hz, 4-C), 165.7 (16, q, $^{3}J_{CH}$ = 4.0 Hz, 3?-$COOCH_3$), 168.2 (25, appears to be two overlapping q with possible fine splitting, 1- and 2?-$COOCH_3$), 174.8 (17, s with fine splitting, 9a-$COOCH_3$); mass spectrum (50 eV, 150 °C; relative intensity >21, M* indicates ^{13}C peak), *m/e* 470 (30, M + 1), 469 (100, M), 411 (24, M - $COOCH_2$ or M* - $COOCH_3$), 410 (86, M - $COOCH_3$), 378 (24, M - $HCOOCH_3$ - OCH_3), 366 (54, M - CH_3OH - C_4H_9N), 351 (72, M - 2 $COOCH_3$), 307 (25, M - $HCOOCH_3$ - OCH_3 - C_4H_9N), 304 (40, M - $COOCH_3$ - $HCOOCH_3$ - OCH_3 - CH_3), 292

(11) A longer and tortuous possible route to **15** can be envisaged in which either **14a** or **14b** would undergo ring enlargement to **16**. Tautomerization of **16** either via proton transfer from its anion (which would be a pseudoaromatic 10π-electron system) or by a sterically difficult 1,7-hydrogen shift antarafacial on the π system could give the intermediate **17**. Stabilization by conjugation of the enamine with the benzene ring in structure **17**, which would be absent in noncoplanar **16** as described earlier, might produce an energetically favorable transformation of **16** to **17**.

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(13) Sodium methoxide in methanol was not a strong enough base to form an anion. Addition of sodium methoxide, enough to make the solution 0.072 M (though not all dissolved, so the solution was decanted, possibly removing some **17** by adsorption) gave a spectrum essentially identical with that in methanol alone, except that the average intensities were lower by about 22% (0.105 log unit) but the relative intensities were not significantly changed.

(24, M - 3 $COOCH_3$), 288 (28, M - $COOCH_3$ - $HCOOCH_3$ - 2 OCH_3), 232 (28, M - 3 $COOCH_3$ - $HCOOCH_3$).

Anal. Calcd for $C_{25}H_{27}NO_8$ (mol wt 469.50): C, 63.96; H, 5.80; N, 2.99. Found: C, 64.21; H, 5.88; N, 2.93.

The compound was also obtained, in 69% yield, from reaction of the 1:1 adduct **13**[4] with 1 equiv of DMAD in refluxing benzene for 8 h, as shown by melting point, mixture melting point, and NMR comparison with the sample prepared from **11**.

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Registry No. **1a**, 31554-37-7; **4**, 76756-25-7; **11**, 39157-79-4; **13**, 76756-26-8; **15**, 76756-27-9; 2,3-dihydro-1*H*-inden-1-one, 83-33-0; pyrrolidine, 123-75-1; dimethyl acetylenedicarboxylate, 762-42-5; 2,3-dihydro-1*H*-inden-2-one, 615-13-4.

(14) The $CHCl_3$ UV solution faded perceptibly visually and the UV spectrum changed with time, even when the solution was kept in the refrigerator most of the time: after 2 days, 266 (4.11), 319 (3.97), 391 (4.05); after 3 days, 277 (4.26), 390 (3.71). In contrast, a concentrated (0.173 M) $CDCl_3$ NMR solution appeared to be more stable. The solution was kept for 8 days and then diluted to 1.23×10^{-4} M with $CHCl_3$ and then run promptly, giving UV ($CHCl_3$) 265 (~4.3) 320 (~4.2), 391 (~4.3).

A Convenient Method for O-Alkylation of N-Substituted Tyrosines Using a Crown Ether[1]

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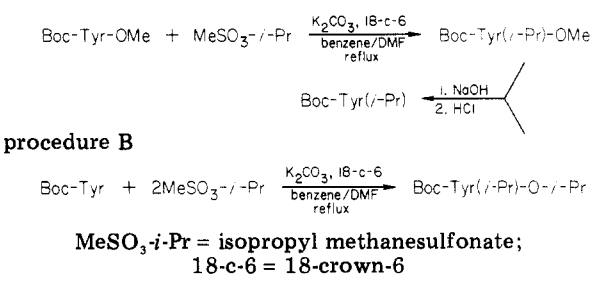
O-Methyltyrosine [Tyr(Me)] and *O*-ethyltyrosine [Tyr(Et)] substitutions at position two in selected analogues of oxytocin and arginine vasopressin (AVP) have proved to be extremely valuable for the design of antagonists of the characteristic biological responses of these peptide hormones.[2] For antidiuretic antagonists the *O*-ethyl-substituted analogues are almost twice as potent as *O*-methyl-containing analogues.[2d] We wished to explore the effects on antidiuretic antagonism of further increasing the size of the *O*-alkyltyrosine substituents, i.e., by the incorporation of *O*-isopropyltyrosine [Tyr(iPr)] and *O*-*n*-propyltyrosine [Tyr(*n*Pr)] in some of our most potent antagonists. The present study was prompted by the unavailability of Tyr(*i*Pr) or Tyr(*n*Pr). Both Tyr(Me) and Tyr(Et) are commercially available as their *tert*-butyloxycarbonyl (Boc) derivatives. Also, higher alkyl ethers of tyrosine, starting from the butyl derivative, can be readily prepared by alkylation of unprotected tyrosine with alkyl halides in the presence of NaOH in H_2O/Me_2SO solution.[3] However, the only reported synthesis of Tyr(*i*Pr) afforded this material in only a 4% yield following an 11-day reaction.[4]

Scheme I



$MeSO_3$-*i*-Pr = isopropyl methanesulfonate; 18-c-6 = 18-crown-6

We now report a new convenient and rapid method for the preparation in good yield of both Boc-Tyr(*i*Pr) and Boc-Tyr(*n*Pr) suitable for direct use in peptide synthesis. The general usefulness of this method is further demonstrated by the synthesis in excellent yields of Boc-L- and -D-Tyr(Me), Boc-L- and -D-Tyr(Et), *N*-(benzyloxy)-carbonyl-Tyr(Et), and *N*-formyl-Tyr(Me) (Table I). This method is an adaptation of a recently described synthesis of ethers of alcohols or phenols from alkyl halides in the presence of catalytic amounts of tetraalkylammonium salts or crown ethers and K_2CO_3 as base.[5] Boc-tyrosine methyl ester (procedure A) or Boc-tyrosine (procedure B), commercially available or readily prepared, can be used as starting materials. Both procedures are illustrated in the following schematic syntheses of Boc-Tyr(*i*Pr) (Scheme I).

The experimental conditions used for the preparation of all the aforementioned *O*-alkyl derivatives are given in Table I. The use of Boc-tyrosine methyl ester as starting material has a number of advantages: (a) it enconomizes on the use of the more expensive higher alkylating reagents; (b) the methyl ester group is more readily removed by hydrolysis; (c) the methyl esters can be used directly in couplings by the azide method. Because short-chain alkyl halides are too volatile for alkylations performed in boiling benzene we used commercial methyl and ethyl sulfates to obtain the methyl and ethyl ethers. The methanesulfonic acid esters of isopropyl and *n*-propyl alcohol were used in the syntheses of the higher homologues because methanesulfonates are better alkylation reagents than sulfates.[6] They are also more readily prepared in the laboratory. The alkylations of N-protected tyrosine with methyl and ethyl sulfates in boiling benzene proceed rapidly (Table I) whereas the reactions with both the propyl and isopropyl methanesulfonates under these conditions are sluggish. The addition of 10% DMF facilitates completion of these alkylations[7] over an extended reaction time.

Both the alkylation reactions and the basic hydrolysis of the tyrosine ester groups proceed with nearly quantitative yields as evidenced by TLC. Losses in varying degrees were incurred during the ensuing crystallizations (Table I). However, the crude products in all cases were

(1) Supported by NIH Grant GM25280.

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