allowed to stand for 3–4 hr. Removal of the ether and excess ethylenimine *in vacuo* gave 19.8 g. (97%) of a thick oil which solidified in the refrigerator.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. VIII. Bicyclic Nitriles and Related Compounds.[1,2] I

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Thirteen new compounds available from Diels-Alder reactions involving fumaronitrile, maleonitrile, acrylonitrile, and tetracyanoethylene as dienophiles and cyclopentadiene, cyclohexadiene, cycloheptadiene, and cyclooctatetraene as dienes are reported. Maleonitrile adds to cyclohexadiene in the *endo* sense.

In the course of a study directed toward examination of various aspects of rearrangements and other reactions of functionally substituted bicyclic hydrocarbons derivable *via* the Diels-Alder synthesis from 1,3-cycloalkadienes and mono- and difunctional dieneophiles, the adduct of furmaronitrile (I)[3-5] and cyclohexadiene[6] was prepared.

The ready accessibility of analogs of this substance prompted us to prepare a series of related compounds, inasmuch as substances of this type have not as yet been examined for possible anticancer activity.

Four nitrile-dieneophiles have been used in the present study: fumaronitrile (I), maleonitrile (II)[7] acrylonitrile (III), and ethylenetetracarbonitrile (tetracyanoethylene) (IV).[8]

Thus far four cyclic dienes have been used for the preparation of new compounds: cyclopentadiene (V), cyclohexadiene (VI), cycloheptadiene (VII), and cyclooctatetraene (VIII).

From the reaction series beginning with III and V the following compounds were prepared: bicyclo[2.2.1]hep-5-ene-2-carbonitrile (X),[4,9] bicyclo[2.2.1]heptane-2-carbonitrile (XI),[9] and the phenyl azide adduct of X (3a, 4,5,6,7,7a-hexahydro-1-phenyl-2,7-methano-benzotriazol-5(or 6)carbonitrile (XII)).[10,11] The new compound, *N*-phenyl-5,6-iminobicyclo[2.2.1]heptane-2-carbonitrile (XIII),[12] was prepared by heating XII to expel nitrogen.

In an attempt to reduce the nitrile group of XI catalytically there was obtained, instead of the expected product,[13] *N*,*N*-bis-2-norbornanemethylamine hydrochloride (XIV).

While the simple adducts of IV with V (bicyclo[2.2.1]hept-5-ene-2,2,3,3-tetracarbonitrile (XV[14])), and with VI (bicyclo[2.2.2]-oct-5-ene-2,2,3,3-tetracarbonitrile, XVI[14]), were both known, their hydrogenation products, bicyclo[2.2.1]heptane-2,2,-3,3-tetracarbonitrile (XVII) and bicyclo[2.2.2]octane-2,2,3,3-tetracarbonitrile (XVIII) are herein reported for the first time.

Reaction of I with VI has not been previously reported. Accordingly, the initial adduct, bicyclo-

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(1) Previous paper in this series, Robert C. Elderfield and R. Stanley McElhinney, *J. Org. Chem.*, 25, 1917 (1961).

(2) Work supported in part by Research Grant CY-2961 from the National Cancer Institute to The University of Michigan, and in part by an Institutional Grant to The University of Michigan (IN-40A) from the American Cancer Institute.

(3) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, 10, 149 (1945).

(4) This compound has been previously examined for toxicity and activity against sarcoma, carcinoma, and myeloid leukemia in mice and was found to be inactive. *Cf.* E. M. Gal, F. Fung, and D. M. Greenberg, *Cancer Res.*, 12, 565 (1952).

(5) A gift of a small sample of fumaronitrile from the Monsanto Chemical Company is gratefully acknowledged. Further supplies were prepared by James Hudson of this laboratory.

(6) A. T. Blomquist and J. Kwiatek, *J. Am. Chem. Soc.*, 73, 2098 (1951).

(7) Prepared by James Hudson of this laboratory.

(8) Generously supplied by the E. I. du Pont de Nemours & Co. Laboratories.

(9) The *endo* and *exo* isomers were not separated. See K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, 91, 1516 (1958).

(10) K. Alder, H. Krieger, and H. Weiss, *Chem. Ber.*, 88, 144 (1955).

(11) Possible positional isomerism of the nitrile group in this compound renders the structure ambiguous. No attempt has been made to resolve this ambiguity. Likewise, the stereochemistry of the azide addition is ambiguous, although addition *cis* to the methylene bridge of XX is probable on steric grounds.

(12) The stereochemistry of the ethyleneimine system is equivocal. If one accepts the suggested *exo*-configuration for the nitrogen portion of the precursor, XII, the configuration in XIII is probably *exo* also.

(13) Reduction of bicyclo[2.2.2]octane-2-carbonitrile[9] afforded the primary 2-aminomethylbicyclo[2.2.2]octane hydrochloride as reported.[10]

(14) W. J. Middleton, R. E. Heckert, E. L. Little, and C. G. Grespan, *J. Am. Chem. Soc.*, 73, 2783 (1958).

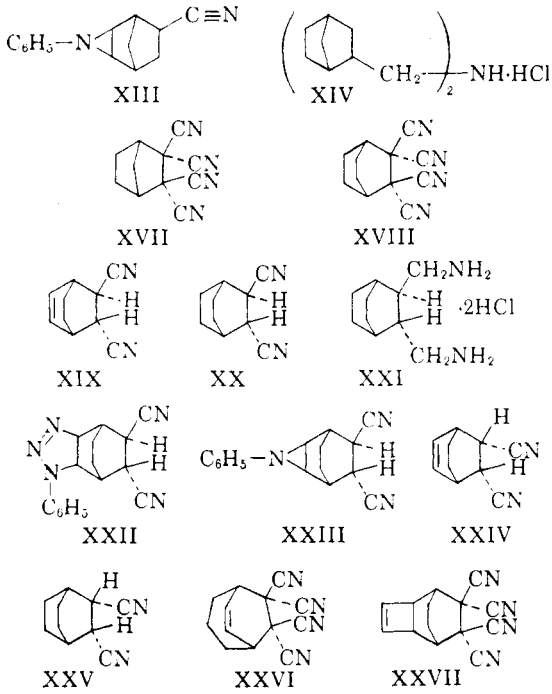

Fig. 1. New Compounds.

[2.2.2]oct-5-ene-*trans*-2,3-dicarbonitrile (XIX), bicyclo[2.2.2]octane-*trans*-2,3-dicarbonitrile (XX), prepared by catalytic hydrogenation from XIX, and *trans*-2,3-bisaminomethylbicyclo[2.2.2]octane dihydrochloride (XXI), prepared by reduction of XX, constitute a new series of bicycloalkane derivatives. The phenyl azide adduct of XIX, 3a,4,5,6,7,7a-hexahydro-1-phenyl-4,7-ethano-1*H*-benzotriazole-*trans*-5,6-dicarbonitrile (XXII), and the corresponding ethylenimine, *N*-phenyl-5,6-iminobicyclo[2.2.2]octane-*trans*-2,3-dicarbonitrile (XXIII) have also been prepared.

The adduct of II with VI, at low temperature, has been prepared (XXIV). Mild hydrolysis of XXIV afforded a lactone-acid (infrared bands at 1779 cm.$^{-1}$ and 1700 cm.$^{-1}$), thus demonstrating that the reaction between II and VI follows the Alder rule of *endo* addition,[15] as the *exo*-adduct could not hydrolyze and then cyclize to a γ-lactone. Under the same conditions, the *trans*-dinitrile (XIX) yielded an isomeric compound, indicating that epimerization on hydrolysis did not occur. The hydrogenation product of XXIV, bicyclo-[2.2.2]-octane-*cis*-2,3-dicarbonitrile (XXV) was also prepared.

The adducts of IV with VII, bicyclo[3.2.2]non-8-ene-6,6,7,7-tetracarbonitrile(XXVI), and with VIII, 5,6-ethenobicyclo[2.2.2]oct-7-ene-2,2,3,3-tetracarbonitrile (XXVII)[16] are reported.

The thirteen new compounds, XIII, XIV, and XVII through XXVII have been submitted to the Cancer Chemotherapy National Service Center of the National Institutes of Health for screening as candidate anticancer drugs, and the synthesis of further analogs of these and related Diels-Alder adducts and their derivatives is currently in progress. Results of the chemotherapeutic investigation will be reported elsewhere.

(15) K. Alder and O. Stein, *Angew. Chem.*, **50**, 510 (1937).

EXPERIMENTAL[17,18]

N-Phenyl-5,6- iminobicyclo[2.2.1]heptane-2-carbonitrile. (XIII). A sample (12.4 g., 0.052 mole) of 3a,4,5,6,7,7a-hexahydro-1-phenyl-4,7-methano-1*H*-benzotriazol-5(or 6)-carbonitrile[10] (XII) was heated at 160–170° for 20 hr. At the end of this period the moderate evolution of nitrogen had completely ceased, leaving a tarry residue. This material afforded 8.5 g. (77.9%) of viscous oil, b.p. 227–230°/22 mm. Redistillation at 144–145°/0.25 mm. afforded a colorless oil.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.70. Found: C, 79.95; H, 6.63.

trans-2,3-Bisaminomethylbicyclo[2.2.2]octane dihydrochloride (XXI). A solution of 10.9 g. (0.0674 mole) of XX in 180 ml. of anhydrous ether and 80 ml. of benzene was added dropwise, with stirring, to a solution of 2.90 g. (0.0766 mole) of lithium aluminohydride in 100 ml. of anhydrous ether. The reaction mixture refluxed gently throughout the addition, which required 20 min., and stirring was continued for 0.5 hr. longer. Next 6.0 ml. of water was added cautiously and then 4.5 ml. of 10% sodium hydroxide, and stirring was continued for 3 hr. After filtration the solution was dried for 20 hr. over sodium hydroxide and then was treated with anhydrous hydrogen chloride for 1 hr., whereupon 13.2 g. (81.4%) of XXI precipitated. It was recrystallized from 95% ethanol, 328° dec. in a sealed capillary.

Anal. Calcd. for $C_{10}H_{22}Cl_2N_2$: C, 49.79; H, 9.20; N, 11.62. Found: C, 50.05; H, 9.20; N, 11.66.

Attempts to isolate the free amine afforded only a solid, m.p. 124–126° dec., which evolved carbon dioxide on treatment with dilute hydrochloric acid.

3a,4,5,6,7,7a-Hexahydro-1-phenyl-4,7-ethano-1H-benzotriazole-trans-5,6-dicarbonitrile (XXII). To 7.9 g. (0.050 mole) of XIX dissolved in 50 ml. of chloroform was added 7.1 g. (0.060 mole) of phenylazide[19] and the mixture was refluxed on a water bath for 2 weeks. On cooling to 0° the product precipitated, and three additional crops were obtained on concentration: yield, 6.8 g. (49%). The crude XXII was thrice recrystallized from methanol to give pure XXII, m.p. 175° dec.

Anal. Calcd. for $C_{16}H_{15}N_5$: C, 69.29; H, 5.45. Found: C, 69.46; H, 5.51.

N-Phenyl-5,6-iminobicyclo[2.2.2]octane-trans-2,3-dicarbonitrile (XXIII). A 2.1-g. sample (0.0072 mole) of XXII was heated at 160–170° for 15 hr. The tarry crude product was taken up in boiling ethyl acetate, treated with activated charcoal, and after addition of petroleum ether (b.p. 60–75°), allowed to crystallize. A 1.3-g. sample (75.5%) of crude XXIII, m.p. 157–159° was obtained. Five crystallizations from petroleum ether (b.p. 60–75°) yielded pure XXIII, m.p. 167–168°.

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.07. Found: C, 76.88; H, 6.15.

(16) The structure assigned is analogous to that established for the maleic anhydride–cyclooctatetraene adduct. See W. Reppe, O. Schlichting, K. Klager, and T. Toepel, *Ann.*, **560**, 1 (1948).

(17) Melting points are uncorrected. Infrared spectra recorded from Nujol mulls on a Model 21 Perkin-Elmer Spectrophotometer.

(18) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(19) L. I. Smith (ed.), *Org. Syntheses*, **22**, 96 (1942).

TABLE I

DIELS-ALDER REACTIONS[a]

Dienophile, Moles	Diene, Moles	Solvent, Ml.	Time, Hr.	Product, %	M.P. (Solvent)		Anal. Calcd.	Anal. Found[18]
I, 0.050	VI, 0.103	Xylene, 20	13	XIX, 74.5	145–146° 2:1 petroleum ether[b]–ethyl acetate	$C_{10}H_{10}N_2$	C, 75.92 H, 6.37 N, 17.71	C, 76.01 H, 6.46 N, 17.58
II, 0.038	VI, 0.063	Abs. ethanol, 10	2[c]	XXIV, 56.1	207–208° 2:1 95% ethanol–ethyl acetate	$C_{10}H_{10}N_2$	C, 75.92 H, 6.37	C, 75.76 H, 6.43
IV, 0.042	VII, 0.042	Benzene, 90, plus acetone, 20	4	XXVI, 68.1	257° dec. benzene	$C_{13}H_{10}N_4$	C, 70.25 H, 4.54	C, 70.46 H, 4.41
IV, 0.050	VIII,[d] 0.050	Benzene, 80	9	XXVII, 63.0	249° dec. 2:1 ethyl acetate–petroleum ether[b]	$C_{14}H_8N_4$	C, 72.40 H, 3.47	C, 72.25 H, 3.50

[a] Reactions run at reflux temperature. [b] B.p. 60–75°. [c] Originally 15 hr. at room temperature. [d] Generously supplied by the General Aniline and Film Corporation some years ago.

TABLE II

HYDROGENATIONS[a]

Compound, Moles	Solvent, Ml.	Catalyst, G.	Product, %	M.P. Solvent		Anal. Calcd.	Anal. Found[18]
IX, 0.17	Ethyl acetate, 100	Adams',[b] 1.9	XIV, 32[c]	345° dec. 2:1 ethyl acetate–ethanol	$C_{16}H_{28}ClN$	C, 71.21 H, 10.41 N, 5.19	C, 71.17 H, 10.41 N, 5.02
XV, 0.045	Acetone, 120	Adams', 0.90	XVII, 92	227–228° absolute ethanol	$C_{11}H_8N_4$	C, 67.33 H, 4.11	C, 67.38 H, 4.12
XVI, 0.047	Dioxane, 120, plus glacial acetic acid, 20	Adams', 0.90	XVIII, 90	280° dec. 1:1 petroleum ether[d]–ethyl acetate	$C_{12}H_{10}N_4$	C, 68.55 H, 4.80	C, 68.50 H, 4.70
XIX, 0.010	Ethyl acetate, 200	5% Pd.C, 1.5	XX, 96	186.5–187.5° ethyl acetate	$C_{10}H_{12}N_2$	C, 74.96 H, 7.55	C, 74.91 H, 7.61
XXIV, 0.027	Absolute ethanol, 100	Adams', 0.50	XXV, 100	192–193° 1:1 petroleum ether[d]–ethyl acetate	$C_{10}H_{12}N_2$	C, 74.96 H, 7.55	C, 75.17 H, 7.54

[a] At ~3 atm. and room temperature. [b] Four days for 82% uptake calcd. for primary amine as product. [c] Crude product dissolved in ether and treated with hydrogen chloride. [d] B.p. 60–75°.

Structure and configuration of XXIV. A 0.40-g. sample of XXIV was warmed on the steam bath with 25 ml. of concd. hydrochloric acid for 0.5 hr. The resulting clear solution was evaporated to dryness by an air stream, and the residue was treated with hot benzene, which dissolved the organic product, leaving ammonium chloride. After filtration and partial evaporation, dilution with petroleum ether (b.p. 60–75°) and cooling, there crystallized a product, m.p. 185–187°. It is readily soluble in 5% sodium bicarbonate, with gas evolution, and its infrared spectrum has strong bands at 1779 cm.$^{-1}$ and 1700 cm.$^{-1}$ Five crystallizations from di-*n*-butyl ether raised the melting point to 196–197°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.31; H, 6.24.

A 2.1-g. sample of bicyclo[2.2.2]oct-5-ene-*trans*-2,3-dicarbonitrile (XIX) was warmed with concentrated hydrochloric acid for 0.5 hr. and then worked up in the manner described above. Six crystallizations from di-*n*-butyl ether produced a compound melting at 182–183°. A mixed melting point determination with the lactone derived from XXIV, as well as comparison of their infrared spectra, indicated that these compounds were not identical.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.42; H, 6.27.

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