Periselective Cycloaddition of Tricarbonyliron Complexes of Seven-Membered Unsaturated Compounds with 1,2,4,5-Tetrazine. Masking and Activating Effects of Tricarbonyliron Complexes

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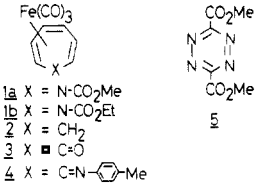
The cycloadditions of 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine (**5**) with tricarbonyl[*N*-(ethoxycarbonyl)-azepine]iron (**1b**), tricarbonyl(cycloheptatriene)iron (**2**), tricarbonyl(tropone)iron (**3**), and tricarbonyl[8-(4-methylphenyl)-8-azaheptafulvene]iron (**4**) were investigated. The adduct of **2** with **5** was verified by X-ray crystallography. The $[4 + 2]\pi$ adducts could lead to novel heterocycles, pyridazino[2,3-*d*]azepine (**8**), pyridazino[2,3-*d*]cycloheptatriene (**10**), and pyridazino[2,3-*d*]-8-(4-methylphenyl)-8-azaheptafulvene (**13**). Additionally these iron-complexed compounds also reacted with other diene components such as 2,3,4,5-tetrachlorothiophene 1,1-dioxide (**14**) (with **1–3**) and methyl coumalate (**15**) (only with **1**).

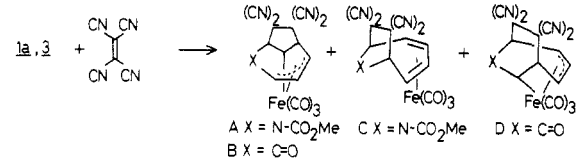
The pericyclic syntheses are very valuable for the stereo-, regio-, and periselective controls. Especially in the past decade, the thermal pericyclic reactions of conjugated medium-ring polyenes have aroused considerable interest, and much effort has been made to establish their capability for cycloaddition.

In general, cycloaddition reactions of medium-ring unsaturated compounds with electron-deficient 2π or 4π components are extensively studied.[1] On the other hand, there is now a substantial body of experimental evidence showing that cycloaddition reactions of coordinated olefins give rise to different products from those derived from the free olefin. It is pointed out that the molecular structures of tricarbonyl[*N*-(methoxycarbonyl)azepine]iron (**1a**) and

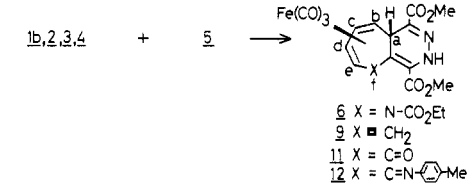


tricarbonyl(tropone)iron (**3**) by X-ray analyses indicate the existence of a localization at C(4)–C(7) of the diene.[2] In this connection,the cycloaddition reactions of **1a** and **3** (Scheme I) with tetracyanoethylene as a 2π acceptor, to the exo 1,3-adducts (A, B $[{}_{\pi}2 + {}_{\pi}2 + {}_{\sigma}2]$) together with the exo 1,6-adduct (C $[{}_{\pi}2 + {}_{\pi}2 + {}_{\sigma}2 + {}_{\pi}2 + {}_{\sigma}2]$, in the case of **1a**) and the exo 1,5-adduct (D) to which B isomerizes, respectively, have been reported.[3] Other previous reports concerning coordinated seven-membered-ring unsaturated compounds are as follows: (i) the cycloaddition reaction of **3** with cyclopentadiene as a 4π component in which the $[4 + 2]\pi$ adduct and sigmatropic rearrangement products were obtained,[4] (ii) the photocycloaddition of **2** with dimethyl acetylenedicarboxylate in which the $[6 + 2]\pi$ adduct was afforded,[5] (iii) the addition reaction of tricarbonyl(tropylium)iron with (η^1-allyl)Fp complexes in which the dinuclear hydroazulene complexes was obtained.[6]

Scheme I



Scheme II



As far as we know, there are few reports concerning the cycloaddition reactions of the coordinated seven-membered unsaturated compounds with 4π components.[4]

We now report the cycloaddition reactions of **5** with **1–4**. In these reactions, the $[4 + 2]\pi$ cycloadducts were afforded periselectively at the C(2)–C(3) position in high yield. The exact structure of **9** was fully established by an X-ray crystallographic study. These results are discussed here in detail with a kinetic study. Additionally, other cycloaddition reactions of **14** and **15** with **1–3** were examined.

Result and Discussion

Cycloaddition Reaction of 3,6-Bis(methoxycarbonyl)-1,2,4,5-tetrazine (5) with Tricarbonyl Complexes of Seven-Membered Unsaturated Compounds. With Tricarbonyl[*N*-(ethoxycarbonyl)azepine]iron (1b). Compound **5** reacted with **1b** in dry methylene chloride to give crystalline 1:1 adduct **6** (mp 163–164 °C dec) in nearly quantitative yield (Scheme II). The 1:1 nature of **6** was shown by elemental analysis and the mass spectrum [*m/e* 419 (M^+ – 2CO), 391 (M^+ – 3CO)]. The structure of the $[4 + 2]\pi$ adduct **6** is mainly assigned on the basis of the spectral data. The IR spectrum exhibited NH band at 3320 cm^{-1}, iron carbonyl bands at 2080 and 1980 cm^{-1}, ester bands at 1740 and 1730 cm^{-1}, and a urethane carbonyl band at 1710 cm^{-1}. In the ^1H NMR spectrum (Table I), a signal for H_b appears in high field [δ 3.22 (in $CDCl_3$)] which is observed in these iron com-

(1) Harano, K.; Yasuda, M.; Ban, T.; Kanematsu, K. *J. Org. Chem.* **1980**, *45*, 4455 and references cited therein.
(2) (a) Paul, I. C.; Johnson, S. M; Paquett, L. A.; Barett, J. H.; Haluska, R. J. *J. Am. Chem. Soc.* **1968**, *90*, 5023. (b) Dodge, R. P. *J. Am. Chem. Soc.* **1964**, *86*, 5429.
(3) Green, M.; Heathcock, S. M.; Turney, T. W.; Mingos, D. M. P. *J. Chem. Soc., Dalton Trans.* **1977**, 204.
(4) Frank-Newman, M.; Martina, D. *Tetrahedron Lett.* **1977**, 2293.
(5) Davis, R. E.; Dodds, T. A.; Hseu, T.-H.; Wagnon, J. C.; Devon, T.; Tancrede, J.; McKennis, J. S.; Pettit, R. *J. Am. Chem. Soc.* **1974**, *96*, 7562.
(6) Genco, N.; Marten, D.; Raghu, S.; Rosenblum, M. *J. Am. Chem. Soc.* **1976**, *98*, 848.

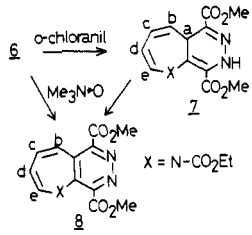
0022-3263/82/1947-0110$01.25/0

Table I. ^{1}H NMR Spectral Data of Products 6-8

compd (solvent)	chemical shift, δ	J, Hz
6 ($CDCl_3$)	1.09-1.48 (m, 3 H, CH_3), 3.22 (d, 1 H, H_b), 3.74, 3.88 (s, 6 H, 2 OCH_3), 4.00-4.20 (m, 2 H, CH_2), 4.08 (s, 1 H, H_a), 4.89 (dd, 1 H, H_c), 5.56 (dd, 1 H, H_d), 5.75 (d, 1 H, H_e), 7.93 (s, 1 H, NH)[a]	J_{bc} = 7.0, J_{cd} = 5.5, J_{de} = 5.0, $J_{CH_2-CH_3}$ = 7.5
6 (C_6D_6)	0.85, 1.04 (t, 3 H, CH_3), 3.17, 3.40 (s, 6 H, 2 OCH_3), 3.30 (d, 1 H, H_b), 3.90 (m, 2 H, CH_2), 4.13 (dd, 1 H, H_c), 4.32 (s, 1 H, H_a), 4.71 (dd, 1 H, H_d), 5.89 (d, 1 H, H_e), 7.70 (s, 1 H, NH)[a]	
7 ($CDCl_3$)	1.23 (t, 3 H, CH_3), 3.80, 3.90 (s, 6 H, 2 OCH_3), 4.01 (m, 1 H, H_a), 4.20 (q, 2 H, CH_2), 5.43 (dd, 1 H, H_d), 5.52 (dd, 1 H, H_b), 5.92 (ddd, 1 H, H_c), 7.29 (d, 1 H, H_e), 8.52 (s, 1 H, NH)[a]	J_{ab} = 4.2, J_{bc} = 9.6, J_{ac} = 2.8, J_{cd} = 6.5, J_{de} = 7.2, $J_{CH_2-CH_3}$ = 7.5
8 (CD_3SOCD_3)	1.07, 1.27 (t, 3 H, CH_3), 3.90-4.38 (m, 8 H, 2 OCH_3, CH_2), 6.18, 6.26 (dd, 1 H, H_c), 6.44 (d, 1 H, H_b), 6.94, 6.95 (dd, 1 H, H_d), 7.22 (d, 1 H, H_e)	J_{bc} = 7.0, J_{cd} = 6.0, J_{de} = 11.0, $J_{CH_2-CH_3}$ = 7.5
8 (CD_3SOCD_3)[b]	1.18 (t, 3 H, CH_3), 3.94, 4.00 (s, 6 H, 2 OCH_3), 4.14 (q, 2 H, CH_2), 6.19 (dd, 1 H, H_c), 6.43 (d, 1 H, H_b), 7.19 (d, 1 H, H_e)	
8 ($CDCl_3$)	1.16, 1.26 (t, 3 H, CH_3), 4.00-4.40 (m, 8 H, 2 OCH_3, CH_2), 6.04 (m, 1 H, H_c), 6.43, 6.51 (d, 1 H, H_b), 6.82 (m, 1 H, H_d), 7.31 (d, 1 H, H_e)	
8 (C_6D_6)	0.76, 0.97 (t, 3 H, CH_3), 3.40-4.20 (m, 8 H, 2 OCH_3, CH_2), 5.26, 5.33 (dd, 1 H, H_c), 6.08, 6.10 (dd, 1 H, H_d), 6.26, 6.48 (d, 1 H, H_b), 7.06 (d, 1 H, H_e)	

[a] Exchangeable by D_2O. [b] Measured at 130 °C.

Scheme III



Scheme IV

plexes,[3] while a signal of H_a appears as a sharp singlet [δ 4.32 (in C_6D_6)]. The reason why H_a does not couple with H_b is that bond angles C–H_b and C–H_a are perpendicular to each other, as indicated by an X-ray structure analysis of **9** (as described below). When the ^{1}H NMR spectrum of **6** was measured in $CDCl_3$, the H_a signal overlapped with the methylene signals, but they did not overlap in C_6D_6 because the methylene signals shifted to high field. In the ^{13}C NMR spectrum (Table III), the signals of coordinated diene carbons appeared in high field (δ 60.59, 73.59, 74.06, 89.18). This observation is well accounted for by the results of X-ray analysis. The spectrum (five sp^3 carbons, seven sp^2 carbons, and four C=O carbons) agreed with the proposed structure **6**.

Subsequently, decomplexation reaction of **6** was carried out with *o*-chloranil, and a product (**7**, mp 153–154 °C) was obtained in 71% yield (Scheme III). The structure of **7** was assigned on the basis of spectroscopic data. The elemental analysis, the mass spectrum [*m/e* 419 (M^+)], and the IR spectrum (no $Fe(CO)_3$ absorption) indicated that **7** is an iron-free product. Furthermore, the ^{1}H NMR and ^{13}C NMR spectra (Tables I and III) agreed with the structure of **7**. Especially it is revealed that H_a is next to H_b from the ^{1}H NMR spectral data as shown in Table I.

On the other hand, oxidative degradation of **6** or **7** with trimethylamine oxide afforded pyridazino[2,3-*d*]azepine (**8**, mp 107–108 °C) in 33% or 70% yield. The ^{1}H and ^{13}C NMR (Tables I and III) spectra were very complicated for the structure **8**. This complexity was caused by the existence of the rotational isomers at room temperature;[7] the spectrum was simple when the ^{1}H NMR spectrum was measured at 130 °C.

It is noted that the stabilization energies for the cycloaddition reactions of 1*H*-azepine with dienes were calculated by treatments with perturbation theory as reported in our previous paper.[1] The calcuated data suggest that the [4 + 2]π adduct [at C(2)–C(3)] is the most energetically unfavorable. Thus it is noteworthy that this cycloaddition reaction, in which **1b** reacted with a 4π component at the C(2)–C(3) position, is the first example for an azepine molecule, by means of the masking effect [C(4)–C(7) position] of tricarbonyliron. This is in sharp contrast to the cycloaddition of *N*-(ethoxycarbonyl)azepine with **5** at the C(4)–C(5) position to give E (Scheme IV).[8]

With Tricarbonyl(cycloheptatriene)iron (2). A cycloaddition of **5** with **2** gave pale yellow crystalline 1:1 adduct **9**: mp 168–170 °C dec; 72% yield. The IR spectrum showed the existence of a carbonyliron and ester moiety. The ^{1}H and ^{13}C NMR spectral data of **9** are summarized in Tables II and III.

The chemical shifts of the methine protons are different, suggesting the influence of the carbonyliron moiety. Then one hydrogen [δ 3.86 (C_6D_6)] coupled with H_e, while the other [δ 1.95 (C_6D_6)] did not. As same as the case of **6**, the signal of H_a is singlet. Furthermore, the configuration of H_a could not be decided from these spectral data.

In order to clarify these obscurities and to account for the stereochemistry, the iron complex **9** was characterized by single-crystal X-ray analysis. The crystal structure was solved by the direct method. Refinement to an *R* factor of 3.8% was obtained by the method of least-squares on 2679 nonzero structure factors.

The configuration of **9** with the numbering sequence used in this paper is illustrated in Figure 1 where each

(7) Günther, H.; Wenzl, R. *Tetrahedron Lett.* **1967**, 4155.

(8) Seitz, G.; Kämpchen, T.; Overheu, W. *Arch. Pharm. (Weinheim, Ger.)* **1978**, *311*, 786.

Table II. ^{1}H NMR Spectral Data of Products 9-13

compd (solvent)	chemical shift, δ	J, Hz
9 ($CDCl_3$)	2.27 (d, 1 H, H_f), 2.78 (d, 1 H, H_b), 3.16 (t, 1 H, H_e), 3.80-4.20 (m, 9 H, 2 OCH_3, CH_2, H_f), 4.04 (s, 1 H, H_a), 5.10-5.46 (m, 2 H, H_c, H_d), 8.01 (s, 1 H, NH)[a]	J_{bc} = 7.0, J_{de} = 6.0, J_{ef} = 6.0, $J_{ff'}$ = 16.0
9 (C_6D_6)	1.95 (d, 1 H, H_f), 2.60 (t, 1 H, H_e), 2.73 (d, 1 H, H_b), 3.11, 3.51 (s, 6 H, 2 OCH_3), 3.86 (dd, 1 H, H_f), 4.04 (s, 1 H, H_a), 4.48-4.76 (m, 2 H, H_c, H_d), 7.88 (s, 1 H, NH)[a]	
10 ($CDCl_3$)	3.12 (d, 2 H, H_f), 4.06, 4.08 (s, 6 H, 2 OCH_3), 5.98 (dt, 1 H, H_e), 6.36 (dd, 1 H, H_d), 7.07 (dd, 1 H, H_c), 7.57 (d, 1 H, H_b)	J_{bc} = 12.0, J_{cd} = 5.0, J_{de} = 9.0, J_{ef} = 7.0
11 ($CDCl_3$)	3.12-3.32 (m, 2 H, H_b, H_e), 3.78, 3.86 (s, 6 H, 2 OCH_3), 4.74 (s, 1 H, H_a), 5.50 (t, 1 H, H_c or H_d), 6.00 (t, 1 H, H_c or H_d), 7.85 (s, 1 H, NH)[a]	J =. 3.0 and 2.5
12 (CD_3SOCD_3)	2.19, 2.28 (s, 3 H, CH_3), 3.20 (m, 1 H, H_b), 3.60-3.96 (m, 7 H, H_e, 2 OCH_3), 4.37, 4.50 (s, 1 H, H_a), 5.84 (m, 1 H, H_c), 6.08 (m, 1 H, H_d), 6.46, 6.66 (d, 2 H, Ph H), 7.00, 7.18 (d, 2 H, Ph H), 10.22, 10.39 (s, 1 H, NH)[a]	J_{Ph-H} = 8.0
13 ($CDCl_3$)	2.33 (s, 3 H, CH_3), 4.05, 4.08 (s, 6 H, 2 OCH_3), 6.54 (dd, 1 H, H_c), 6.71 (dd, 1 H, H_b), 6.96 (ddd, 1 H, H_d), 7.42 (d, 1 H, H_e), 6.76 (d, 2 H, Ph H), 7.13 (d, 2 H, Ph H)	J_{bc} = 5.0, J_{cd} = 10.5, J_{bd} = 2.0, J_{de} = 12.0, J_{Ph-H} = 8.0

[a] Exchangeable by D_2O.

Table III. ^{13}C NMR[a] Spectral Data of Products 6-10

compd	carbon type	chemical shift, ppm
6	sp^3	14.47 (q), 36.21 (d), 52.38 (q), 52.85 (q), 62.34 (t)
	sp^2	60.59 (d), 73.59 (d), 74.06 (d), 89.18 (d), 119.47 (s), 121.70 (s), 132.07 (s)
	C=O	151.17 (s), 160.19 (s), 164.17 (s), 208.76 (s)
7	sp^3	14.24 (q), 37.79 (d), 52.56 (q), 63.40 (t)
	sp^2	105.64 (d), 114.31 (s), 121.05 (s), 125.21 (d), 127.91 (d), 129.14 (s), 135.70 (d)
	C=O	151.99 (s), 161.60 (s), 164.06 (s)
8	sp^3	13.89 (q), 14.47 (q), 53.44 (q), 62.87 (t), 63.22 (t)
	sp^2	120.59 (d), 121.11 (d), 125.74 (d), 126.33 (d), 133.18 (s), 133.36 (s), 134.53 (d), 135.29 (d), 136.58 (d), 137.05 (d), 149.59 (s), 150.17 (s), 151.58 (s), 152.17 (s)
	C=O	152.87 (s), 162.89 (s), 163.36 (s) 163.83 (s)
9	sp^3	31.93 (t), 37.68 (d), 52.32 (q)
	sp^2	57.07 (d), 61.82 (d), 87.83 (d), 88.48 (d), 121.35 (s), 122.87 (s), 129.49 (s)
	C=O	161.48 (s), 164.47 (s), 209.88 (s)
10	sp^3	28.83 (t), 53.26 (q)
	sp^2	125.62 (d), 127.27 (d), 128.44 (d), 131.19 (s), 132.19 (s), 137.23 (d), 150.23 (s), 151.46 (s)
	C=O	164.82 (s)

[a] $CDCl_3$.

atom is represented as an ellipsoid with 20% probability. The bond distances, along with their respective standard deviations, are listed in Table IV.

The cycloheptadiene ring has a tub conformation in the complex. Carbons C(18)-C(11) are nearly planar. The bond betweetn C(9) and C(10), a formal single bond, is shorter than the formal double bond between C(8) (C(10)) and C(9) (C(11)). This distortion was also found in the structures of the analogous 1,3-diene iron tricarbonyl system.[9] The H(18) (H_a) atom occupies the cis configuration with respect to the iron. The dihedral angle H-(18)-C(18)-C(8)-H(8) (H_a-C_a-C_b-H_b) is 71.4°, which is consistent with the ^{1}H NMR result [H(18) (H_a) does not interact with H(8) (H_b)] as described above (Table I).

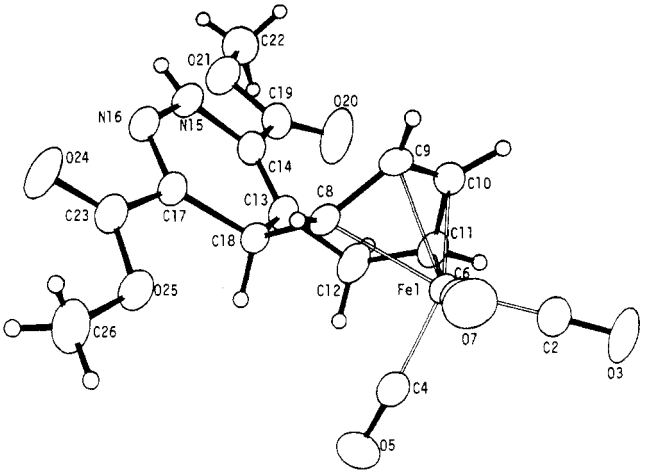
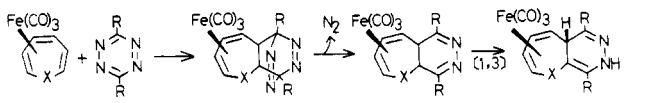


Figure 1. Drawing to indicate the numbering sequence used in this paper for the 26 independent nonhydrogen atoms.

Table IV. Interatomic Distances (Å) and Their Estimated Standard Deviations for the Complex 9

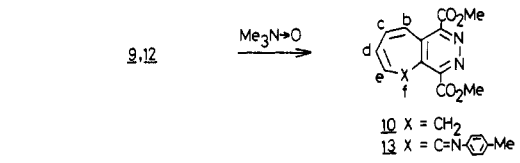
Fe(1)-C(2)	1.795 (4)	C(12)-C(13)	1.502 (5)
Fe(1)-C(4)	1.771 (4)	C(13)-C(14)	1.338 (5)
Fe(1)-C(6)	1.782 (4)	C(13)-C(18)	1.502 (5)
Fe(1)-C(8)	2.110 (3)	C(14)-N(15)	1.403 (4)
Fe(1)-C(9)	2.055 (3)	C(14)-C(19)	1.488 (5)
Fe(1)-C(10)	2.054 (4)	N(15)-N(16)	1.341 (4)
Fe(1)-C(11)	2.110 (4)	N(16)-C(17)	1.287 (4)
C(2)-O(3)	1.136 (5)	C(17)-C(18)	1.523 (4)
C(4)-O(5)	1.137 (5)	C(17)-C(23)	1.459 (5)
C(6)-O(7)	1.140 (5)	C(19)-O(20)	1.193 (5)
C(8)-C(9)	1.427 (5)	C(19)-O(21)	1.314 (5)
C(8)-C(18)	1.532 (4)	O(21)-C(22)	1.444 (5)
C(9)-C(10)	1.398 (5)	C(23)-O(24)	1.204 (5)
C(10)-C(11)	1.421 (5)	C(23)-O(25)	1.342 (4)
C(11)-C(12)	1.522 (5)	O(25)-C(26)	1.446 (5)

Scheme V



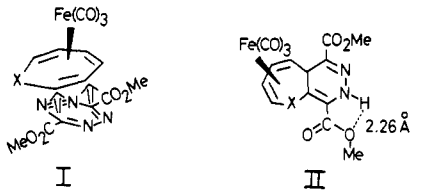
(9) Peason, A. J.; Mincione, E.; Chandler, M.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2774.

Scheme VI



The Fe-complexing carbon atom distances range from 2.05 to 2.11 Å. The iron atom lies about 1.57 Å above the best plane through carbon atoms C(8), C(9), C(10), and C(11).

The reaction pathway is described in Scheme V. From the fact that H_a occupied a cis position with respect to the iron, the tetrazine **5** only attacks the ring anti to the metal moiety (structure I). The [1,3] hydrogen shift of the



following step might occur to yield the stabilization energy of hydrogen bonding since the distance between N–H and O–Me in **9** is 2.26 Å as depicted in structure II. There could be some further driving force like release of steric strain or perhaps the formation of a homoaromatic ring.[10]

Then, decomplexation reaction of **9** with trimethylamine oxide (Scheme VI) gave **10**: mp 131–132 °C; 33% yield. The ^1H and ^{13}C NMR spectral data are summarized in Tables II and III.

With Tricarbonyl(tropone)iron (3). Similar treatment of **5** and **3** gave pale yellow crystalline 1:1 adduct **11**: mp 218–219 °C dec; 89% yield. The ^1H NMR spectral data are summarized in Table II. The [4 + 2]π adduct **11** could not be decomplexed by various oxidation reagents such as *o*-chloranil, trimethylamine oxide, and ceric ammonium nitrite, suggesting the dominant interaction of electronic factors in stabilization by carbonyl conjugation.

With Tricarbonyl[8-(4-methylphenyl)-8-azaheptafulvene]iron (4). The reaction of **5** and **4** afforded yellow crystalline 1:1 adduct **12**: mp 190–193 °C dec; 74% yield. From the spectral data, the product **12** was assigned the [4 + 2]π adduct. In the ^1H NMR spectrum (Table II), two stereoisomers (concerning the relationship of the tricarbonyliron and the 4-methylphenyl group) were observed. Similar stereoisomers exist in **4**.[11] The decomplexation reaction of **12** gave product **13**: mp 122–123 °C; 33% yield.

Kinetics of the Cycloaddition Reactions. The pseudo-first-order rate constants of these reactions at various conditions were obtained by following the disappearances of the absorption band of 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine (**5**) in the visible region (510–540 nm) by ultraviolet (UV) spectrometry.

The second-order rate constants (k_2), the relative rates, and the activation parameters calculated in the usual manner are summarized in Table V.

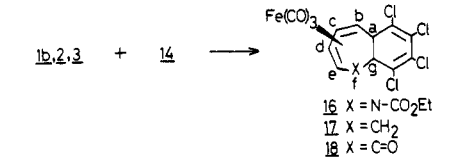
From these results, **2** is the most reactive in comparison with **1**, **3**, and **4**. The reasons for the different reactivities are explained by steric and electronic factors: **1** and **4** are more bulky than **2**, and **3** has a carbonyl which is an electron-withdrawing group.

Table V. Rate Constant Data for Cycloaddition of Iron Complexes 1–4 with 3,6-Bis(methoxycarbonyl)-1,2,4,5-tetrazine (5)

compd	temp, °C	solv	[compd]/[5]	10^3k,[a] s^{-1}	k(compd)/k(1)
1	34.1	B[b]	100	1.22	
	34.1	CB[c]	100	1.26	1[f]
	34.1	CB	50	1.36	
	34.1	CB	25	1.31	
	34.1	CB	10	1.26	
	30.0	CB	100	1.11	
	40.0	CB	100	1.67	
	45.0	CB	100	2.31	
	50.0	CB	100	2.84	
	34.1	DCE[d]	100	2.84	
	34.1	AN[e]	100	1.64	
2	34.1	B	100	16.6	
	34.1	CB	100	34.5	27.3
	34.1	CB	10	32.8	
	34.1	CB	5	35.7	
	34.1	DCE	100	73.4	
	34.1	AN	5	37.0	
3	34.1	CB	100	5.11	4.06
	34.1	AN	50	8.21	
	34.1	AN	25	6.48	
	34.1	AN	1	6.61	
4	34.1	CB	100	4.62	3.38
	34.1	AN	100	3.57	

[a] The average error is ±3%. [b] Benzene. [c] Chlorobenzene. [d] Dichloroethane. [e] Acetonitrile. [f] E_a = 9.55 ± 1.4 kcal/mol and $\Delta S^{\ddagger}$ = −42.7 ± 4.5 eu.

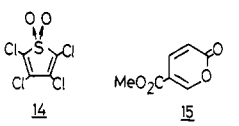
Scheme VII



The lack of dependence of rate on change in solvent polarity, and the large entropy value ruled out a dipolar intermediate, and supported a concerted mechanism for these reactions. The entropy value (−42.3 ± 4.5 eu) shows that the transition state is very rigid due to by the influence of tricarbonyliron moiety.

Furthermore, the charge-transfer mechanism is ruled out by the fact that the rates do not depend on the concentrations of the mixture.

With Other Diene Components. We examined the cycloadditivities of tricarbonyliron complexes with two diene components: one is 2,3,4,5-tetrachlorothiophene 1,1-dioxide (**14**), which showed high reactivity toward many dienophiles,[12] and the other is methyl coumalate, which reacted with cycloheptatriene to give a cage compound.[13]



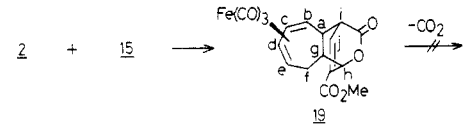
Cycloaddition Reaction of 2,3,4,5-Tetrachlorothiophene 1,1-Dioxide (14) with Tricarbonyl[*N*-(ethoxycarbonyl)azepine]iron (1b). Reaction of **14** with **1b** gave crystalline 1:1 adduct **16**: mp 126–128 °C; 66% yield (Scheme VII). The structure of **16** was assigned on the basis of the spectral data. The ^1H NMR spectrum was summarized in Table VI.

(10) We are greatful to a referee for the comment.
(11) Gandolfi, R.; Toma, L. *Tetrahedron* **1980**, *36*, 935.
(12) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856.
(13) Sasaki, T.; Kanematsu,K.; Yukimoto, Y.; Hiramatsu, T. *J. Am. Chem. Soc.* **1974**, *96*, 2536.

Table VI. ^{1}H NMR Spectral Data of Products 16–19

compd (solvent)	chemical shift, δ	J, Hz
16 ($CDCl_3$)	1.20–1.50 (m, 3 H, CH_3), 2.80 (d, 1 H, H_b), 2.96 (d, 1 H, H_a), 4.10–4.40 (m, 2 H, CH_2), 4.88 (m, 1 H, H_d), 5.20–5.70 (m, 3 H, H_c, H_e, H_g)	
17 ($CDCl_3$)	2.15 (dd, 1 H, H_f), 2.44–2.60 (m, 2 H, H_b, H_g), 2.64–3.04 (m, 3 H, H_a, H_e, H_f), 5.23–5.48 (m, 2 H, H_c, H_d)	J_{ab} = 3.0, J_{ag} = 7.0, J_{fg} = 4.0, $J_{ff'}$ = 17.0
17 (C_6D_6)	1.44 (dd, 1 H, H_f), 1.80–2.20 (m, 4 H, H_b, H_e, H_f, H_g), 2.53 (dd, 1 H, H_a), 2.53 (dd, 1 H, H_a), 4.26 (dd, 1 H, H_c or H_d), 4.52 (dd, 1 H, H_c or H_d)	
18 ($CDCl_3$)	2.95 (d, 1 H, H_b), 3.20 (d, 1 H, H_e), 3.57 (s, 2 H, H_a, H_g), 5.56 (dd, 1 H, H_c), 5.86 (dd, 1 H, H_d)	J_{bc} = 8.0, J_{cd} = 5.0, J_{de} = 6.5
19 ($CDCl_3$)	1.86 (dd, 1 H, H_f), 2.32–2.92 (m, 4 H, H_b, H_e, H_f, H_g), 3.02 (m, 1 H, H_a), 3.68 (dd, 1 H, H_i), 3.84 (s, 3, H, OCH_3), 4.98–5.20 (m, 3 H, H_c, H_d, H_h), 7.25 (dd, 1 H, H_j)	J_{ai} = 3.0, J_{fg} = 3.5, J_{gh} = 3.0, J_{hj} = 2.0, J_{ij} = 7.0, $J_{ff'}$ = 19.0
19 (C_6D_6)	1.41 (dd, 1 H, H_f), 1.70–2.04 (m, 3 H, H_b, H_f, H_g), 2.14 (m, 1 H, H_e), 2.38 (m, 1 H, H_a), 3.13 (dd, 1 H, H_i), 3.34 (s, 3 H, OCH_3), 4.08 (m, 1 H, H_c), 4.24 (m, 1 H, H_d), 4.86 (dd, 1 H, H_h), 6.76 (dd, 1 H, H_j)	

Scheme VIII



With Tricarbonyl(cycloheptatriene)iron (2). Compound **14** reacted with **2** to give crystalline 1:1 adduct **17**: mp 130–132 °C; 85% yield. The structure of **17** was assigned on the basis of the spectral data (Table VI).

With Tricarbonyl(tropone)iron (3). A mixture of **14** and **3** gave crystalline 1:1 adduct **18**: mp 168–169.5 °C; 92% yield. The structure of **18** was assigned on the basis of the spectral data (Table VI).

Cycloaddition Reaction of Methyl Coumalate (15) with Tricarbonyl(cycloheptatriene)iron (2). Compound **15** reacted with **2** to give crystalline 1:1 adduct **19**: mp 90–92 °C; 86% yield. Elemental analysis, the mass spectrum [*m/e* 358 (M^+ – CO), 330 (M^+ – 2CO), 302 (M^+ – 3CO)], and the IR spectrum [2070, 1960 ($Fe(CO)_3$), 1760 (lactone), 1718 (ester) cm^{-1}] indicated the structure **19** which has a lactone moiety. It is not sure certain, but the structure of **19** was considered to be as shown in Scheme VIII. In the ^{1}H NMR spectrum (Table VI), the signals of the H_a and H_h coupled with those of H_j and H_i, respectively. From these data, the stereochemistry of methoxycarbonyl was indicated to be syn with respect to the methylene of cycloheptadiene moiety. The relationship of the tricarbonyliron and methoxycarbonyl groups could not be decided. Further attempts at decarboxylation by thermolysis were unsuccessful.

Experimental Section

Melting points were measured with a Yanagimoto micro melting point apparatus and uncorrected. ^{1}H NMR spectra were taken with a JEOL PS-100 spectrometer with Me_4Si as an internal standard; chemical shifts are expressed in δ values. ^{13}C NMR spectra were recorded on a JEOL FX-100 with Me_4Si as an internal standard. IR spectra were taken with a JASCO DS-701G infrared spectrophotometer. The UV spectra were determined with a Hitachi ESP-3T spectrometer. Mass spectra were obtained with a JEOL-01SG double-focusing spectrometer operating at an ionization potential of 75 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 150–200 °C.

Cycloaddition Reaction of 3,6-Bis(methoxycarbonyl)-1,2,4,5-tetrazine (5) with Tricarbonyl[*N*-(ethoxycarbonyl)-azepine]iron (1b). A solution of **5** (0.99 g, 5.0 mmol) and **1b** (1.83 g, of 6.0 mmol) in 20 mL of dry methylene chloride was stirred at room temperature for 7 h. The solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column with *n*-hexane and ethyl acetate (3:2) to give an adduct (**6**; 2.18 g, 92%) as yellow crystals: mp 163–164 °C dec (methanol); mass spectrum, *m/e* 419 (M^+ – 2CO), 391 (M^+ – 3 CO); IR (Nujol) 3320 (m) (NH), 2080 (s), 1980 (s) ($Fe(CO)_3$), 1740 (sh), 1730 (s, ester), 1710 (s, urethane) cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_3O_9Fe$: C, 45.50; H, 3.61; N, 8.84. Found: C, 45.41; H, 3.77; N, 8.97.

Oxidative Degradation of 6 with *o*-Chloranil. A solution of **6** (475 mg, 1.0 mmol) and *o*-chloranil (295 mg, 1.2 mmol) in 10 mL of dry chloroform was stirred at room temperature for 10 min. The solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column by using chloroform and methanol (100:1) to give a product **7**: 238 mg (71%); yellow crystals; mp 153–154 °C (methanol); mass spectrum, *m/e* 335 (M^+); IR (Nujol) 3380 (m, NH), 1750 (m), 1740 (sh, ester), 1710 (s, urethane) cm^{-1}. Anal. Calcd for $C_{15}H_{17}N_3O_6$: C, 53.75; H, 5.11; N, 12.53. Found: C, 53.86; H, 5.15; N, 12.36.

Aromatization of 7 with Trimethylamine Oxide.[14] A solution of **7** (200 mg, 0.597 mmol) and trimethylamine oxide (90 mg, 1.2 mmol) in 20 mL of dry benzene was refluxed for 2 h under nitrogen. The mixture was filtered and evaporated under reduced pressure. The residue was chromatographed on a silica gel column by using chloroform to give a product **8**: 142 mg (70%); pale yellow crystals; mp 107–109 °C (*n*-hexane); mass spectrum, *m/e* 333 (M^+); IR (Nujol) 1740 (sh), 1725 (s, ester), 1705 (sh, urethane) cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_3O_6$: C, 54.06; H, 4.54; N, 12.61. Found: C, 54.10; H, 4.66; N, 12.43.

Oxidative Degradation of 6 with Trimethylamine Oxide. A solution of **6** (475 mg, 1.0 mmol) and trimethylamine oxide (600 mg, 8.0 mmol) in 40 mL of dry benzene was refluxed for 2 h under nitrogen. The mixture was filtered and evaporated under reduced pressure. The residue was chromatographed on a silica gel column by using *n*-hexane and ethyl acetate (3:2) to give product **8**, 106 mg (32%).

Cycloaddition Reaction of 5 with Tricarbonyl(cycloheptatriene)iron (2). A suspension of **5** (0.8 g, 4.04 mmol) and **2** (1.3 g, 5.60 mmol) in 10 mL of dry methylene chloride was stirred at room temperature for 15 min. The solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column by using chloroform to give adduct **9**: 1.624 g (73%); pale yellow crystals; mp 165–167 °C dec (ether); mass spectrum, *m/e* 374 (M^+ – CO), 346 (M^+ – 2CO), 318 (M^+ – 3CO); IR (Nujol) 3270 (m, NH), 2060 (s), 1980 (s), 1950 (s, $Fe(CO)_3$), 1720 (s, ester) cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_7Fe$: C, 47.79; H, 3.51; N, 6.97. Found: C, 47.87; H, 3.60; N, 701.

Oxidative Degradation of 9 with Trimethylamine Oxide. A solution of **9** (500 mg, 1.244 mmol) and trimethylamine oxide (1.8 g, 24.0 mmol) in 30 mL of dry benzene was stirred at room temperature for 1 h under nitrogen. The mixture was filtered

(14) The trimethylamine oxide was used anhydrous. (The commercially available hydrated one was dried by heating at 105 °C (5 mm) and sublimation.)

and evaporated under reduced pressure. The residue was chromatographed on a silica gel column by using *n*-hexane and ethyl acetate (2:1) to give product **10**: 108 mg (33%); colorless crystals; mp 125–127 °C (methanol); mass spectrum, *m/e* 260 (M^+); IR (Nujol) 1730 (m, ester) cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 59.98; H, 4.65; N, 10.76. Found: C, 60.04; H, 4.78; N, 10.64.

Cycloaddition Reaction of 5 with Tricarbonyl(tropone)iron (3). A solution of **5** (1.7 g, 8.586 mmol) and **3** (2.23 g, 9.065 mmol) in 10 mL of dry methylene chloride was stirred at room temperature overnight. Pale yellow crystals were filtered, and the mother liquor was chromatographed on a silica gel column by using *n*-hexane and ethyl acetate (2:1). Both were combined to give product **11**: 3.189 g (89%); pale yellow crystals; mp 218–219 °C (methanol); mass spectrum, *m/e* 416 (M^+), 388 (M^+ – CO), 360 (M^+ – 2CO), 332 (M^+ – 3CO); IR (Nujol) 3240 (m, NH), 2110 (s), 1990 (s, $Fe(CO)_3$), 1740 (s), 1720 (s, ester), 1635 (s, tropone CO) cm^{-1}. Anal. Calcd for $C_{16}H_{12}N_2O_8Fe$: C, 46.18; H, 2.91; N, 6.67. Found: C, 45.95; H, 2.94; N, 6.78.

Cycloaddition Reaction of 5 with Tricarbonyl[8-(4-methylphenyl)-8-azaheptafulvene]iron (4). A solution of **5** (90 mg, 0.455 mmol) and **4** (237 mg, 0.707 mmol) in 5 mL of dry methylene chloride was stirred at room temperature overnight. Crystals separated out were filtered and recrystallized to give an adduct **12**: 168 mg (74%); yellow crystals; mp 190–193 °C dec (chloroform); mass spectrum, *m/e* 449 (M^+ – 2CO), 421 (M^+ – 3CO); IR (Nujol) 3220 (w, NH), 2100 (s), 2020 (s), 1990 (s, $Fe(CO)_3$), 1730 (m), 1715 (m, ester) cm^{-1}. Anal. Calcd for $C_{23}H_{19}N_3O_7Fe$: C, 54.67; H, 3.79; N, 8.32. Found: C, 54.23; N, 3.84; N, 8.19.

Oxidative Degradation of 12 with Trimethylamine Oxide. A suspension of **12** (142 mg, 0.281 mmol) and trimethylamine oxide (169 mg, 2.253 mmol) in 10 mL of dry benzene was stirred at room temperature for 30 min under nitrogen. The mixture was filtered and evaporated under reduced pressure. The residue was chromatographed on a silica gel column by using *n*-hexane and ethyl acetate (2:1) to give product **13**: 35 mg (34%); yellow crystals; mp 122–123 °C (methanol); mass spectrum, *m/e* 363 (M^+); IR (Nujol) 1735 (sh), 1725 (m, ester) cm^{-1}. Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56. found: C, 65.83; H, 4.84; N, 11.30.

Kinetics. Various solvents containing 3,6-bis(methoxycarbonyl)-1,2,4,5-tetrazine (**5**, 1×10^{-3} M) and iron tricarbonyl complex (various concentrations) were prepared. The rate was followed at a given temperature by the loss of the long-wavelength absorbance of the **5** chromophore in the visible spectrum (510–540 nm) by using a 10 × 10 mm Pyrex cell which was thermostated with flowing water at constant temperature. All spectra were calculated by means of a nonweighted least-squares program.

Cycloaddition Reaction of 2,3,4,5-Tetrachlorothiophene 1,1-Dioxide (14) with Tricarbonyl[*N*-(ethoxycarbonyl)azepine]iron (1b). A solution of **14** (830 mg, 3.268 mmol) and **1b** (500 mg, 1.639 mmol) in 5 mL of dry benzene was refluxed for 6 h. The solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column by using *n*-hexane and ethyl acetate (10:1) to give adduct **16**: 532 mg (66%); pale yellow crystals; mp 126–128 °C (ether); mass spectrum, *m/e* 495 (M^+ + 2), 469 (M^+ – CO + 4), 467 (M^+ – CO + 2), 465 (M^+ – CO); IR (Nujol) 2080 (s), 1985 (s), 1960 (s, $Fe(CO)_3$), 1710 (s, urethane) cm^{-1}. Anal. Calcd for $C_{16}H_{11}NO_5Cl_4Fe$: C, 38.83; H, 2.24; N, 2.83. Found: C, 38.68; H, 2.27; N, 2.79.

Cycloaddition Reaction of 14 with Tricarbonyl(cycloheptatriene)iron (2). A solution of **14** (200 mg, 0.787 mmol) and **2** (450 mg, 0.516 mmol) in 3 mL of dry benzene was left for 24 h. The solvent was removed. The same workup (column chromatography with *n*-hexane) gave adduct **17**: 281 mg (85%); pale yellow crystals; mp 131–132 °C (ether): mass spectrum, *m/e* 424 (M^+ + 4), 422 (M^+ + 2), 420 (M^+); IR (Nujol) 2080 (s), 1970 (s), 1940 (s, $Fe(CO)_3$) cm^{-1}. Anal. Calcd for $C_{14}H_8O_3Cl_4Fe$: C, 39.86; H, 1.91. Found: C, 39.78; H, 2.05.

Cycloaddition Reaction of 14 with Tricarbonyl(tropone)iron (3). A solution of **14** (410 mg, 1.614 mmol) and **3** (810 mg, 3.293 mmol) in 5 mL of dry methylene chloride was left at room temperature for 2 days. The same workup [*n*-hexane and ethyl acetate (20:1), column chromatography] gave adduct **18**: 644 mg (92%); yellow crystals; mp 168–169.5 °C (ether); mass spectrum, *m/e* 438 (M^+ + 4), 436 (M^+ + 2), 434 (M^+); IR (Nujol) 2080 (s), 1990 (s, $Fe(CO)_3$), 1640 (m, tropone CO) cm^{-1}. Anal. Calcd for $C_{14}H_8O_4Cl_4Fe$: C, 38.58; H, 1.39. Found: C, 38.55; H, 1.41.

Cycloaddition Reaction of 15 with 2. A solution of **15** (100 mg, 0.649 mmol) and **2** (400 mg, 1.724 mmol) in 3 mL of dry benzene was heated in a sealed tube at 80 °C for 30 h. The same workup [*n*-hexane and ethyl acetate (3:1), column chromatography] gave adduct **19**: 215 mg (86%); pale yellow crystals; mp 90–92 °C (methanol); mass spectrum, *m/e* 358 (M^+ – CO), 330 (M^+ – 2CO), 302 (M^+ – 3CO); IR (Nujol) 2070 (s), 1960 (s, $Fe(CO)_3$), 1760 (s, lactone), 1718 (s, ester) cm^{-1}. Anal. Calcd for $C_{17}H_{14}O_7Fe$: C, 52.88; H, 3.65. Found: C, 52.87; H, 3.66.

X-ray Crystallographic Study of the Complex 9. Suitable single crystals of the complex **9** were obtained by slow crystallization of a methanol–acetone solution. A crystal of the complex **9** with approximate dimensions 0.6 × 0.4 × 0.3 mm was mounted on a glass fiber with epoxy cement such that the longest crystal dimension was approximately parallel to the fiber axis.

Unit cell parameters and the orientation matrix were determined on a Syntex $P\bar{1}$ four-circle diffractometer equipped with a graphite monochromator and using Mo Kα radiation. Fifteen reflections whose 2θ values ranged from 6.0 to 24.1° were used in least-squares refinement of the lattic parameters and orientation matrix. Unit cell parameters obtained were a = 10.683 (4) Å, b = 12.527 (5) Å, c = 7.058 (2) Å, α = 94.98 (3)°, β = 101.10 (3)°, γ = 114.55 (3)°, and V = 828 (1) Å^3. The calculated density of 1.613 g cm^{-3} for two formula units per unit cell agrees with the experimental censity of 1.603 g cm^{-3} measured by the flotation method with a mixture of H_2O and KI. The space group $P\bar{1}$ was selected from the number of molecules per unit (Z = 2) and was later confirmed in the course of the structure refinement.

Intensity data were collected by using θ–2θ scans to a limit of 2θ = 50° with X-ray source and monochromator settings identical with those used for determination of the unit cell parameters. A variable scan rate from 24.0 to 4.0 min^{-1} was used. The 26 reflections whose peak-counting rate exceeded 5×10^4 counts/s were remeasured with a lower beam intensity to minimized counting losses. Three reflections, monitored at regular intervals during the data collection, showed no significant variation in intensity. Of 2937 independent reflections, 2679 were treated as observed ($I > 2.3\sigma(I)$). The intensities were corrected for Lorentz and polarization effects, but no correction was applied for absorption.

Observed structure factors were converted into normalized structure factor amplitudes. $|E|$ values, by use of the scale factor and overall temperature factor, were obtained from Wilson's statistics. The distribution of $|E|$ values indicated the centrosymmetric space group.

The structure was solved by the direct method using MULTAN 78.[15] An E map calculated with 500 signed E's ($|E| \geq 1.39$), which gave the combined figure of merit of 2.497, revealed the position of 25 of the nonhydrogen atoms. The position of the remaining one atom was located on a subsequent difference Fourier map. Six cycles of block-diagonal least-squares minimizing of $\sum w(|F_o| - k|F_c|)^2$ by varying the positions and isotropic vibrational amplitudes of the C, N, O, and Fe atoms led to R = 0.115. Seven further cycles of least-squares refinement of atomic parameters with anisotropic vibrational amplitudes for the C, N, O, and Fe atoms converged to R = 0.054. A difference Fourier map calculated at this stage revealed peaks of density appropriate to all hydrogen atoms. Keeping the vibrational amplitudes for the hydrogens fixed (B(H) = B(C) + 1.0 Å^2) and refining with anisotropic U's for all the C, N, O, and Fe atoms resulted in a final R of 0.038. The weighting schemes used were $w^{1/2}$ = 0 for the unobserved reflections and $w^{1/2} = 1/\sigma(F)$ for the observed ones, where $\sigma(F)$ was calculated for each reflection on the basis of counting statistics.

A final difference Fourier map revealed no significant features. The atomic scattering factors were taken from the literature.[16]

All the calculations were performed on the FACOM M-200 computer in the computer center of Kyushu University with the

(15) Main, P.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. "MULTAN 78, a System of Computer Programs for Automatic Solution of Crystal Structures from X-ray Diffraction Data"; University of York: York, England, 1978.

(16) "International Tables for X-ray Chrystallography"; Kynoch Press: Birmingham, England, 1975; Vol. 4.

universal crystallographic computation program system UNICS II.[17]

Registry No. 1b, 12193-69-0; **2**, 36343-88-1; **3**, 33614-96-9; **4**, 79814-94-1; **5**, 2166-14-5; **6**, 79792-50-0; **7**, 79770-04-0; **8**, 79770-05-1; **9**, 79802-89-4; **10**, 79770-06-2; **11**, 79792-51-1; **12**, 79792-52-2; **13**, 79770-07-3; **14**, 72448-17-0; **15**, 6018-41-3; **16**, 79792-53-3; **17**, 79792-54-4; **18**, 79792-55-5; **19**, 79802-90-7.

(17) (a) Sakurai, T.; Iwasaki, J.; Watanabe, Y.; Kobayashi, K.; Bando, Y.; Nakamichi, Y. *Rikagaku Kenkyusho Hookoku* **1974**, *50*, 75–91. (b) Kawano, S. *Koho, Computer Center of Kyushu University*, **1980**, *13*, 39–50.

Supplementary Material Available: Bond angles and their estimated standard deviations (Table VII), ^{13}C NMR spectral data of products **16–19** (Table VIII), atomic parameters (Table IX), and coordinates for hydrogen atoms (Table X) (4 pages). Ordering information is given on any current masthead page.

Pteridines. 49. Synthesis of 2,4-Diamino-6,8-dihydro-7-aryl-8-oxopyrrolo[3,4-*g*]pteridines[1a,b]

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Reaction of ethyl 4-chloro-2-oximino-3-oxobutyrate (**14**) with aminomalononitrile tosylate followed by deoxygenation of the resulting pyrazine 1-oxide provides 2-amino-6-carbethoxy-5-(chloromethyl)-3-cyanopyrazine (**11**). Treatment of **11** with arylamines gives 2-amino-5-[(arylamino)methyl]-6-carbethoxy-3-cyanopyrazines (**12**) which are readily cyclized to 1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazines (**13**). Condensation of **13** with guanidine acetate in dimethylformamide then provides the title compounds.

We have recently described the synthesis of a series of 2,4-diaminocycloalka[*g*]pteridines (**1**), many of which exhibited inhibitory activity against dihydrofolate reductase.[2] As a consequence, we have initiated a program directed toward the preparation of analogues of these compounds possessing additional structural features present in the potent antineoplastic agent methotrexate (**2**).[3] In particular, we have sought methods for the synthesis of analogues of **1** which incorporate an arylamino group in the fused aliphatic ring. We report here on a synthesis of the title compounds, 2,4-diamino-6,8-dihydro-7-aryl-8-oxopyrrolo[3,4-*g*]pteridines (**3a,b**), which bear an intriguing structural resemblance to rhizopterin (**4**)[4] and to the coenzyme N^{10}-formyltetrahydrofolic acid (**5**; Chart I).[3b]

In connection with other studies we had in hand both 2-amino-6-(carbomethoxy)-3-cyano-5-(dimethoxymethyl)pyrazine (**6**) and its corresponding *N*-oxide **7**,[5] which appeared to be well suited for further elaboration to pyrrolo[3,4-*g*]pteridines (see Scheme I). Both **6** and **7** were readily converted to the corresponding aldehydes **8** and **9** by treatment with 1 N HCl. Condensation of **9** with ethyl *p*-aminobenzoate in refluxing toluene containing a catalytic amount of *p*-TsOH gave the Schiff base **10**, but surprisingly, no imine could be prepared from **8**. Attempted reduction of **10** (sodium borohydride or sodium cyanoborohydride) led to complex mixtures of products as did attempted deoxygenation (phosphorus trichloride, sodium dithionite, or trimethyl phosphite), while reduction of **10** with Raney nickel gave an unstable compound of undetermined structure which rapidly decomposed on attempted isolation.

Since we had previously shown that 2-amino-3-cyano-5-(halomethyl)pyrazines readily alkylated aromatic amines to give 5-[(arylamino)methyl]pyrazines,[6] we investigated an alternate route to **3** utilizing pyrazine **12**, potentially available from **11** under similar conditions, as a precursor to 1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazines (**13**). The required starting material for the synthesis of **11**, ethyl 4-chloro-2-oximino-3-oxobutyrate (**14**), has been prepared by monochlorination of ethyl 2-oximino-3-oxobutyrate and described as a pale yellow oil used without further purification.[7] Since we anticipated difficulties in controlling the degree of chlorination in this reaction, an alternate synthesis was developed which involved oximation of ethyl 4-chloroacetoacetate (**15**) with nitrosyl chloride in dry THF; this procedure provided **14** in 53% yield as a colorless, low-melting solid. Although reaction of **14** with aminomalononitrile tosylate in 2-propanol[8] gave a complex mixture of products, condensation in the presence of a catalytic amount of HCl gave the pyrazine *N*-oxide **16** in 53% yield. Deoxygenation with trimethyl phosphite[9] then provided **11** in 77% yield.

As anticipated, reaction of **11** with methyl *p*-aminobenzoate in acetonitrile solution in the presence of potassium carbonate readily gave the desired [(arylamino)methyl]pyrazine **12a** (76%), which was quantitatively converted to the 1,3-dihydro-1-oxopyrrolo[3,4-*b*]pyrazine

(1) (a) For the previous paper in this series, see Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1981**, *46*, 1394–1402. (b) We are indebted to F. Hoffmann-La Roche & Co., Ltd., and to the National Cancer Institute, National Institutes of Health (Grant 1 ROC CA28351), for support of this work. (c) Recipient of an American Can Co. Predoctoral Fellowship.

(2) Taylor, E. C.; Berrier, J. V.; Cocuzza, A. J.; Kobylecki, R.; McCormack, J. J. *J. Med. Chem.* **1977**, *20*, 1215–1218.

(3) For reviews of the medicinal chemistry of methotrexate and its analogues, see (a) Jaffe, N.; Howell, S. In "Advances in Cancer Chemotherapy"; Rosowsky, A., Ed.; Marcel Dekker: New York, 1979; pp 111–142. (b) Pratt, W. B.; Ruddon, R. W. "The Anticancer Drugs"; Oxford University Press: Oxford, 1979; pp 98–113.

(4) Wolf, D. E.; Anderson, R. C.; Kaczka, E. A.; Harris, S. A.; Arth, G. E.; Southwick, P. L.; Mozingo, R.; Folkers, K. *J. Am. Chem. Soc.* **1947**, *69*, 2753–2759.

(5) Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1980**, *45*, 2485–2489.

(6) Taylor, E. C.; Portnoy, R. C.; Hochstetler, D. C.; Kobayashi, T. *J. Org. Chem.* **1975**, *40*, 2347–2351.

(7) Hatanaka, M.; Ishimaru, T. *J. Med. Chem.* **1973**, *16*, 978–984.

(8) Under the same conditions, β-chloropyruvaldoxime readily provides 2-amino-3-cyano-5-(chloromethyl)pyrazine 1-oxide: Taylor, E. C.; Kobayashi, T. *J. Org. Chem.* **1973**, *38*, 2817–2821.

(9) Dirlam, J. P.; McFarland, J. W. *J. Org. Chem.* **1977**, *42*, 1360–1364.

0022-3263/82/1947-0116$01.25/0