[Chem. Pharm. Bull. 33(11)4723—4731(1985)]

Reaction of Heteroaromatic Analogs of Homophthalic Anhydride: Synthesis of Hetero Analogs of *peri*-Hydroxy Polycyclic Aromatic Compounds, Isocoumarins, Isoquinolinones, and Related Compounds

YASUYUKI KITA, SHIN-ICHIRO MOHRI, TERUHISA TSUGOSHI, HATSUO MAEDA, and YASUMITSU TAMURA*

Faculty of Pharmaceutical Sciences, Osaka University, 1–6, Yamadaoka, Suita, Osaka 565, Japan

(Received March 4, 1985)

The reactions of heterohomophthalic anhydrides, 3-carboxy-1-methylindole-2-acetic anhydride (**4**), 2-carboxybenzo[*b*]furan-3-acetic anhydride (**5**), 2-carboxythiophene-3-acetic anhydride (**6**), and 3-carboxy-1,4-dimethylpyrrole-2-acetic anhydride (**23**) with carbon–carbon multiple bonds (C=C and C≡C), acylating agents, and cyclic imines are described. Treatment of the anhydrides (**4**—**6**) with various compounds containing carbon–carbon multiple bonds (**7**—**10**) in the presence of a strong base caused cycloaddition with spontaneous extrusion of carbon dioxide to give the corresponding linearly condensed *peri*-hydroxy heteroaromatic compounds (**11**—**19**), regioselectively. Base-catalyzed acylation of **4** with acetic anhydride and *β,β*-dimethylacryloyl chloride gave 3,5-dimethylpyrano[4,3-*b*]indol-1(5*H*)-one (**21**) and 3,3,11-trimethyl-3,4-dihydropyrano[4′,3′:2,3]-pyrano[4,5-*b*]indole-1,6(11*H*)-dione (**22**), respectively. Reaction of the anhydrides (**4**, **6**, and **23**) with 3,4-dihydroisoquinoline (**24**) gave the corresponding condensation products, 14-carboxy-13-methyl-5,6,14,14a-tetrahydrobenz[*a*]indolo[3,2-*g*]quinolizin-8(13*H*)-one (**25**), 12-carboxy-5,6,12,-12a-tetrahydrobenzo[*a*]thieno[2,3-*g*]quinolizin-8-one (**26**) and 12-carboxy-11-methyl-5,6,12,12a-tetrahydrobenzo[*a*]pyrrolo[3,2-*g*]quinolizin-8(11*H*)-one (**27**), in high yields.

Keywords——heterohomophthalic anhydride; regiospecific cycloaddition; heteroaromatic orthoquinodimethane; polycyclic *peri*-hydroxy heteroaromatic compound; pyranoindole; benz[*a*]-indolo[3,2-*g*]quinolizinone; benzo[*a*]thieno[2,3-*g*]quinolizinone; benzo[*a*]pyrrolo[3,2-*g*]quinolizinone

Homophthalic anhydrides (**1**) are very important intermediates in organic synthesis because they have two active sites toward nucleophiles (C_1 and C_3 positions) and another active site toward electrophiles (C_4 position). They have been used for the construction of various types of compounds, such as isoquinolinones,[1] isocoumarins,[2] phthalazines,[3] and

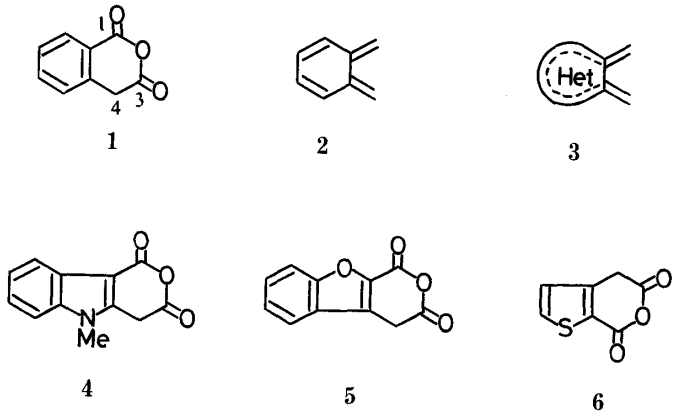


Fig. 1

peri-hydroxy polycyclic aromatic compounds,[4] leading to alkaloids, antibiotics, and pharmacologically important compounds. In a recent communication, we have briefly reported[5] the cycloaddition reaction of heteroaromatic analogs of **1** leading to polycyclic *peri*-hydroxy heteroaromatic compounds, and we now give a full account of this work and additional studies concerning the reaction of **1** with acylating agents and cyclic imines.

Cycloaddition of Heterohomophthalic Anhydrides (4—6) with Carbon–Carbon Multiple Bonds (7—10)

Since the utilization of so-called orthoquinodimethane intermediates (**2**) is well established for the annulation of polycyclic aromatics, including alkaloids, steroids, and terpenes,[6] the application to heteroaromatic systems is quite attractive for the synthesis of polycyclic heteroaromatic compounds such as indole, benzofuran, and thiophene derivatives. Many methods have been devised for the generation of **2**, but few routes are applicable to the heteroaromatic orthoquinodimethanes (**3**).[7] In the case of indole-2,3-orthoquinodimethanes, a [1,5]-sigmatropic shift of 2-alkyl-3-vinylindole[8] or 3-alkyl-2-vinyl-indole[9] and a 1,4-elimination from the fluoride ion-induced benzylsilane fragmentation[10] have been explored recently. The generation of benzofuran- and thiophene-2,3-orthoquinodimethanes has not appeared in the literature, and furanoic homologs of **2** have been generated only by a flash vacuum thermolysis of the corresponding tetrahydrofurans.[11] In the past few years, we have developed the strong base-induced cycloaddition of **1** *via* the orthoquinodimethane-like intermediates and its application to an efficient synthesis of polycyclic *peri*-hydroxy aromatic compounds including anthracyclinones and antibiotic SS-228R.[4] We have now applied this method to the synthesis of various types of polycyclic *peri*-hydroxy indole-, benzofuran-, and thiophene compounds from 3-carboxy-1-methylindole-2-acetic anhydride (**4**), 2-carboxybenzo[*b*]furan-3-acetic anhydride (**5**), and 2-carboxythiophene-3-acetic anhydride (**6**) in a single step.

Generally, the anhydrides (**4—6**) were deprotonated by treatment with NaH in tetrahydrofuran (THF) under mild conditions and reacted with 1.0—1.2 eq of dienophiles (**7—10**) to give considerable yields of the corresponding linearly condensed adducts (**11—19**). A

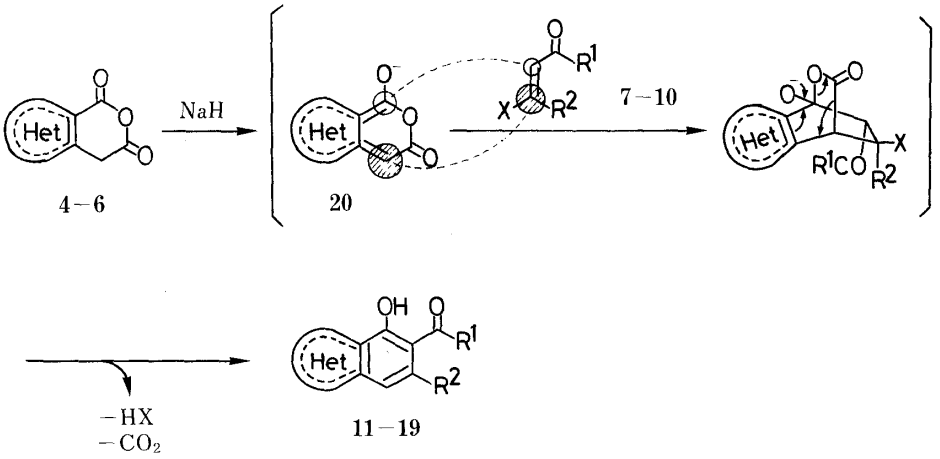
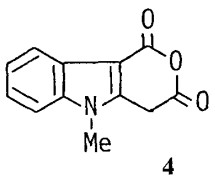
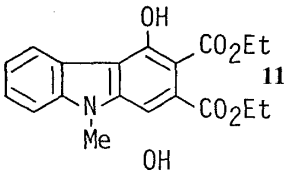
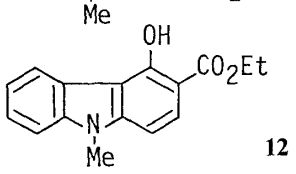
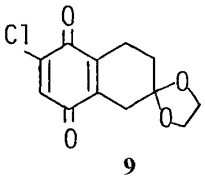
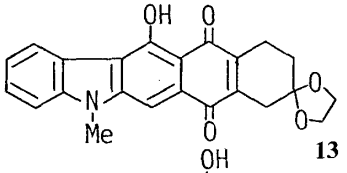
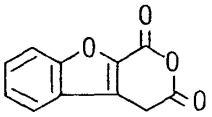
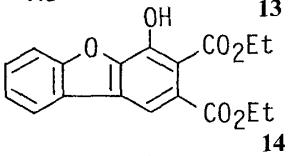
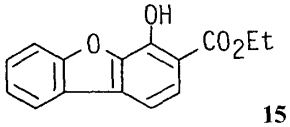
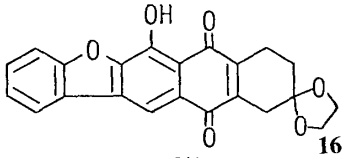
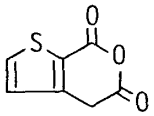
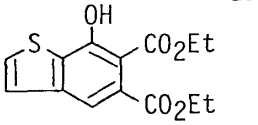
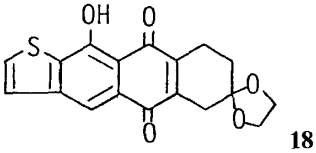
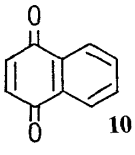
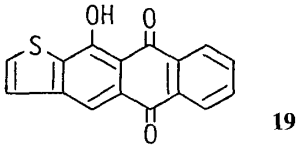


Chart 1

typical experimental procedure is as follows for the reaction of **4** with diethyl acetylenedicarboxylate (**7**). After deprotonation of **4** by treatment with NaH in THF at room temperature for several minutes, a THF solution of **7** was added to the mixture, and the whole was stirred for 3 h under the same conditions to give 2,3-diethoxycarbonyl-4-hydroxy-9-methylcarbazole (**11**). The structures of all unknown compounds (**11—19**) were determined on the basis of microanalyses and infrared (IR), proton nuclear magnetic resonance (^{1}H-

TABLE I. Results of Cycloaddition Reactions of Heterohomophthalic Anhydrides (**4**—**6**)

Run	Starting anhydrides	Dienophiles	Reaction conditions	Products	Yield (%)
1	 **4**	$EtO_2C-C\equiv C-CO_2Et$ **7**	r.t., 3 h	 **11**	45
2	**4**	$EtO_2C-C\equiv CH$ **8**	Reflux, 4.5 h	 **12**	21
3	**4**	 **9**	Reflux, 5 h	 **13**	27
4	 **5**	**7**	r.t., 3 h	 **14**	76
5	**5**	**8**	Reflux, 5 h	 **15**	17
6	**5**	**9**	r.t., 0.5 h	 **16**	31
7	 **6**	**7**	r.t., 2 h	 **17**	67
8	**6**	**9**	r.t., 5 h	 **18**	28
9	**6**	 **10**	r.t., 1 h	 **19**	60

r.t., room temp.

NMR), and mass spectral (MS) data.

The cycloaddition occurred regioselectively in that the nucleophilic end (C_4-position) of the heteroaromatic orthoquinodimethane-like intermediate (**20**) reacted at the electrophilic site of the dienophiles, as observed in the reaction with ethyl propiolate or haloquinone (Runs 2, 3, 5, 6, and 8). The regiochemistry is well explained by the frontier orbital theory:[12] since both the nucleophilic site (C_4-position) of **20** and the electrophilic site of dienophiles have

large coefficients in this normal electron-demand Diels–Alder reaction (reaction of a diene having an electron-donating group and a dienophile having an electron-withdrawing group), the carbon–carbon bond formation occurs regioselectively in this way.

The reaction conditions, products and yields of the products (**11**—**19**) are summarized in Table I.

Reaction of 3-Carboxy-1-methylindole-2-acetic Anhydride (4) with Some Acylating Agents

Base-catalyzed acylation of the reactive methylene (C_4-position) of **1** with acetic, propionic, and butyric anhydrides[13] or β,β-dimethylacryloyl chloride[14] is known to give 3-alkylisocoumarins or 3,3-dimethyl-1(1*H*)-oxo-3,4-dihydropyrano[4,3-*c*]isocoumarin. We have examined the reaction of **4** with acetic anhydride and β,β-dimethylacryloyl chloride in pyridine, and found that the reaction proceeded similarly to give moderate yields of the heteroaromatic analogs (**21** and **22**) of the above isocoumarins as visualized in Chart 2. The structures of **21** and **22** were supported by their microanalyses and IR, NMR, and MS data.

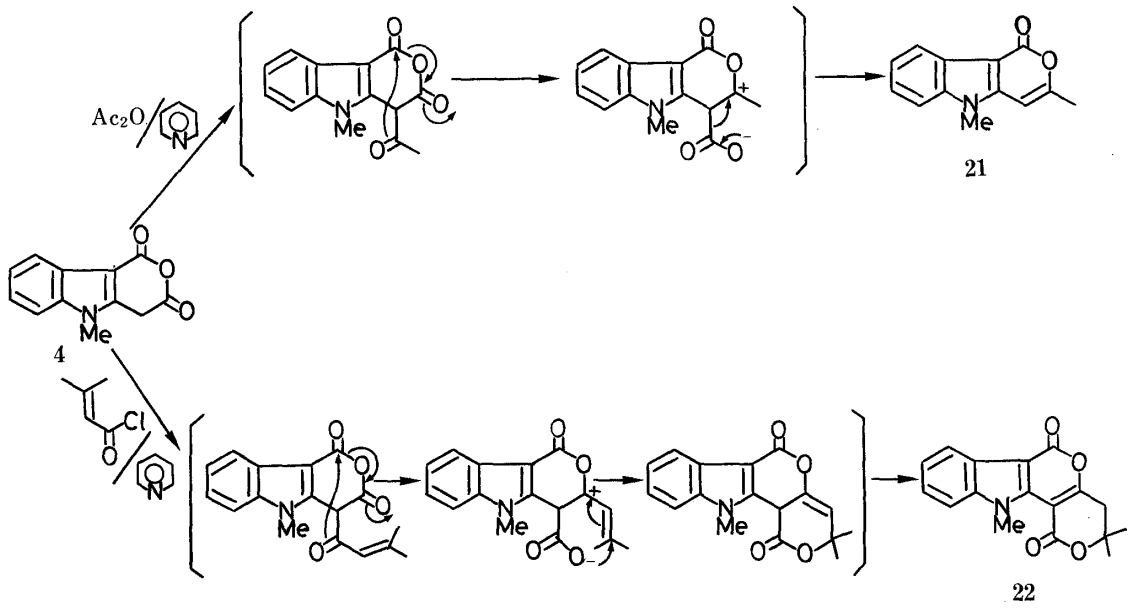
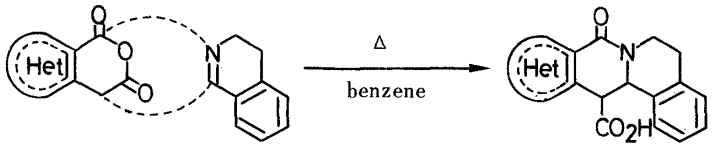


Chart 2

Condensation Reaction of Heterohomophthalic Anhydrides (4, 6, and 23) with 3,4-Dihydroisoquinoline (24)

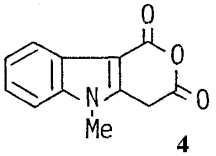
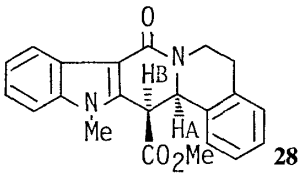
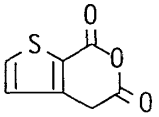
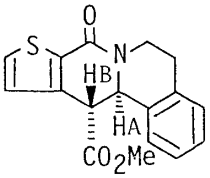
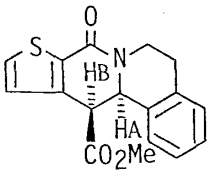
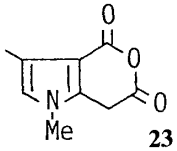
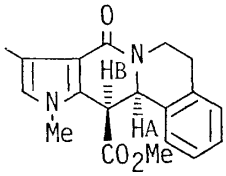
The reaction of **1** with cyclic imines has been shown to afford 3,4-dihydro-1(2*H*)-isoquinolinones, berbin-8-ones, hexahydroyohimbane-21-ones, and 5,6-dihydro-8*H*-dibenzo[*a*,*g*]-quinolizine-8-ones, and was applied to the synthesis of protoberberine and benzophenanthridine alkaloids.[15] In this work, we investigated the reaction of structurally similar heterohomophthalic anhydrides (**4**, **6**, and **23**) with a typical cyclic imine, 3,4-dihydroisoquinoline (**24**). Treatment of the anhydride **4** with **24** in refluxing benzene for a few hours gave 14-carboxy-13-methyl-5,6,14,14a-tetrahydrobenz[*a*]indolo[3,2-*g*]quinolizin-8-(13*H*)-one (**25**). Other anhydrides (**6** and **23**) reacted similarly with **24** to give the corresponding annulated compounds (**26** and **27**) (Chart 3). The assignment of the stereochemistry was made based on NMR studies of their methyl esters (**28**—**30**) and comparison of the coupling constants with those ($J_{A,B}$)[1,16] of related *cis* and *trans* isomers. Thermodynamically more stable *cis* diastereomers (**28**$_{cis}$; $J_{A,B}=4$ and **30**$_{cis}$; $J_{A,B}=5$ Hz) were obtained in the case of indole and pyrrole systems, and the *trans* isomer (**29**$_{trans}$; $J_{A,B}=9$ Hz) in the case of the



4,6,23 24 25—27

Chart 3

TABLE II. Condensation Reaction of Heterohomophthalic Anhydrides (**4**, **6**, and **23**)

Run	Starting anhydrides	Reaction conditions	Products	Yield (%)
1	 **4**	i) In benzene, reflux, 2 h ii) CH_2N_2	 **28**	78
2	 **6**	i) In benzene, reflux, 0.5 h ii) CH_2N_2	 $\mathbf{29}_{trans}$	71
3	**6**	i) In benzene, reflux, 1 h ii) In benzene, AcOH, reflux, 18 h iii) CH_2N_2	 $\mathbf{29}_{cis}$	63
4	 **23**	i) In benzene, reflux, 2 h ii) CH_2N_2	 $\mathbf{30}_{cis}$	78

thiophene system, though the *cis* isomer ($\mathbf{29}_{cis}$; $J_{A,B}=5$ Hz) could be obtained by refluxing the benzene solution of **6** and **24** for a long period in the presence of acetic acid. The reaction conditions and yields of the methylated produts (**28**—**30**) are summarized in Table II.

Spectral data for all unknown compounds (**6**, **11**—**19**, and **21**—**30**) are listed in Table III.

Experimental

All melting points are uncorrected. IR absorption spectra were recorded on a JASCO IRA-1 spectrometer, and ^{1}H-NMR spectra on a Hitachi R-22 (90 MHz), or JEOL JNM-FX 90Q FT-NMR (90 MHz) spectrometer (with tetramethylsilane as an internal standard). Low- and high-resolution MS were obtained with a JEOL JMS D-300 instrument, with a direct inlet system. For column chromatography, E. Merck Silica-gel (0.063—0.200 mm, 70—230 mesh ASTM) was used.

The starting anhydrides, **4**[17] and **5**[18] were prepared by the reported methods.

2-Carboxythiophene-3-acetic Anhydride (6)——Acetyl chloride (3.3 ml) was added to a solution of 2-

TABLE III. Spectral Data for Unknown Compounds

Compounds	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
6	1785, 1730[a]	4.24 (2H, s), 7.21 (1H, d, J=5 Hz), 8.09 (1H, d, J=5 Hz)[b]
11	3500—3100, 1740, 1675	1.40 (3H×2, t, J=8 Hz), 3.80 (3H, s), 4.35 (2H, q, J=8 Hz), 4.38 (2H, q, J=8 Hz), 6.92 (1H, s), 7.15—7.45 (3H, m), 8.3—8.45 (1H, m), 11.87 (1H, s)
12	3500—3100, 1660	1.43 (3H, t, J=7 Hz), 3.79 (3H, s), 4.40 (2H, q, J=7 Hz), 6.79 (1H, d, J=9 Hz), 7.25—7.45 (3H, m), 7.86 (1H, d, J=9 Hz), 8.37 (1H, dd, J=7, 2 Hz), 11.81 (1H, s)
13	3500—3100, 1650, 1630, 1620, 1600	1.8—2.0 (2H, m), 2.75—3.6 (4H, m), 3.92 (3H, s), 4.05 (4H, s), 7.3—7.55 (3H, m), 7.70 (1H, s), 8.35—8.5 (1H, m), 13.47 (1H, s)
14	3450—3100, 1725, 1675	1.40 (3H×2, t, J=7 Hz), 4.35 (2H, q, J=7 Hz), 4.41 (2H, q, J=7 Hz), 7.3—7.75 (3H, m), 7.55 (1H, s), 7.85—8.0 (1H, m), 11.11 (1H, s)
15	3400—3050, 1675	1.45 (3H, t, J=7 Hz), 4.44 (2H, q, J=7 Hz), 7.3—8.0 (4H, m), 7.38 (1H, d, J=9 Hz), 7.81 (1H, d, J=9 Hz), 11.31 (1H, s)
16	3400—3050, 1640, 1615	1.75—2.0 (2H, m), 2.75—3.0 (4H, m), 4.04 (4H, s), 7.3—7.75 (3H, m), 7.9—8.05 (1H, m), 8.18 (1H, s), 12.73 (1H, s)
17	3600—2600, 1720 1665	1.35 (3H×2, t, J=7 Hz), 4.32 (2H, q, J=7 Hz), 4.37 (2H, q, J=7 Hz), 7.28 (1H, d, J=5 Hz), 7.37 (1H, s), 7.63 (1H, d, J=5 Hz), 11.65 (1H, s)
18	3500—3100, 1650, 1635, 1605	1.8—2.0 (2H, m), 2.7—3.0 (4H, m), 4.01 (4H, s), 7.40 (1H, d, J=5 Hz), 7.69 (1H, d, J=5 Hz), 8.00 (1H, s), 13.24 (1H, s)
19	3700—2700, 1660, 1625, 1590	7.48 (1H, d, J=5 Hz), 7.65—7.85 (3H, m), 8.27 (1H, s), 8.2—8.4 (2H, m), 13.83 (1H, s)
21	1710, 1630	2.36 (3H, s), 3.70 (3H, s), 6.24 (1H, s), 7.2—7.5 (3H, m), 8.05—8.25 (1H, m)
22	1735, 1715	1.59 (3H×2, s), 3.04 (2H, s), 4.07 (3H, s), 7.25—7.5 (3H, m), 8.05—8.3 (1H, m)
23	1775, 1730[a]	2.27 (3H, s), 3.53 (3H, s), 3.87 (2H, s), 6.40 (1H, s)
25$_{cis}$	3200—2300,[a] 1725, 1590	[c]
26$_{trans}$	3600—2600,[a] 1720, 1600	2.7—3.4 (3H, m), 4.16 (1H, d, J=9 Hz), 4.5—4.8 (1H, m),[d] 5.55 (1H, d, J=9 Hz), 6.95—7.25 (5H, m), 7.41 (1H, d, J=4 Hz), 11.20 (1H, s)
27$_{cis}$	3600—2300,[a] 1720, 1595	[c]
28$_{cis}$	3100—2800, 1740, 1640	2.5—3.0 (1H, m), 3.0—3.45 (2H, m), 3.70 (3H, s), 3.72 (3H, s), 4.54 (1H, d, J=4 Hz), 4.65—4.95 (1H, m), 5.49 (1H, d, J=4 Hz), 6.9—7.35 (7H, m), 8.0—8.25 (1H, m)
29$_{trans}$	3000—2800, 1735, 1635	2.8—3.2 (3H, m), 3.78 (3H, s), 4.05 (1H, d, J=9 Hz), 4.6—4.9 (1H, m), 5.41 (1H, d, J=9 Hz), 6.83 (1H, d, J=5 Hz), 7.0—7.3 (4H, m), 7.45 (1H, d, J=5 Hz)
29$_{cis}$	3150—2800, 1735 1630	2.65—3.25 (3H, m), 3.28 (3H, s), 4.27 (1H, d, J=5 Hz), 4.65—4.95 (1H, m), 5.24 (1H, d, J=5 Hz), 6.96 (1H, d, J=5 Hz), 7.05—7.3 (4H, m), 7.44 (1H, d, J=5 Hz)
30$_{cis}$	3000—2800, 1735, 1630	2.21 (3H, s), 2.6—3.2 (3H, m), 3.48 (3H, s), 3.72 (3H, s), 4.21 (1H, d, J=5 Hz), 4.6—5.0 (1H, m), 5.36 (1H, d, J=5 Hz), 6.24 (1H, s), 7.0—7.3 (4H, m)

a) Measured in KCl disc. *b*) Measured in acetone-d_6. *c*) Insoluble in $CDCl_3$. *d*) Measured in pyridine-d_5 : $CDCl_3$ (2:5).

carboxythiophene-3-acetic acid[19] (220 mg, 1.18 mmol) in dioxane (22 ml). The mixture was heated at reflux for 2 h and concentrated *in vacuo* to give a quantitative yield of **6**, which was used for the next reaction without purification. Recrystallization from benzene gave pure **6**, mp 138—140 °C. *Anal.* Calcd for $C_7H_4O_3S$: C, 50.00; H, 2.40. Found: C, 50.06; H, 2.35.

General Procedure for the Cycloaddition of Heterohomophthalic Anhydrides (4—6) to Dienophiles (7—10)——A mixture of the anhydride (1 mmol) and NaH (60% in mineral oil, 1 mmol) in anhydrous THF (29 ml) was stirred at room temperature for several minutes, then a solution of dienophile (1 mmol) in anhydrous THF (2 ml) was added. The reaction mixture was stirred under the conditions indicated in Table I, then quenched with saturated aqueous

NH_4Cl (5 ml) and partitioned between 5% hydrochloric acid (5 ml) and methylene chloride (59 ml). The organic layer was washed with saturated aqueous NaCl (10 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using benzene, chloroform, or benzene–ether as the eluting solvent to give the corresponding adduct.

2,3-Diethoxycarbonyl-4-hydroxy-9-methylcarbazole (11)——This was prepared from **4** (54 mg, 0.25 mmol) and **7** (43 mg, 0.25 mmol). Recrystallization from ligroin gave pure **11**, mp 130.5 °C. *Anal.* Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.90; H, 5.55; N, 4.16.

3-Ethoxycarbonyl-4-hydroxy-9-methylcarbazole (12)——This was prepared from **4** (54 mg, 0.25 mmol) and **8** (25 mg, 0.25 mmol). Recrystallization from ligroin gave pure **12**, mp 132—133 °C. Exact mass Calcd for $C_{16}H_{15}NO_3$: 269.1051. Found: 269.1061.

9,9-Ethylenedioxy-13-hydroxy-5-methyl-8,9,10,11-tetrahydronaphtho[2,3-*b*]carbazole-7,12-dione (13)——This was prepared from **4** (54 mg, 0.25 mmol) and **9** (64 mg, 0.25 mmol). Recrystallization from benzene–*n*-hexane gave pure **13**, mp 273—275 °C. Exact mass Calcd for $C_{23}H_{18}NO_5$: 389.1261. Found: 389.1261.

2,3-Diethoxycarbonyl-4-hydroxydibenzofuran (14)——This was prepared from **5** (51 mg, 0.25 mmol) and **7** (43 mg, 0.25 mmol). Recrystallization from ligroin gave pure **14**, mp 132 °C. Exact mass Calcd for $C_{18}H_{16}O_6$: 328.0946. Found: 328.0946.

3-Ethoxycarbonyl-4-hydroxydibenzofuran (15)——This was prepared from **5** (51 mg, 0.25 mmol) and **8** (25 mg, 0.25 mmol). Recrystallization from ligroin gave pure **15**, mp 128 °C. Exact mass Calcd for $C_{15}H_{12}O_4$: 256.0736. Found: 256.0746.

10,10-Ethylenedioxy-6-hydroxy-8,9,10,11-tetrahydroanthra[2,3-*b*]benzofuran-7,12-dione (16)——This was prepared from **5** (32 mg, 0.16 mmol) and **9** (40 mg, 0.16 mmol). Recrystallization from benzene gave pure **16**, mp 233—235 °C. *Anal.* Calcd for $C_{22}H_{18}O_6$: C, 70.21; H, 4.28. Found: C, 70.13; H, 4.14.

5,6-Diethoxycarbonyl-7-hydroxybenzo[*b*]thiophene (17)——This was prepared from **6** (30 mg, 0.18 mmol) and **7** (31 mg, 0.18 mmol). Recrystallization from methylene chloride-*n*-hexane gave pure **17**, mp 78—79 °C. *Anal.* Calcd for $C_{14}H_{14}O_5S$: C, 57.13; H, 4.80. Found: C, 57.48; H, 4.83.

7,7-Ethylenedioxy-11-hydroxy-6,7,8,9-tetrahydroanthra[2,3-*b*]thiophene-5,10-dione (18)——This was prepared from **6** (60 mg, 0.36 mmol) and **9** (91 mg, 0.36 mmol). Recrystallization from chloroform gave pure **18**, mp 253—255 °C. Exact mass Calcd for $C_{18}H_{14}O_5S$: 342.0559. Found: 342.0533.

11-Hydroxyanthra[2,3-*b*]thiophene-5,10-dione (19)——This was prepared from **6** (60 mg, 0.36 mmol) and **10** (57 mg, 0.36 mmol). Recrystallization from chloroform gave pure **19**, mp 274—275 °C. *Anal.* Calcd for $C_{16}H_8O_3S$: C, 68.56; H, 2.88. Found: C, 68.55; H, 2.89.

3,5-Dimethylpyrano[4,3-*b*]indole-1(5*H*)-one (21)——A mixture of **4** (300 mg, 1.4 mmol), pyridine (0.1 ml), and acetic anhydride (10 ml) was heated at reflux for 30 min, then cooled, and the resulting solid was collected. Recrystallization of the solid from acetonitrile gave a 71% yield (212 mg) of pure **21**, mp 229—230 °C (lit.[17] 223—224 °C). *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.42; H, 5.14; N, 6.61.

3,3,11-Trimethyl-3,4-dihydropyrano[4′,3′:2,3]pyrano[4,5-*b*]indole-1,6(11*H*)-dione (22)——A mixture of **4** (300 mg, 1.4 mmol), β,β-dimethylacryloyl chloride (249 mg, 2 mmol) and dry pyridine (0.5 ml) was heated at reflux for 3 h, then cooled, diluted with ether (5 ml), and shaken. A clean brown solid was obtained by filtration. Additional product was obtained from the ether extract by washing it with 1 N hydrochloric acid and then evaporating off the ether. Purification of the combined crude solid by column chromatography on silica gel (with ethyl acetate–*n*-hexane as the eluting solvents) gave a 41% yield (170 mg) of **22**, mp 229—230 °C. *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.50; H, 5.04; N, 4.66.

3-Carboxy-1,4-dimethylpyrrole-2-acetic Anhydride (23)——A mixture of 3-carboxy-1,4-dimethylpyrrole-2-acetic acid[20] (788 mg, 4 mmol) and acetic anhydride (4.8 ml) was heated at 160 °C for 3 min, then cooled, and the resulting solid was collected. The solid was washed with *n*-hexane to give **23** in 84% yield (600 mg). This product was used for the next reaction without purification. Exact mass Calcd for $C_9H_9NO_3$: 179.0580. Found: 179.0569.

General Procedure for the Condensation of Heterohomophthalic Anhydrides (4, 6, and 23) with 3,4-Dihydroisoquinoline (24)——A solution of the anhydride (1 mmol) and **24** (1 mmol) in benzene (3 ml) was refluxed for the period indicated in Table II, then cooled to 10 °C, and the resulting crystals were collected and washed with *n*-hexane to give the condensation product.

***cis*-14-Carboxy-13-methyl-5,6,14,14a-tetrahydrobenz[*a*]-indolo[3,2-*g*]quinolizin-8(13*H*)-one (25_{cis})**——This was prepared from **4** (215 mg, 1.0 mmol) and **24** (131 mg, 1.0 mmol). Recrystallization from methanol gave pure **25**, mp 187—189 °C. *Anal.* Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.55; H, 5.15; N, 7.81.

***trans*-12-Carboxy-5,6,12,12a-tetrahydrobenzo[*a*]thieno[2,3-*g*]quinolizin-8-one (26_{trans})**——This was prepared from **6** (70 mg, 0.41 mmol) and **24** (54 mg, 0.41 mmol). Recrystallization from methanol gave pure **26**, mp 187—190 °C. *Anal.* Calcd for $C_{16}H_{13}NO_3S$: C, 64.20, H, 4.38; N, 4.68. Found: C, 64.46; H, 4.29; N, 4.49.

***cis*-12-Carboxy-11-methyl-5,6,12,12a-tetrahydrobenzo[*a*]-pyrrolo[3,2-*g*]quinolizin-8(11*H*)-one (27_{cis})**——This was prepared from **23** (90 mg, 0.5 mmol) and **24** (79 mg, , 0.6 mmol). Recrystallization from methanol gave pure **27**, mp 199—201 °C. Exact mass Calcd for $C_{18}H_{18}N_2O_3$: 310.1317. Found: 310.1345.

General Procedure for the Methylation of the Condensation Products (25—27)——A solution of the condensation

product (0.5 mmol) in ethyl acetate (25 ml) was slowly added to a solution of diazomethane (*ca.* 0.5 g) in ether (10 ml) at 0 °C. After 2 h at 0 °C, the excess diazomethane was evaporated off by bubbling nitrogen through the solution (under a hood), and the solvent was evaporated off to give a residue, which was purified by column chromatography on silica gel or by recrystallization to give the pure methyl ester.

***cis*-14-Methoxycarbonyl-13-methyl-5,6,14,14a-tetrahydrobenz[*a*]indolo[3,2-*g*]quinolizin-8(13*H*)-one (28_{cis})**——This was prepared from **25** (200 mg, 0.58 mmol). Recrystallization from benzene–*n*-hexane gave pure **28**, mp 174—177 °C. *Anal.* Calcd for $C_{22}H_{20}N_2O_3$: C, 73.31; H, 5.58; N, 7.77. Found: C, 73.15; H, 5.53; N, 7.71.

***trans*-12-Methoxycarbonyl-5,6,12,12a-tetrahydrobenzo[*a*]-thieno[2,3-*g*]quinolizin-8-one (29_{trans})**——This was prepared from **26** (60 mg, 0.2 mmol). Purification by column chromatography on silica gel (with ether and benzene as the eluting solvents) gave **29**, which was recrystallized from benzene–*n*-hexane to give an analytical sample, mp 144—145 °C. *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 65.15; H, 4.83; N, 4.47. Found: C, 64.76; H, 4.76; N, 4.40.

***cis*-12-Methoxycarbonyl-5,6,12,12a-tetrahydrobenzo[*a*]-thieno[2,3-*g*]quinolin-8-one (29_{cis})**——A solution of **6** (84 mg, 0.50 mmol) and **24** (66 mg, 0.50 mmol) in benzene (2 ml)) was refluxed for 1 h, then cooled to room temperature. Acetic acid (1 ml) was added to the solution, and the reaction mixture was heated at reflux for 18 h and concentrated *in vacuo* to give an oil. The residual oil was taken up in ethyl acetate (25 ml) and added to a solution of diazomethane (*ca.* 0.5 g) in ether (10 ml) at 0 °C. Work-up as described for the general procedure gave a pure sample of $\mathbf{29}_{cis}$ as a syrup. Exact mass Calcd for $C_{17}H_{15}NO_3S$: 313.0773. Found: 313.0779.

***cis*-12-Methoxycarbonyl-9,11-dimethyl-5,6,12,12a-tetrahydrobenzo[*a*]pyrrolo[3,2-*g*]quinolizin-8(11*H*)-one (30_{cis})**——This was prepared from **27** (80 mg, 0.26 mmol). Purification by column chromatography on silica gel (with ether and benzene as the eluting solvents) gave **30**, which was recrystallized from benzene–*n*-hexane to give an analytical sample, mp 215—216 °C. Exact mass Calcd for $C_{19}H_{20}N_2O$: 324.1473. Found: 324.1478.

References and Notes

1) M. A. Haimova, N. M. Mollov, S. C. Ivanova, A. I. Dimitrova, and V. I. Ognyanov, *Tetrahedron*, **33**, 331 (1977); M. Cushman, J. Gentry, and F. W. Dekow, *J. Org. Chem.*, **42**, 1111 (1977); M. A. Haimova, V. I. Ognyanov, and N. M. Mollov, *Synthesis*, **1980**, 845; M. Cushman, T.-C. Choong, J. T. Valko, and M. P. Koleck, *J. Org. Chem.*, **45**, 5067 (1980); G. M. Coppola, *J. Heterocyl. Chem.*, **18**, 767 (1981); M. Cushman, A. Abbaspour, and Y. P. Gupta, *J. Am. Chem. Soc.*, **105**, 2873 (1983); M. Cushman, P. Mohan, and E. C. R. Smith, *J. Med. Chem.*, **27**, 544 (1984).
2) E. Muller, *Justus Liebigs Ann. Chem.*, **491**, 251 (1931); J. Knabe and K. Schaller, *Arch. Pharm.* (Weinheim. Ger.), **300**, 62 (1967) [*Chem. Abstr.*, **67**, 2970*y* (1967)]; W. Diekmann, *Ber. Dtsch. Chem. Ges.*, **47**, 1428 (1914); K. Nozawa, M. Yamada, Y. Tsuda, K. Kawai, and S. Nakajima, *Chem. Pharm. Bull.*, **29**, 2491, 3486 (1981).
3) K. D. Deodhar and S. D. Deval, *Synthesis*, **1983**, 421.
4) Y. Tamura, A. Wada, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, **22**, 4283 (1981); *idem, Chem. Pharm. Bull.*, **31**, 2691 (1983); Y. Tamura, A. Wada, M. Sasho, K. Fukunaga, H. Maeda, and Y. Kita, *J. Org. Chem.*, **47**, 4376 (1982); Y. Tamura, M. Sasho, K. Nakagawa, T. Tsugoshi, and Y. Kita, *ibid.*, **49**, 473 (1984); Y. Tamura, M. Sasho, S. Akai, A. Wada, and Y. Kita, *Tetrahedron*, **40**, 4539 (1984); Y. Kita and Y. Tamura, *Yuki Gosei Kagaku Kyokai Shi*, **42**, 860 (1984); Y. Tamura, F. Fukata, M. Sasho, T. Tsugoshi and Y. Kita, *J. Org. Chem.*, **50**, 2273 (1985).
5) Y. Tamura, S. Mohri, H. Maeda, T. Tsugoshi, M. Sasho, and Y. Kita, *Tetrahedron Lett.*, **25**, 309 (1984).
6) For general reviews of orthoquinodimethanes in synthesis, see: T. Kametani and K. Fukumoto, *Heterocycles*, **3**, 29 (1975); W. Oppolzer, *Synthesis*, **1978**, 793; J. J. McCullough, *Account. Chem. Res.*, **13**, 270 (1980); R. L. Funk and K. P. C. Vollhardt, *Chem. Soc., Reviews*, **9**, 41 (1980); and references cited therein.
7) For a review, see: C. Kaneko and T. Naito, *Heterocycles*, **19**, 2183 (1982).
8) J. Bergman and R. Carlsson, *Tetrahedron Lett.*, **1977**, 4663.
9) S. Kano, E. Sugino, S. Shibuya, and S. Hibino, *J. Org. Chem.*, **46**, 2979 (1981).
10) E. R. Marinelli, *Tetrahedron Lett.*, **23**, 2745 (1982); *cf.* G. Hugel and J. Levy, *Tetrahedron*, **39**, 1539 (1983). Other analogues of indole-2,3-quinodimethane, see: H. Plieninger, W. Muller, and K. Weinerth, *Chem. Ber.*, **97**, 667 (1964); M. G. Saulnier and G. W. Gribble, *Tetrahedron Lett.*, **24**, 5435 (1983); *idem, J. Chem. Soc., Chem. Commun.*, **1984**, 168; C. J. Moody, *ibid.*, **1984**, 925; C. May and C. J. Moody, *ibid.*, **1984**, 926; C.-K. Sha, K.-S. Chuang, and J.-J. Young, *ibid.*, **1984**, 1552. Magnus has recently reported an intermolecular indole-2,3-quinodimethane cyclization that gives fused pentacyclic compounds, and this reaction has been applied to an efficient and elegant synthesis of (+)-aspidospermidine, see: P. Magnus "Strategies and Tactics in Organic Synthesis," ed. by T. L. Lindberg, Academic Press, Inc., New York, 1984, p. 83.
11) J. Jullien, J. M. Pechine, F. Perez, and J. J. Piade, *Tetrahedron Lett.*, **1979**, 3079; *idem, ibid.*, **21**, 611 (1980).
12) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975); I. Fleming, "Frontier Orbital and Organic Chemical Reactions," John Wiley & Sons Ltd., London, 1976, p. 86.
13) R. B. Tirodkar and R. N. Usgaonkar, *J. Ind. Chem. Soc.*, **46**, 935 (1969); *idem, Ind. J. Chem.*, **8**, 123 (1970); *idem, ibid.*, **16B**, 320 (1978); *idem, ibid.*, **10**, 1060 (1972); *idem, Curr. Sci.*, **41**, 679 (1972).

14) D. R. Nadkarni and R. N. Usgaonkar, *Ind. J. Chem.*, **19B**, 253 (1980).
15) C. K. Yu, D. B. MacLean, R. G. A. Rodrigo, and R. H. F. Manske, *Can. J. Chem.*, **48**, 3673 (1970); M. Cushman and F. W. Dekow, *Tetrahedron*, **34**, 1435 (1978).
16) By analogy with related protoberberines, the NMR spectrum of the *trans* isomer is expected to display a larger coupling constant between protons H_A and H_B than the corresponding *cis* diastereomer and the *cis* isomer is expected to be thermodynamically more stable: see G. R. Lens, *J. Org. Chem.*, **41**, 2201 (1976); T. Kametani, T. Takahashi, T. Honda, K. Ogasawara, and K. Fukumoto, *ibid.*, **39**, 447 (1974); T. R. Govindachari, K. Nagarajan, R. Charubaba, B. R. Pai, and P. S. Subramanian, *Ind. J. Chem.*, **8**, 769 (1970).
17) G. A. Bahadur, A. S. Bailey, N. W. Middleton, and J. M. Peach, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1688.
18) J. N. Chatterjea and R. P. Sahai, *J. Ind. Chem. Soc.*, **57**, 633 (1980).
19) D. E. Ames and O. Ribeiro, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1390.
20) J. R. Carson and S. Wong, *J. Med. Chem.*, **16**, 172 (1973).