allowed to stand overnight before it was evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH (dried at 100° and 0.07 mmole over P_2O_5): yield 163 mg (62%); mp 144–146° (MT); λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 239 (10.7), 265 nm (12.6); pH 7, 214 (15.2), 277 nm (11.6); pH 13, 226 (12.7), 287 nm (11.4). *Anal.* ($C_{13}H_{20}N_4O$) C, H, N.

N-Alkylpurine-6(1*H*)-thiones. A stirred solution of the *N*-alkylhypoxanthine in pyridine (14 ml/mmole) containing P_2S_5 (3.7 equiv) was heated for 4–8 hr. The filtered mixture was diluted with H_2O, acidified with HOAc, and evaporated to dryness *in vacuo*. Acidification of a filtered solution of the residue in 1 *N* NaOH gave a precipitate, which was recrystallized from EtOH with charcoal treatment. Yields, melting points, and spectra data are given in Table II.

Acknowledgment. The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Reserach Institute for spectral and microanalytical data, to Dr. L. L. Bennett, Jr., and Mrs. Margaret H. Vail for the cytotoxicity data, and to Dr. W. R. Laster, Jr., for the leukemia L1210 results.

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Medicinal Chemistry of [10]Annulenes and Related Compounds. 2. *N*-(2-Chloroethyl) Derivatives of 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[1]

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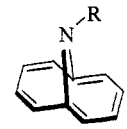
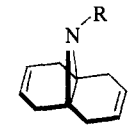
1,6-Imino[10]annulene (**1**) represents an aromatic 10π-electron system with a nitrogen atom held rigidly above the ring. Such a system is unique, and we were interested in investigating the biological activity of compounds containing such a nitrogen atom by studying the series‡ **1**, **2**, and **3**.

The compounds of this series range from the fully aromatic [10]annulene to the saturated decalin. That **1** is a member of this series can be seen from the valence tautomer **4**.§



1, R = H



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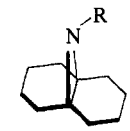


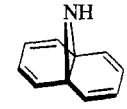
3, R = H

5, R = $ClCH_2C(=O)$
8, R = $ClCH_2CH_2$

6, R = $ClCH_2C(=O)$
9, R = $ClCH_2CH_2$

7, R = $ClCH_2C(=O)$
10, R = $ClCH_2CH_2$
11, R = $HOCH_2CH_2$

This paper discusses the synthesis and α-adrenergic blocking activity of the *N*-(2-chloroethyl) derivatives of these three amines.



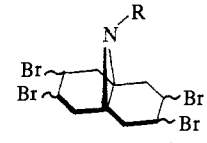
4

Synthesis. Amines **1** and **2** were prepared by modification of literature procedures[1,3] and the synthesis of **3** was reported by us earlier.[1] The general route for the preparation of the β-chloroethyl compounds **8**, **9**, and **10** was *via* the chloroacetyl derivatives **5**, **6**, and **7**.

Aziridine **2** was readily acylated in high yield with chloroacetyl chloride to give **6** as a white crystalline solid. Amide **7** was obtained in low yields (20%) as a yellow oil by similar treatment of aziridine **3**. Much higher yields were obtained in this case if chloroacetic anhydride was used as the acylating agent. The lower basicity[1] of amine **1** made acylation more difficult, but 30% yields (after recrystallization) of amide **5** could be obtained with chloroacetyl chloride.

Reduction of the amide carbonyl without concomitant reduction of the carbon-halogen bond of amides **5**, **6**, and **7** was accomplished in yields of 43, 60, and 30%, respectively, with aluminum hydride.[4]

Several alternate synthetic routes were also tried. Treatment of **2** or **3** with methyllithium followed by 1,2-dichloroethane gave only the starting aziridine. Treatment of the lithium salt of **3** with ethylene oxide gave **11**, the *N*-(β-hydroxyethyl) derivative, but in very low yields. Reduction of amide **6** with diimide failed to give amide **7**; starting material was recovered. An alternate route to the aromatic **8** involved conversion of amide **6** to the tetrabromide **12** in high yield. Although the corresponding *N*-acetyl derivative **13** could be dehydrobrominated in base[3] to the aromatic [10]annulene system, similar treatment of **12** failed to give amide **5**.

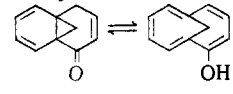


12, R = $ClCH_2C(=O)$
13, R = Ac

†Taken in part from the thesis submitted by Ann M. Warner to the Graduate School of the University of Kansas in partial fulfillment of the requirement for the Ph.D. degree, Aug 1970. A preliminary account of this work was presented at the Fifth Midwest Regional Meeting of the American Chemical Society, Kansas City, Mo., Oct 31, 1969, Abstract No. 427.

‡The preferred nomenclature is given in the title for 3, 2, and 1, respectively.

§No evidence for the existence of 4 could be found by low-temperature nmr studies on 1. It could be viewed also as a possible minor resonance contributor to 1, in analogy to the Dewar (1,4-bonded) resonance structure of benzene. In some [10]annulenes, however, structures analogous to 4 represent discrete tautomers, such as in the keto–enol pair i and ii.[2]



i ii

Pharmacological Results. The pharmacological evaluation of the *N*-(β-chloroethyl) compounds **8**, **9**, and **10** was hampered by their low water solubility, even with the addition of dilute hydrochloric acid and/or ethanol. Compound **9** was the most soluble.

All three compounds were without effect on the isolated rat vas deferens[5] or isolated rabbit jejunum[6] at bath concentrations of 10^{-6} to 10^{-4} *M*.

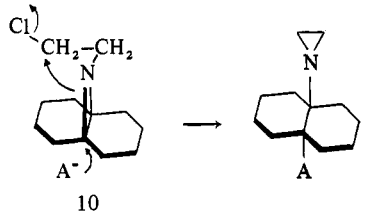
In the anesthesized (pentobarbital, 30 mg/kg) male cat (2.0 kg), 10 ml of a 10^{-3} *M* solution of **9** reduced the blood pressure increase from a 1 μg/kg dose of norepinephrine. Phenoxybenzamine at the same dose showed a longer lasting and greater reduction of the norepinephrine response. Limited solubilities prevented similar evaluation of **8** or **10**, and of **9** at higher concentrations.

Discussion

Of interest for the possible α-adrenergic blocking activity of the *N*-(β-chloroethyl)amines **8**, **9**, and **10** is the formation of the aziridinium species (*e.g.*, **14** from **8**). No evidence for the formation of **14** could be seen in the nmr spectrum of **8** in the method used[7] for other β-haloethyl adrenergic blockers. The failure to form **14** in concentrations high enough to observe in the nmr spectrum is consistent with the low basicity of the nitrogen in **1**. Although *N*-aryl-β-haloethylamines are usually poor α-adrenergic blockers, **14** would be expected to have shown adrenergic blocking activity, if formed, because of the structural similarity to the known blocker, *N*,*N*-dimethyl-2-phenylaziridinium.[8]

14 15

In the case of aziridines **9** and **10**, the corresponding spiral species would be unlikely (*e.g.*, **15**). However, alkylation by **9** or **10** could occur by attack of a receptor nucleophile (A^-) as shown for **10**.



10

Work is in progress on other derivatives of amines **1**, **2**, and **3** to overcome the limited solubility and to allow a more thorough biological evaluation.

Experimental Section#

N-(**2-Chloroacetamido**)-**11-azatricyclo[4.4.1.0^{1,6}]undecane** (**7**). **Method A.** Amine **3** (3.0 g, 0.02 mole) was mixed with pyridine (3 ml, 0.04 mole) in 100 ml of anhyd Et_2O at 0°. $ClCH_2COCl$ (1.5 ml, 0.02 mole) in 10 ml of Et_2O was added rapidly, and the reaction was allowed to warm to room temp and stirred an addnl 4 hr. Aqueous $NaHCO_3$ (50 ml, 20%) was added and the Et_2O fraction sepd, dried ($MgSO_4$), and evapd to yield 1.0 g (22%) of **7** as a brown oil. This was chromatographed on 50 g of basic alumina with CH_2Cl_2; 50-ml fractions were collected to give 0.9 g (20%) of **7** in fractions 1-3 as a pale yellow oil. *Anal.* ($C_{12}H_{18}ClNO$) C, H, N.

Method B. Amine **3** (2.0 g, 0.013 mole) was mixed with pyridine (4.0 ml, 0.05 mole) in 100 ml of anhyd Et_2O at room temp, chloroacetic anhydride (2.20 g, 0.013 mole) was added rapidly as the solid, and the reaction was stirred 12 hr at room temp. Work-up as in method A gave 1.6 g (54%) which was chromatographed as above to give 1.4 g (48%) of pure **7**.

N-(**2-Chloroethyl**)-**11-azatricyclo[4.4.1.0^{1,6}]undecane** (**10**). Aluminum hydride was prepared by a modification of the procedure of Brown[4] from 60 ml of a 1.55 *M* soln of LAH in THF added to 40 ml of THF in a dry reaction flask fitted with a rubber septum and maintained at 0°. Concd H_2SO_4 (2.64 ml, 0.047 mole) was added at a rate to avoid excessive foaming. The mixt was then stirred 1.5 hr at 0°. Amide **7** (3.0 g, 0.026 mole) in 10 ml of anhyd THF was added rapidly, the reaction mixt was stirred for 3 hr at room temp, THF-H_2O (1:1, 20 ml) was added slowly to decompose excess AlH_3, and the reaction mixt was poured into aqueous $NaHCO_3$ (150 ml, 20%). The resulting suspension was extd with Et_2O (2 × 100 ml) and hexane (2 × 100 ml). The exts were combined, dried (Na_2SO_4), and evapd to give 2.4 g of impure **10**, which was purified by chromatography on 150 g of neutral alumina (50% $CHCl_3$-cyclohexane; 50-ml fractions) to give 0.85 g (30%) of the pure amine (**10**) in fractions 1-3.

A satisfactory elemental analysis was not obtained, but a high-resolution mass spectrum showed a molecular ion of 213.1284 (calcd 213.1283).

N-(**2-Chloroacetamido**)-**11-azatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene** (**6**). Amine **2** (25 g, 0.17 mole) was allowed to react with $ClCH_2COCl$ in pyridine as above for **7** to give a white solid which was recrystd from Me_2CO to yield 30 g (79%) of **6**, mp 103-103.5°. *Anal.* ($C_{12}H_{14}ClNO$) C, H, N.

N-(**2-Chloroethyl**)-**11-azatricyclo[4.4.1.0^{1,6}]undeca-3,8-diene** (**9**). As above for **10**, 3 g (0.025 mole) of **6** was reduced with AlH_3 to yield 2.4 g of crude product which was chromatographed on alumina to yield 1.7 g (60%) of pure **9** as a light yellow oil which was a solid below 0° and was stable enough to be distd, bp 57° (0.019 mm).

The tetraphenyl borate salt of **9** was prepd, for elemental analysis, by treatment of **9** (1.0 g, 0.004 mole) with MeI (10 ml) at −50° for 30 min. After removal of the unreacted MeI *in vacuo*, the quaternary amine was dissolved in H_2O, and $NaBPh_4$ (1.5 g) was added to yield a white ppt which was washed with H_2O and Et_2O and dried. *Anal.* ($C_{37}H_{39}BClN$) C, H, N.

N-(**2-Chloroacetamido**)-**11-azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene** (**5**). To a soln of annulene **1** (1.0 g, 0.007 mole) and pyridine (1.0 ml, 0.015 mole) in 20 ml of $CHCl_3$ was added $ClCH_2COCl$ (0.70 ml, 0.008 mole) in 7 ml of $CHCl_3$, and the reaction mixt was warmed on a water bath for 1 hr. Work-up as for **7** gave 0.65 g (40%) of crude **5** which was purified by washing with cold Et_2O and recrystn from EtOH to give 0.50 g (30%) of yellow cryst solid, mp 126-126.5°. *Anal.* ($C_{12}H_{10}ClNO$) C, H, N.

N-(**2-Chloroethyl**)-**11-azabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene** (**8**). Amide **5** (0.500 g, 0.0025 mole) was reduced with AlH_3 as above to give a brown oil which was chromatographed on a 20 × 20 cm alumina (Brinkman) prep tlc plate with 50% $CHCl_3$-cyclohexane. Elution of the band (R_f 0.89) with $CHCl_3$ gave 0.20 g (43%) of yellow solid **8** which was recrystd from MeOH: mp 49-50°; nmr (CCl_4) δ 7.8-6.9 (m, 8, aromatic), 2.8-2.4 (t, 2, J = 7 Hz, CH_2Cl), and 1.2-0.8 ppm (t, 2, J = 7 Hz, NCH_2); mass spectrum *m/e* (rel intensity) 205 (M^+, 65), 156 (100), 142 (80), 128 (100), 115 (63). *Anal.* ($C_{12}H_{12}ClN$) C, H, N.

N-(**2-Chloroacetamido**)-**3,4,8,9-tetrabromo-11-azatricyclo-[4.4.1.0^{1,6}]undecane** (**12**). Amide **6** (5.0 g, 0.022 mole) was dissolved in 150 ml of CH_2Cl_2 and cooled to −70°. Bromine (2.30 ml, 0.044 g-atom) in 20 ml of CH_2Cl_2 was added slowly. The reaction was stirred an addnl 30 min at −70°, and the solvent was removed *in vacuo* at room temp to give 11.5 g (96%) of **12**; recrystn from EtOAc gave a powdery white solid, mp 146-147°. *Anal.* ($C_{12}H_{14}Br_4ClNO$) C, H, N.

#Melting points were obtd on a Thomas-Hoover Uni-Melt calibrated with known compounds. Nmr data were recorded with Varian Associates Models A-60 and A-60A spectrometers (Me_4Si) and mass spectra on a Finnigan Model 1015 spectrometer. Microanalyses were performed on an F & M Model 185 CHN Analyzer in these laboratories and by Midwest Microlab, Inc., Indianapolis, Ind. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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New Compounds

Hydroxylamine Derivatives as Potential Antimalarial Agents. 2. Hydroxamates and Amidoximes†

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In the preceding paper it was reported that terephthalohydroxamic acid (**1a**), as well as its dibenzoylated derivative **1b**, displayed significant antimalarial activity.[1] In the same year, the antimalarial properties of bis(trihalomethyl)arenes such as **2** were also reported.[2] A total of 24 compounds related to one or both of these structures was prepared and evaluated for possible activity enhancement.

1,4-$RONHCOC_6H_4CONHOR$

1a, R = H
1b, R = C_6H_5CO

1,4-$CCl_3C_6H_4CCl_3$

2

These included trihalomethylbenzohydroxamates (**3–7**), amidoximes (**8–12**), *N,O*-bis(trihalomethylbenzoyl)hydroxylamines (**13–19**), and derivatives of **1b** (**20–26**) (*cf.* Tables I, II, and III). None of these displayed significant activity against *Plasmodium berghei* in mice.[3,‡] In view of these results as well as those obtained earlier,[1] it appears doubtful that significant activity enhancement can be obtained by structural modification of **1a**.

It should be noted that the amidoximes **8**, **9**, **10**, and **12** showed significant toxicity.§ This was particularly disappointing in the case of **8**, which can be considered to be isosteric with one of the tautomeric forms of **1a**. However, several of the amidoximes were subsequently used to prepare a series of bis(trihalomethyl-1,2,4-oxadiazoles), which will be described in a forthcoming communication.

Experimental Section

Each of the raw materials employed in this research was obtained commercially with the exception of 4-trichloromethylbenzoyl chloride. The latter compound was prepared according to the literature method involving the $FeCl_3$-catalyzed hydrolysis of $\alpha,\alpha,\alpha,\alpha',\alpha',\alpha'$-hexachloro-*p*-xylene.[4] Compounds **3** and **4** were prepared from this acid chloride by reaction with the appropriate hydroxylamine hydrochloride in the presence of imidazole according to the method of Koenig and Deinzer.[1,5] Compound **5** was prepared from methyl 3-trifluoromethylbenzoate by reaction with hydroxylamine in the presence of excess NaOH in MeOH.[1]

4-Trifluoromethylbenzohydroxamic Acid (6). To a solution of 21 g (0.1 mole) of 4-trifluoromethylbenzoyl chloride in 300 ml of Et_2O was added 7.0 g (0.1 mole) of $NH_2OH \cdot HCl$ and 11.0 g of Na_2CO_3. Next, 20 ml of H_2O was added dropwise over 2 hr and the stirring was continued for 3 hr longer. The solid which formed was separated by filtration and then combined with the residue resulting from evaporation of the Et_2O layer. After washing with H_2O the solid was recrystallized from H_2O (*cf.* Table I).

2-Trifluoromethylbenzohydroxamic Acid (7). To a mixture of 3.5 g of $NH_2OH \cdot HCl$ (0.025 mole), 5.5 g of Na_2CO_3, and 150 ml of Et_2O was added 5.5 ml of H_2O. Then 5.25 g (0.025 mole) of 2-trifluoromethylbenzoyl chloride was added dropwise with stirring at room temperature over 0.5 hr. The solid which separated was removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. Extraction of the residue with 70 ml of Et_2O and evaporation yielded a white solid which was purified by recrystallization from EtOAc.

Amidoximes (8–10 and 12). Compounds 10 and 12 were prepared according to the literature methods (*cf.* Table I). Terephthal- and isophthalamidoximes, **8** and **9**, were obtained by heating the appropriate nitrile at reflux with 4 equiv of NH_2OH, obtained by neutralizing the hydrochloride with NaOH in EtOH for 24 and 48 hr, respectively.

4-(Hydroxycarbamyl)benzamidoxime (11). A solution of 3.4 g of MeONa (0.063 mole) in 50 ml of MeOH was added to 4.35 g (0.025 mole) of $NH_2OH \cdot HCl$ in 60 ml of MeOH. After filtration, 4.4 g (0.025 mole) of ethyl 4-cyanobenzoate was added followed by an additional 3.4 g of MeONa. After stirring at room temperature for 6 days, the white solid was separated by filtration and dissolved in 10 ml of H_2O. Adjusting the pH to 5.5 with 1 *N* HCl and cooling produced the crude crystalline solid.

***N,O*-Bis(4-trichloromethylbenzoyl)hydroxylamine (13).** Numerous attempts were made to prepare 4-trichloromethylbenzohydroxamic acid. However, the only compound which could be isolated from any of the procedures in pure form was **13**. The following example afforded the title compound in poor yield but high purity. A mixture of 3.1 g of imidazole, 1.0 g (0.015 mole) of $NH_2OH \cdot HCl$, and 100 ml of MeCN was stirred in a system protected from moisture for 0.5 hr. Next, 7.7 g (0.03 mole) of 4-trichloromethylbenzoyl chloride was added dropwise over 1 hr. After stirring at room temperature for 4 hr, the solution was added to 300 ml of cold H_2O, and the resulting solid was separated by filtration and washed several times with H_2O.

***N,O*-Bis(trihalomethylbenzoyl)hydroxylamines (14–19).** Each of these compounds was prepared in a similar manner. The following procedure for compound **14** is representative. To a stirred solution of 2.1 g (0.01 mole) of 4-trifluoromethylbenzohydroxamic acid (**6**) in 10 ml of pyridine was added dropwise 2.1 g (0.01 mole) of 4-trifluoromethylbenzoyl chloride over 0.5 hr. After stirring for an additional 3 hr at room temperature, the mixture was poured into 12 ml of HCl (37%) containing 12 g of ice. The crude solid which formed was separated by filtration, washed with H_2O, and vacuum dried over P_2O_5.

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‡Testing of all compounds was carried out by Dr. L. Rane of the University of Miami.

§Deaths due to toxicity occur in 3–5 days (mean survival time for controls was 6.1 days).