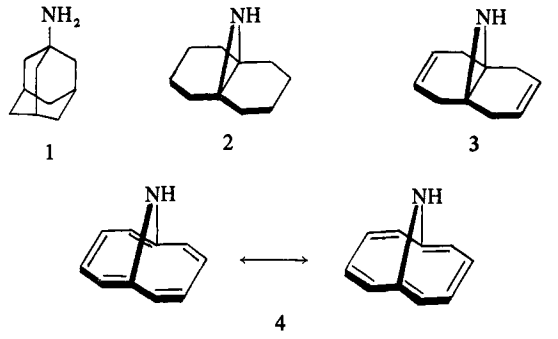
Medicinal Chemistry of [10]Annulenes and Related Compounds. 1. 11-Azatricyclo[4.4.1.0^{1,6}]undecane, 11-Azatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene, and 11-Azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene as Antiviral Agents†

Gary L. Grunewald,* Ann M. Warner,‡ Sheryl J. Hays,§
Department of Medicinal Chemistry, School of Pharmacy
Robert H. Bussell, and Marilyn K. Seals
Department of Microbiology, The University of Kansas, Lawrence, Kansas 66044. *Received October 27, 1971*

The title compounds were compared with 1-aminoadamantane (1) as antiviral agents against influenza virus A2 Japan 305/57 *in ovo* to investigate the effect of incorporating the nitrogen into a strained ring system and, simultaneously, to examine the effect of increased unsaturation of the hydrocarbon moiety on antiviral activity. The saturated aziridine 2, previously unknown, was shown to be the most active of the series. Its decreased activity compared to 1 appears largely due to a lower pK_a.

The observed antiviral activity of 1-aminoadamantane (1) and related compounds[1-3] prompted the synthesis and antiviral evaluation of a large number of saturated polycyclic hydrocarbons bearing an amino[4-8] or guanidino[9] function.

We chose to investigate the antiviral activity of aziridines 2 and 3 and annulene 4. The latter two are known[10-12] and

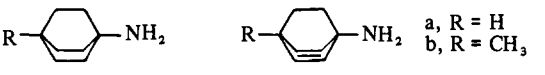


1 2 3 4

were of interest to us as intermediates for another study.# These compounds would aid in an evaluation of the importance of the pK_a of the nitrogen, the effect of incorporating the nitrogen into a strained aziridine ring, and the π-electron character of the hydrocarbon moiety on the antiviral activity. Aziridine 2 is isomeric with 1, and similarly to 1, all compounds of this study have a nitrogen held above a ring system. The ring systems, however, have a wide variation in π-electron character ranging from the saturated 2 to the aromatic 4.

Compounds related to 1 are primarily active against infections of influenza and similar viruses. Although the detailed mechanism of action of 1 is unknown, it has been shown[2] that it is not virucidal at effective antiviral concentrations, does not block virus adsorption to the host cell, and does not affect viral neuraminidase. These observations were interpreted[2] to favor an inhibition of viral penetration into the host cell as the mechanism of action. More recent studies[13] (using a fowl plague virus related antigenically to influenza virus type A) suggest instead that 1 has minimal effect on viral penetration but produces its antiviral action by an inhibition of uncoating of the virus following penetration of the host cell membrane. Although these two proposals conflict, it appears likely that 1 acts early in the viral infection process. Action at either of the above steps would be consistent with a hydrophobic binding of the cyclic hydrocarbon residue of 1 to the host cell membrane or the protein coat of the virus. This would result in a protruding protonated (at physiological pH) amino residue on the cell membrane or virus coat.

The lipophilic character of the hydrocarbon moiety and the basicity of the amino function would thus be of prime importance to the antiviral activity. Whether the hydrophobic interaction of the hydrocarbon residue with host cell membrane or viral coat is nonspecific has not been determined but would seem likely since many polycyclic hydrocarbon residues show antiviral activity if they bear an amino group.[4-8] However, practically all known examples have had a saturated cyclic system, and the possibility of a more specific component, *e. g.*, π-complex, to the binding is unknown. It has been shown that a C_6H_5 substituent on the adamantane ring decreases activity,[5] but a decrease is also observed for saturated substituents of similar bulk. A better example is a comparison between the bicyclo[2.2.2]-octane and -oct-2-ene systems **5** and **6** where the added un-



5 6

saturation in **6** does not add steric bulk. In animal studies, it was reported[4] that the unsaturated compounds (**6**) had similar antiviral action to the saturated analogs (**5**); *e. g.*, **6a** was more active than **5a** but the opposite was true for **5b** and **6b**.

The effect of basicity of the nitrogen has not been systematically investigated. Compounds **5a** and **5b** have very similar pK_a values (10.22 and 10.14, respectively) yet **5b** shows[4] much higher antiviral activity than **5a**, consistent with increased lipophilic character in **5b**.

Synthesis. 9,10-Iminodecalin (**2**)** was prepared by three methods. The addition[14] of NOCl to Δ^9-octalin[15] to

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#G. L. Grunewald and A. M. Warner, unpublished results; manuscript in preparation.

11-Azatricyclo[4.4.1.0^{1,6}]undecane is the preferred nomenclature for **2, 11-azatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene for **3**, and 11-azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene for **4**.

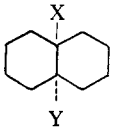
Table I. pK_a Values

Compound	$pK_a \pm 0.04$
2	8.59[a]
3	8.14[a]
1	9.58[a]
1	9.82[b]

[a]In water-CH_3OH (99:1). [b]In water.

give **7a** followed by reduction to **7b** and alkaline ring closure gave an average 40% yield of **2**. The addition of NOCl gave widely variable yields of **7a** on successive runs and the general aziridine synthesis of Hassner[16] proved superior. Addition of iodine azide to Δ^9-octalin gave the azide **7c** in high yield. LAH reduction of **7c** to the amine **7d** followed by treatment with NaOH gave **2** in overall average yields of 60%. A third, and less satisfactory, route was catalytic hydrogenation of **3** over Rh-Al_2O_3. After chromatography and distillation, a yield of only 15% of **2** was obtained. Two unsuccessful attempts to prepare **2** from intermediates in the synthesis of **3** and **4** included catalytic hydrogenation of **8a** over Pd/C (1,4-dihydronaphthalene was the major product) and treatment of the tetrabromide **9** with tri-*n*-butyltin hydride.

Aziridine **3**** was prepared[12,14] from isotetralin[17] using the NOCl route (**8a** → **8b** → **3**) in an overall yield of 60%. The iodine azide route could not be used because addition



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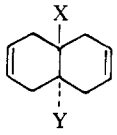

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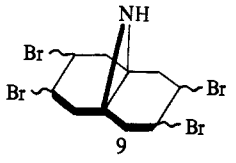
7a, 8a, X = NO; Y = Cl
7b, 8b, X = $NH_2 \cdot HCl$; Y = Cl
7c, X = N_3; Y = I
7d, X = NH_2; Y = I

occurs more readily to disubstituted olefins than to tetrasubstituted ones; the reverse is true for NOCl.

Both aziridines **2** and **3** were stable oils and aqueous solutions were stable for at least 3 weeks.

The aromatic annulene **4** was prepared as communicated by Vogel[11,12] by bromination of **3** to tetrabromide **9** followed by NaOMe elimination of HBr. In addition to **4**,



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some β-bromonaphthalene was produced. A reasonable explanation of the latter might be isotetralin contamination of **3** which was subsequently brominated and then dehydrobrominated (loss of 5HBr). That this is not the explanation was shown by bromination of isotetralin and dehydrobromination of the product under identical conditions to those for **2** and **9**. The major product from this sequence was naphthalene and no β-bromonaphthalene was detected. It must, therefore, arise from **9**.

Despite the reported[12] aromatic stability of **4**, it was more difficult to purify than **2** or **3** and rapidly discolored on exposure to air.

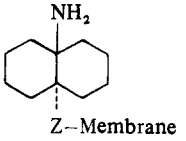
An attempt to prepare **4** directly by dehydrogenation of aziridine **3** using 2,3-dichloro-5,6-dicyanoquinone was unsuccessful, although this method has been used to prepare 1,6-methano[10]annulenes.[18]

pK_a Values. The pK_a values of **1**, **2**, and **3** were determined by $HClO_4$ titration using the method of Buist and Lucas.[19] Annulene **4** was too weakly basic to be measured by this method. The results are shown in Table I.

Antiviral Testing. Compounds **1**-**4** were evaluated for antiviral activity *in ovo* against influenza virus type A2 Japan 305/57 following established procedures.[3] The results are summarized in Table II. Acute toxicity data are given in Table III.

Discussion

None of the compds studied were as active as **1**. An examination of Tables I and II suggests that the basicity of the nitrogen is of major importance. Aziridine **2**, which is isomeric with **1**, showed an activity *ca.* 15-20% that of **1** based on the dosage (3 mg for **2** and 0.5 mg for **1**) required to lower the hemagglutinin value to similar levels. If one assumes that the amine must be protonated to show activity, the difference in basicity between **1** and **2** (*ca.* 1 pK_a unit) would be significant as, at equilibrium at constant pH, there would be ten times more unprotonated **2** present than **1**. That **3** is less active than **2** may also be due to pK_a differences (Table I). That the role of the hydrocarbon part of the molecule does not involve a π-complex component to binding is also consistent with the inactivity of **3** compared to **2**.



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The possibility that **2** or **3** could act to prolong binding through covalent bond formation by host cell membrane or viral coat nucleophilic (Z) opening of the aziridine ring, *e.g.*, **10**, also seems unlikely due to the observed low activity and

Table II. Antiviral Results

Compound	mg per embryo	Treated[b] No. HA[a] positive/total	Treated[b] Geom mean HA titer	Control No. HA[a] positive/total	Control Geom mean HA titer
2	1	7/17	59	6/17	36
	2	11/14	110	11/15	170
	3	7/13	98	8/13	226
3	1	9/15	93	7/15	98
	2	5/10	92	8/10	73
	3	8/11	151	10/11	160
4	1.25	11/14	181	13/14	169
1·HCl	0.5	1/15	80	10/15	226

[a]HA = hemagglutinin. [b]The compds were inoculated *via* the chorioallantoic cavity of 9- to 10-day-old chick embryos approx 30 min prior to inoculation with influenza A2 Japan 305/57 by the same route. Controls received virus only. All embryos were incubated for 48 hr at 36° prior to harvesting the individual chorioallantoic fluids. HA tests were performed to determine the number of positive embryos, and titrations were performed on all positive fluids.

Table III. Acute Toxicities in Chick Embryo

Compound	mg/embryo	No. dead/total
2	1.0	3/13
	2.0	2/10
	3.0	3/12
3	1.0	1/9
	2.0	1/8
	3.0	0/5
4	1.0	0/3
	1.25	0/5
	1.5	0/3
	2.0	0/3
1	0.5	0/6

the high stability of aqueous solutions of 2 and 3. However, such an alkylation would be consistent with the higher toxicity of 2 and 3 compared to 1 or 4 (Table III).

The antiviral results obtained *in ovo* do not, of course, necessarily relate to whole animal studies.[20] In the latter, transport and metabolism may result in a different order of activity than would be obtained in the *in ovo* case.

Experimental Section††

9-Nitroso-10-chlorodecalin (7a). Using a modification of the procedure of Closs,[14] Δ^9-octalin[15] (13.6 g, 0.10 mole) in 20 ml of $CHCl_3$ was cooled to −70° and NOCl was bubbled into the soln until a dark brown color was obtd. When an aliquot, upon warming to room temp, showed formation of the blue cryst product, the addn of NOCl was discontinued and the cooling bath removed. Unreacted NOCl was removed by bubbling air through the mixt. Acetone (50 ml) was added to the residue, and the soln was cooled to −70°; 7a was obtd as a blue cryst solid, 8.6 g (43%), by filtration, mp 90–92° (lit.[15] 91°).

9-Amino-10-chlorodecalin Hydrochloride (7b). In a modification of the method of Closs,[14] stannous chloride (90.7 g, 0.41 mole) was dissolved in 250 ml of HCl (37%) and 7a (10.3 g, 0.041 mole) was added in one portion. The reaction flask was heated slightly with a warm water bath to initiate the reaction, followed by stirring at room temp for 12 hr. The resulting white suspension was filtered to give 7b contaminated with HCl. This material was used directly in the next step without further purification.

11-Azatricyclo[4.4.1.$0^{1,6}$]undecane (2). Method A. Compd 7b, isolated in the previous reaction, was added to a cold concd NaOH soln (60 g, 250 ml) and the pH maintained at 11 with 20% NaOH. The basic soln was kept at room temp for 12 hr, extd with Et_2O, dried ($MgSO_4$), and evapd to yield 7.2 g of 2 (92.2% based on 7a). It was purified by distn (bp 50° (1.2 mm)) and by chromatog (basic alumina, CCl_4) giving a colorless oil; ir (liquid film) 3200–3400 (NH), 2910 (CH), and 1440 cm^{-1} (CH_2); nmr (CCl_4) δ 2.2–1.0 (m, 16, ring protons), and 0.5 ppm (broad s, 1, N-H); mass spectrum *m/e* (rel intensity) 151 (M^+, 8), 137(47), 136(5), 82(36), 40(100). This aziridine remained stable in aqueous soln 3 weeks as indicated by the ir of the Et_2O extract.

To obtain a solid deriv for analysis, 2 (2.0 g, 0.013 mole) was treated with MeLi (7.6 ml of 2 *M* soln) followed by addn of MeI (0.81 ml). The reaction mixt was stirred 1 hr and filtered. The filtrate was concd and the residue added to an excess of MeI (20 ml) at −50° and stirred for 30 min. The white solid quaternary amine was collected, dissolved in H_2O, and treated with $NaBPh_4$ (2.5 g) to give a white solid. *Anal.* ($C_{36}H_{42}BN$) C, H, N.

Method B. Using a modification of the method of Hassner,[16] ICl (18.3 g, 0.113 mole) was added over a period of 10 min to a stirred slurry of NaN_3 (15 g, 0.25 mole) in 100 ml of MeCN at 0°. The reaction mixt was stirred an addnl 5 min; Δ^9-octalin[15] (13.6 g, 0.1 mole) was added rapidly and the reaction stirred at room temp 21 hr. The red-brown slurry was poured into 250 ml of H_2O and extd with Et_2O. The dark brown Et_2O ext was washed with $Na_2S_2O_3$ (150 ml, 15%), dried (Na_2SO_4), and evapd *in vacuo* at room temp to give 23.6 g (79%) of 7c as a yellow oil.

LAH (7.5 g, 0.2 mole) was added slowly to 250 ml of anhyd Et_2O and cooled to 0°. Azide 7c (23.6 g, 0.076 mole) was added slowly, and the reaction was stirred at room temp 8 hr. Aqueous NaOH (20 ml, 20%) was added cautiously, and the reaction stirred an addnl 45 min. The resulting suspension was filtered and the ppt washed well with Et_2O. The Et_2O filtrate was dried (Na_2SO_4) and evapd to yield 8.5 g (74%) of 2, identical with that prepd by method A.

Method C. Aziridine 3 (2.0 g, 0.13 mole) was mixed with Rh-Al_2O_3 (0.3 g, 5%) in 75 ml of EtOH and hydrogenated at 3.5 kg cm^{-2} for 18 hr at room temp. The reaction mixt was filtered and evapd to yield a brown oil which was chromatographed on silica gel (100 g) with $CHCl_3$ to give 0.3 g (15%) of 2.

9-Nitroso-10-chloro-1,4,5,8,9,10-hexahydronaphthalene (8a). Isotetralin[17] (13.2 g, 0.1 mole) was reacted with NOCl in CH_3OH similarly to the procedure for 7a. Recrystn from pentane gave 16.9 g (85%) of 8a, mp 118–118.5° (lit.[21] 118–120°). This compd was unstable at room temp and was used immediately in the next step.

11-Azatricyclo[4.4.1.$0^{1,6}$]undeca-3,8-diene (3). Compd 8a (15.6 g, 0.079 mole) was converted to 8b by the method used to prep 7b. This was treated with NaOH as done with 7b to give 9.0 g (85%) of crude 3 which was distd, bp 56° (0.22 mm) (lit.[10] 76–77° (0.6 mm)), and then chromatographed (250 g of basic alumina, CCl_4) to yield 7.0 g (66%) of colorless oil.

For analysis, the acetamide was prepd using AcCl in Et_2O, mp 72–72.5° (lit.[10] 73–74°). *Anal.* ($C_{12}H_{15}NO$) C, H, N.

11-Azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene (4). Bromination of 3 using a modification of the procedure of Vogel[12] gave a 60% yield of 9, mp 150–151° (lit.[12] 152–153°). Dehydrobromination of 9 (28.9 g, 0.06 mole) at 0° with NaOMe (20 g, 0.37 mole) in 20 ml of MeOH and 200 ml of THF was carried out over an 8-hr period. The crude product was extd with hexane, dried ($MgSO_4$), and evapd. The residue was chromatographed (200 g of basic alumina, CCl_4). The first product eluted was identified as β-bromonaphthalene (ir comparison with an authentic sample). This was followed by 6.0 g of 4 which was distd, bp 71° (0.1 mm) (lit.[12] 60° (0.02 mm)), to give 6.0 g of yellow oil. Crystn from cold MeOH gave 4.5 g (49%) of yellow 4, mp 15° (lit.[12] 16°).

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††Melting points were obtd on a calibrated Thomas-Hoover Uni-Melt and are cor. Ir data were recorded on a Beckman IR-10 spectrophotometer, nmr data with Varian Associates Models A60 and A60A spectrometers (Me_4Si), and mass spectra on a Finnigan Model 1015 spectrometer. Microanalyses were performed on an F and M Model 185 CHN analyzer in this department and by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtd for those elements were within ±0.4% of the theoretical values.

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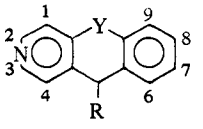
Derivatives of 10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptene and Related Compounds. 6. Aminoalkyl Derivatives of the Aza Isosteres†,[1]

Frank J. Villani,* Peter J. L. Daniels, Claire A. Ellis, Thomas A. Mann, Kai-Chih Wang, and Elizabeth A. Wefer

Department of Medicinal Chemistry, Schering Corporation, Bloomfield, New Jersey 07003. *Received August 27, 1971*

The synthesis, antianaphylactic and antihistaminic potency, and structure-activity relationships of a series of aminoalkyl derivatives of the aza isosteres of 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene are described. Compound 33, azatadine dimaleate, 6,11-dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine, conveniently designated as a member of the 4-aza-10,11-dihydrodibenzocycloheptene series, has shown very potent biological properties which have been confirmed in clinical trials in man.

Our studies of aminoalkyl derivatives of dibenzocycloheptenes[2,3] have included the synthesis and biological evaluation of the isosteric aza analogs, I.‡ The synthesis of



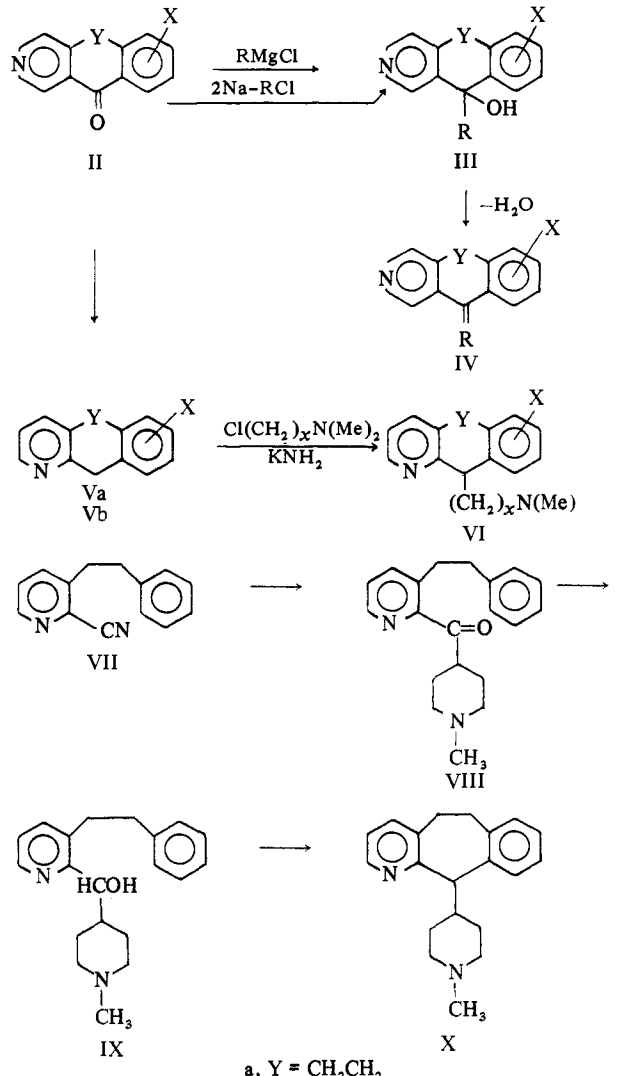
Ia, Y = CH_2CH_2
Ib, Y = CH=CH

R values given in Tables I, II, and III

these compounds is shown in Scheme I. Aza ketones II[4] were treated with a Grignard reagent to give the corresponding tertiary carbinols listed in Table I. In those cases wherein R is a dialkylaminoethyl or when the Grignard reagent would not form readily, the novel reductive alkylation procedure[5] gave good yields of III. The carbinols were subjected to the usual acid dehydrating conditions and gave the unsaturated compounds listed in Table II. In the 4-aza series, *i.e.*, those compounds wherein the pyridyl nitrogen is attached to a carbon atom which is α to the carbinol group, vigorous dehydrating conditions are required.[6] In these cases prolonged heating at 160-165° in the presence of excess PPA or the use of 85% H_2SO_4 is necessary to effect the dehydration. A number of the compounds listed in Table II were obtained as a mixture of the cis and trans isomers and no effort was made to separate the mixture for preliminary biological evaluation.§

Since it soon was apparent that maximum antianaphylactic and antihistaminic activity was found in the 4-aza series we concentrated our synthetic efforts in this area. The 4-aza ketones were converted to the 4-aza hydrocarbons V by a modified Wolff-Kischner reduction. Alkylation of V in the presence of KNH_2 with a variety of alkylaminoalkyl halides

Scheme I



a, Y = CH_2CH_2
b, Y = CH=CH

†Presented in part before the Division of Medicinal Chemistry Section of the 124th National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

‡For clarity throughout, we prefer to name these compounds as derivatives of azadibenzocycloheptenes and to standardize the number around the ring as shown in I. Thus, compound 33 (Table II) is named 4-aza-5-(1-methyl-4-piperidylidene)-10,11-dihydrodibenzo[*a,d*]cycloheptene. The Chemical Abstract name for this compound is 6,11-dihydro-11-(1-methyl-4-piperidylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine.

§Compound 31 (Table II) showed some interesting CNS properties and was separated into the cis and trans isomers. A future communication from this laboratory will describe this work.