Novel Polycyclic Heterocycles. XIV. Diels-Alder Adducts of 11,12-Dihydropyrido[2,1-*b*][1,3]benzodiazepine, 6*H*-Pyrido[1,2-*c*][1,3,5]-benzoxadiazepines, and 6*H*-Pyrido[1,2-*c*][1,3,5]benzothiadiazepine and their Hydrogenation Products (1)

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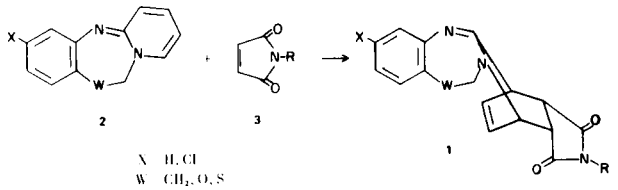
Pentacyclic heterocycles of the general structure **1** have been prepared from their precursor tricyclic derivatives, **2**, and a maleimide, **3**. The reactions were carried out in xylene, under reflux, and were monitored by tlc; the times required for the tricycles, **2**, to react completely, varied from 16 hours to 6 days.



2 3 1

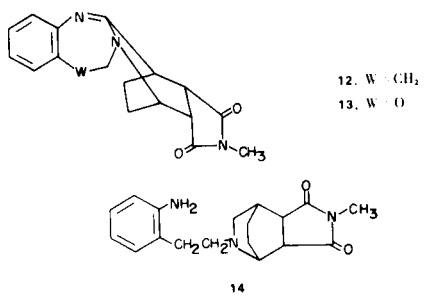
X = H, Cl
W = CH_2, O, S

Derivatives of 1:

4. W = CH_2, X = H, R = CH_3
6. W = O, X = H, R = CH_3
9. W = O, X = Cl, R = CH_3
10. W = O, X = H, R = Ph
11. W = S, X = H, R = CH_3

X-Ray crystallographic analysis was carried out on a single crystal of one compound, **9** (**1**, X = Cl, R = CH_3) (4), in order to establish (a) its intrinsic structure (5) and (b) that the *endo*-adduct had formed (6).

The catalytic hydrogenation of either **4** or **6** over Raney nickel at 50 psi and ambient temperature ceased after the absorption of one molar equivalent of hydrogen and gave the 4,13-ethano derivatives, **12** and **13**, respectively; over platinum, under the same conditions with **4**, three molar equivalents of hydrogen were absorbed and resulted in both hydrogenation of the 4,13-etheno linkage as well as hydrogenolysis of the 11,12-carbon-nitrogen bond to give **14**.



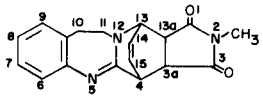
12. W = CH_2
13. W = O

14

EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated oil bath and are uncorrected. The ir spectra were obtained on mineral oil mulls, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on deuteriochloroform, deuterium oxide, or DMSO-d_6 solutions with a Perkin-Elmer R12B or a Varian Associates XL-100-15 spectrophotometer. The uv spectra were determined in methanol on a Cary 15 recording spectrophotometer. The mass spectra were obtained by Dr. P. T. Funke on an AEI-MS902 spectrometer operating at 70 eV, using a direct-insertion technique, with a probe temperature of 140-180°. The microanalyses were carried out by Mr. J. F. Alicino and his associates.

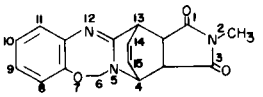
3a,4,10,11,13,13a-Hexahydro-2-methyl-4,13-etheno-1*H*-pyrrolo-[3′,4′:4,5]pyrido[2,1-*b*][1,3]benzodiazepine-1,3(2*H*)dione, **4**.



A solution of 1.96 g. (0.01 mole) of 11,12-dihydropyrido-[2,1-*b*][1,3]benzodiazepine, **5**, (1), 1.68 g. (0.015 mole) of *N*-methylmaleimide, **6**, and 50 ml. of xylene was heated under nitrogen and under anhydrous conditions for 23 hours. Only after this time period, did tlc [methanol:chloroform (5:95) on alumina] show the absence of **5** and a single major spot with R_f 0.9; in this system, **5** had R_f 0.7. The tan-colored adduct that crystallized from the black reaction mixture weighed 3.07 g., m.p. 216-218°. Recrystallization from 50 ml. of toluene gave 2.04 g. (66% yield) of **4**, m.p. unchanged at 216-218°; ir: ν 1775 (m), 1690 (s), 1620 (s), 1605 (m), 1585 (s), 1480 (m), 1450 (s), 1425 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.75-3.10 (m, 5H, N-C*H*$_3$, 10-C*H*$_2$), 3.15-3.60 (m, 2H, 3a-*H*, 13a-*H*), 3.60-3.95 (m, 2H, 11-C*H*$_2$), 4.13 [q (J = 2.5, 6.0 Hz), 1H, 4-*H*], 4.31 [q (J = 2.5, 6.0 Hz), 1H, 13-*H*], 6.46 [t (J = 3.5 Hz), 2H, 14-*H* plus 15-*H*], 6.80-7.40 (m, 4H, 4 Ar-*H*); uv: λ 283 nm (ϵ, 13,800).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.42; H, 5.58; N, 13.69. Found: C, 70.40; H, 5.57; N, 13.48.

3a,4,13,13a-Tetrahydro-2-methyl-4,13-etheno-1*H*,6*H*-pyrrolo-[3′,4′:4,5]pyrido[1,2-*c*][1,3,5]benzoxazepine-1,3(2*H*)dione, **7**.



A solution of 1.98 g. (0.01 mole) of 6*H*-pyrido[1,2-*c*][1,3,5]-benzoxazepine, **8** (1), 1.68 g. (0.015 mole) of **6**, and 50 ml. of xylene were reacted for 23 hours, as described for **4**. During the heating period there was a progressive increase in the amount of yellow solid that separated. The product was filtered and washed repeatedly with fresh portions of boiling xylene, and then dried *in vacuo*. The yield of **7** was 2.43 g. (79%), m.p. 252-253°; ir: ν 1775 (m), 1690 (s), 1635 (s), 1605 (m), 1585 (s), 1475 (s), 1465 (m), 1445 (m), 1435 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.87 (s, 3H, N-C*H*$_3$), 3.37 [q (J = 3.0, 6.0 Hz), 1H, 3a-*H* or 13a-*H*], 3.44 [q (J = 3.0, 6.0 Hz), 1H, 13a-*H* or 3a-*H*], 4.12 [q (J = 4.0, 6.0 Hz), 1H, 13-*H*], 4.53 [q (J = 4.0, 6.0 Hz), 2H, 14-*H*, 15-*H*], 4.95 [q (J = 8.0, 16.0 Hz), 2H, O-C*H*$_2$], 6.80-7.50 (m, 4H, 4 Ar-*H*); uv: λ 225 (sh), 288, 297 nm (ϵ, 12,750, 13,850, 13,100).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.07; H, 4.89; N, 13.59. Found: C, 65.79; H, 5.12; N, 13.48.

10-Chloro-3a,4,13,13a-tetrahydro-2-methyl-4,13-etheno-1*H*,6*H*-pyrrolo[3′,4′:4,5]pyrido[1,2-*c*][1,3,5]benzoxadiazepine-1,3(2*H*)-dione, **9**.

The reaction between 0.58 g. (0.0025 mole) of 2-chloro-6*H*-pyrido[1,2-*c*][1,3,5]benzoxadiazepine (1) and 0.41 g. (0.0037 mole) of **6**, in 30 ml. of xylene required 6 days for completion. The yield of **9** was 0.60 g., m.p. 250-251°; ir: ν 1890 (w), 1765 (m), 1685 (s), 1635 (s), 1585 (m), 1570 (s), 1535 (m), 1510 (w), 1465 (s), 1445 (s) cm^{-1}; pmr (DMSO-d_6): δ 2.76 (s, 3H, N-C*H*$_3$), 3.10-4.00 (m, 3H, 3a-*H*, 13-*H*, 13a-*H*), 4.70-5.05 (m, 1H, 4-*H*), 5.11 [q (J = 8.0, 10.0 Hz), 2H, O-C*H*$_2$], 6.35-6.70 (m, 2H, 14-*H*, 15-*H*), 6.85-7.30 (m, 3H, 3 Ar-*H*).

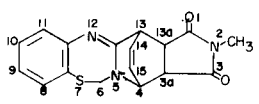
Anal. Calcd. for $C_{17}H_{14}ClN_3O_3$: C, 59.35; H, 4.10; N, 12.22; Cl, 10.31. Found: C, 59.39; H, 4.30; N, 12.38; Cl, 10.45.

3a,4,13,13a-Tetrahydro-2-phenyl-4,13-etheno-1*H*,6*H*-pyrrolo-[3′,4′:4,5]pyrido[1,2-*a*][1,3,5]benzoxadiazepine-1,3(2*H*)dione, **10**.

A solution of 1.98 g. (0.01 mole) of **8**, 2.07 g. (0.012 mole) of *N*-phenylmaleimide, and 80 ml. of xylene was heated under reflux for 21 hours. The crude product, 3.50 g. was recrystallized from 250 ml. of toluene to give 1.56 g. of **10**, m.p. 243-244°; ir: ν 1775 (w), 1705 (s), 1645 (s), 1605 (m), 1590 (m), 1495 (s), 1480 (s), 1455 (s), 1440 (s), 1415 (m) cm^{-1}; pmr (deuteriochloroform): δ 3.56 [q (J = 8.0, 14.0 Hz), 1H, 3a-*H* or 13a-*H*], 3.61 [q (J = 7.0, 12.0 Hz), 1H, 13a-*H* or 3a-*H*], 4.05-4.40 (m, 1H, 13-*H*), 4.50-4.85 (m, 1H, 4-*H*), 5.01 [q (J = 10.0, 14.0 Hz), 2H, OC*H*$_2$], 6.62 [t (J = 3.5 Hz), 2H, 14-*H*, 15-*H*], 6.83-7.62 (m, 9H, 9 Ar-*H*).

Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.22; H, 4.62; N, 11.33. Found: C, 71.40; H, 4.88; N, 11.17.

3a,4,13,13a-Tetrahydro-2-methyl-4,13-etheno-1*H*,6*H*-pyrrolo-[3′,4′:4,5]pyrido[1,2-*c*][1,3,5]benzothiadiazepine-1,3(2*H*)dione, **11**.



A solution of 0.80 g. (0.0037 mole) of 6*H*-pyrido[1,2-*c*][1,3,5]-benzothiadiazepine (1), 0.60 g. (0.0054 mole) of **5**, and 30 ml. of xylene was heated under reflux for 16 hours to give 1.03 g. of crude product. Recrystallization from 200 ml. of toluene gave 0.60 g. of **11**, m.p. 285-287° dec.; ir: ν 1765 (m), 1685 (s), 1625 (s), 1610 (s), 1575 (s), 1450 (s), 1440 (s), 1420 (m) cm^{-1}; pmr (deuteriochloroform): δ 2.85 (s, 3H, N-C*H*$_3$), 3.35 [q (J = 4.0, 8.0 Hz), 1H, 13a-*H* or 3a-*H*], 3.57 [q (J = 4.0, 8.0 Hz), 1H, 3a-*H* or 13a-*H*], 4.10 [q (J = 4.0, 8.0 Hz), 1H, 13-*H*], 4.38 [q (J = 4.0, 8.0 Hz), 1H, 4-*H*], 4.60 (s, 2H, S-C*H*$_2$), 6.46 (t, 2H, 14-*H*, 15-*H*), 6.72-7.30 (m, 4H, 4 Ar-*H*).

Anal. Calcd. for $C_{17}H_{15}N_3O_2S$: C, 62.82; H, 4.65; N, 12.93; S, 9.87; m/e, 325. Found: C, 62.94; H, 4.59; N, 13.14; S, 9.85; m/e, 325.

3a,4,10,11,13,13a-Hexahydro-2-methyl-4,13-ethano-1*H*-pyrrolo-[3′,4′:4,5]pyrido[2,1-*b*][1,3]benzodiazepine-1,3(2*H*)dione, Hydrochloride, Monohydrate, **12**.

To 1.53 g. (0.005 mole) of **4** in 100 ml. of methanol was added *ca.* 1 g. of pyrophoric Raney nickel (stored under water but leached repeatedly with methanol prior to use). Hydrogen uptake, 0.005 mole, at an initial pressure of 50 psi and ambient temperature required 0.33 hours. The filtered solution was concentrated to dryness, the solid residue was dissolved in 2-propanol, and the solution treated with an excess of 2-propanolic hydrogen chloride. The crystalline product was filtered and recrystallized from 500 ml. of 2-propanol to give 1.18 g. (65% yield) of **12**, sinters at 320°, melts at 344-347°; ir: ν 3400 (broad, m), 1780 (m), 1685 (s), 1635 (s), 1595 (m), 1575 (s), 1540 (w), 1500 (s) cm^{-1}; pmr (DMSO-d_6): δ 1.50-1.90 (m, 5H, 13-*H*, 14-C*H*$_2$, 15-C*H*$_2$), 2.91 (s, 3H, N-C*H*$_3$), 3.10-4.50 (overlapping multiplets, 9H, 3a-*H*, 4-*H*, 6-C*H*$_2$, 7-C*H*$_2$, *H*$_2$O, 13a-*H*), 7.15-7.90 (m, 4H, 4 Ar-*H*).

Anal. Calcd. for $C_{19}H_{19}N_3O_2 \cdot HCl \cdot H_2O$: C, 59.39; H, 6.09; N, 11.55; Cl, 9.69; m/e, 309. Found: C, 59.84; H, 6.43; N, 11.59; Cl, 9.64; m/e, 309.

3a,4,13,13a-Tetrahydro-2-methyl-4,13-ethano-1*H*,6*H*-pyrrolo-[3′,4′:4,5]pyrido[1,2-*c*][1,3,5]benzoxadiazepine-1,3(2*H*)dione, **13**.

To 1.54 g. (0.005 mole) of **6** in 150 ml. of methanol was added *ca.* 1 g. of pyrophoric Raney nickel and the whole hydrogenated as with **12**. The yield of **13**, after recrystallization from 40 ml. of toluene, was 1.11 g. (71%), m.p. 222-224°; ir: ν 1770 (w), 1760 (w), 1685 (s), 1615 (s), 1585 (s), 1475 (m), 1430 (s) cm^{-1}; pmr (deuteriochloroform): δ 1.47-2.00 (m, 5H, 13-*H*, 14-*H*, 15-C*H*$_2$), 3.00 (s, 3H, N-C*H*$_3$), 3.25 (broad s, 2H, 3a-*H*, 13a-*H*), 3.89 (broad s, 1H, 4-*H*), 5.05 (s, 2H, O-C*H*$_2$), 6.80-7.35 (m, 4H, 4 Ar-*H*).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.65; H, 5.51; N, 13.51; m/e, 311. Found: C, 65.38; H, 5.63; N, 13.41; m/e, 311.

5-[2-(2-Aminophenyl)ethyl]hexahydro-2-methyl-4,7-ethano-1*H*-pyrrolo[3,4-*c*]pyridine-1,3(2*H*)dione, Hydrochloride, **14**.

Hydrogenation at 50 psi of a mixture of 2.30 g. (0.0075 mole) of **4**, 0.5 g. of platinum oxide in 150 ml. of methanol at ambient temperature ceased spontaneously after 0.67 hour when 0.0225 moles of hydrogen had been absorbed. Workup of the reaction mixture gave the *base*, 2.00 g. as a viscous oil. The oil, 1.77 g. in 80 ml. of acetonitrile was treated with an excess of 2-propanolic hydrogen chloride. The solid that separated was filtered and dried; it weighed 2.14 g. Recrystallization from 210 ml. of 82% ethanol-18% water gave 1.06 g. (47% yield) of **14**, sinters at 250°, melts at 275-277° dec.; ir: ν 2610-2660 (w), 2380 (broad, w), 2020 (m), 1970 (w), 1775 (m), 1685 (s), 1620 (w), 1580 (m), 1565 (m), 1525 (m) cm^{-1}. The pmr spectrum of **14** in deuterium oxide was poorly resolved and was difficult to interpret and integrate; it consisted of overlapping multiplets (δ 1.40-4.20) and two singlets [δ 3.05 (N-C*H*$_3$) and δ 7.52 (Ar-*H*)].

Anal. Calcd. for $C_{18}H_{23}N_3O_2 \cdot 2\,HCl$: C, 56.01; H, 6.55; N, 10.89; Cl, 18.37; m/e, 313. Found: C, 56.28; H, 6.58; N, 10.91; Cl, 18.26; m/e, 313.

REFERENCES

(1) The synthesis of the tricyclic intermediates employed in these Diels-Alder reactions has been reported previously; *cf.* R. B. Petigara and H. L. Yale, *J. Heterocyclic Chem.*, 11, 331 (1974).

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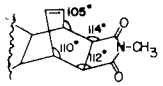
(4) The X-ray crystallographic studies were carried out by Dr. J. Z. Gougoutas and Mrs. B. Toeplitz. They report that the crystals of **9** belong to the triclinic space group $P\bar{1}$; the unit cell constants were a = 13.00, b = 8.21, c = 7.46 Å, α = 76.9, β = 91.7 and γ = 91.2°; and, the density, by flotation, was 1.4724 g/cm^3. There were two molecules in the unit cell. Search for the chlorine atom on the Patterson map gave ambiguous results, hence a direct method approach resulting in an E map was employed. Both molecules in the unit cell were plotted, but they proved to be symmetry related. The final R factor, with no least squares refinement, was 0.156. The pertinent angles of the *endo*-adduct are shown below. Analysis



of the pmr spectrum of **9** was done by Dr. M. S. Puar. The protons at positions-3a and -13a, with a coupling constant of 3.5 Hz are probably *cis*. The coupling constant between the protons at position-4 and -13 is 7-8 Hz, and their stereochemistry relative to the protons at positions-3a and -13a cannot be assigned at this time.

(5) Compounds of the general structure **2** possess *two* conjugated diene systems, -C=C-C=C- and -C=C-C=N-; there are, however, no reports in the literature of 1,4-cycloaddition reactions involving the latter system, *cf.* J. Hamer, "1,4-Cycloaddition Reactions. The Diels-Alder Reaction in Heterocyclic Syntheses," Academic Press, N.Y., N.Y., 1967, pp. 180-200.

(6) While the *endo*-adduct is the product of the Diels-Alder reaction as it is usually carried out, *i.e.* at the lowest practical temperature and for the shortest possible time, the *exo*-form is considered to be thermodynamically more stable; hence, under the prolonged heating times (16 hours to 6 days) under reflux, at *ca.* 130°, employed in the present study, the *exo*-isomer should have accumulated at the expense of the initially formed *endo*-adduct. *cf.* L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., N.Y., N.Y., 1961, p. 207.