When final products, compds II were converted to their hydrochlorides and purified as shown in Table II.

N-Methyl Derivatives of *o*-Terpenylaminomethylphenols (Table II). To 0.1 mole of the appropriate II, 0.375 mole of 88% HCOOH, and 0.375 mole of a 35% HCHO soln were added with cooling. The mixt was first heated slowly and then refluxed for a time varying from 24 to 90 hr. It was then cooled and basified with 10% KOH soln, and the basic material was filtered off or extd with Et_2O and worked up in the usual manner.

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References

(1) A. Mantegani and G. Bonardi, *Chim. Ther.*, 7, in press (1972) (paper 12).
(2) A. Burger, "Medicinal Chemistry," 3rd ed, Wiley-Interscience, New York, N. Y., 1970, p 1360.
(3) F. Arch, *Arzneim.-Forsch.*, 13, 480 (1963).
(4) B. Silvestrini and C. Pozzati, *Arch. Int. Pharmacodyn. Ther.*, 129, 249 (1960).
(5) W. F. Perry and E. M. Boyd, *J. Pharmacol. Exp. Ther.*, 73, 65 (1941).
(6) W. N. Krestinskii and I. I. Bardishev, *J. Gen. Chem. USSR*, 10, 1894 (1940); *Chem. Abstr.*, 35, 4366³ (1941).
(7) A. C. Cope and E. M. Acton, *J. Amer. Chem. Soc.*, 80, 355 (1958).
(8) W. Hückel, H. Kindler, and H. Woloski, *Chem. Ber.*, 77B, 220 (1944).
(9) B. Shive, J. Horeczy, G. Wash, and H. L. Lochte, *J. Amer. Chem. Soc.*, 64, 385 (1942).
(10) A. W. Ingersoll and H. D. De Witt, *ibid.*, 73, 3360 (1951).
(11) N. L. McNiven and J. Read, *J. Chem. Soc.*, 153 (1952).

Derivatives of 3,5-Dihydro-4*H*-benzo[2,3]diazepin-4-one†

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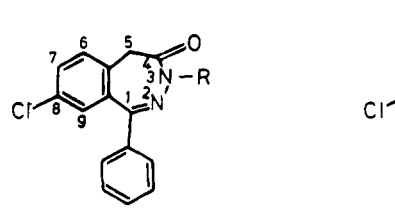
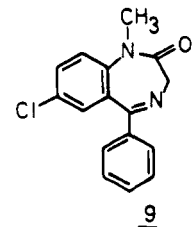
As part of a program for the synthesis and biological evaluation of potentially psychoactive compounds, we became interested in derivatives of 3,5-dihydro-4*H*-benzo[2,3]diazepin-4-one, in particular, in **1**, an isomer of diazepam.[1] Compounds having the title structure and bearing a hydrogen or methyl group, respectively, at C-1 have been made by condensation of 2-formyl- and 2-phenylacetic acids with hydrazine, but their biological properties have not been described.[2] We have prepared **1** and **2** by thermal cyclization of the methyl hydrazone and hydrazone, respectively, of 2-benzoyl-4-chlorophenylacetic acid. Likewise, compds **3** and **4** were prepared from 2-benzoyl-4,5-dimethoxyphenylacetic acid and compd **5** from 2-acetyl-4,5-dimethoxyphenylacetic acid. A water-soluble by-product was isolated in the last reaction and was assigned the 2-amino-3-isoquinolone structure **8**. The guanylhydrazone **11** of 2-acetyl-4,5-dimethoxyphenylacetic acid failed to cyclize to a 2,3-diazepine derivative. Treatment of **2** and **5** with an appropriate dialkylaminoalkyl halide afforded compds **6** and **7**, respectively.‡

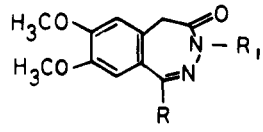
Pharmacology. The compds examined were suspended in a 0.2% agar suspension and given orally (po) or parenterally (ip) for evaluation of the neuropharmacological profile

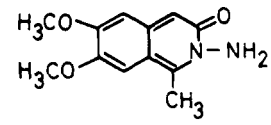




9

1 R = CH_3
2 R = H
6 R = $CH_2CH_2CH_2N(CH_3)_2$





8

3 R = Ph ; R_1 = CH_3
4 R = Ph ; R_1 = H
5 R = CH_3 ; R_1 = H
7 R = CH_3 ; R_1 = $CH_2CH_2NEt_2$

in CF male mice.[4] Compd **8** showed dose-dependent CNS effects of sedation, ptosis, and ataxia, and its effective dose was 100 mg/kg po and 50 mg/kg ip. In contrast to compd **9**, muscular relaxation and hypotonia were not observed. Similar effects were observed with compd **5** at 250 mg/kg po and 100 mg/kg ip. Compds **1**, **3**, and **4** demonstrated sedation and ptosis at doses above 250 mg/kg po, but these effects were not dose dependent. Compd **1** at 50 mg/kg ip showed equal activity to compd **8**. However, compd **1** required 10 times the parenteral dose to produce equivalent CNS effects by the oral route. The lethal dose in mice for compds **1**, **3**, **4**, **5**, and **8** was more than 1000 mg/kg po.

Compd **2** showed no evidence of CNS activity up to 1000 mg/kg, whereas evidence of CNS stimulation was observed in compds **6** and **7**. The lethal dose of **6** and **7** was 1000 mg/kg po. In mice there was no evidence of antielectroshock activity, specific antagonism to mescaline-induced "scratch stereotypy" or antagonism to the acetic acid induced writhing phenomenon,[5] up to 100 mg/kg po.

In conclusion it appears that **1**, which differs from **9** in the disposition of NCH_3 and CH_2 groups, is biologically much less active. The diminished activity of **1** and other 2,3-benzodiazepine congeners described herein, compared to the 1,4-diazepine analogs may be due to decreased basicity of the former and/or different juxtaposition of potential binding sites. The disappointing results encountered for the 2,3-diazepine series discouraged us from expanding the project, although the present method would have easily permitted the synthesis of a larger number of analogs of **1** and **3**.

Experimental Section§

1-Phenyl-3-methyl-3,5-dihydro-8-chloro-4*H*-benzo[2,3]diazepin-4-one (1). 2-Benzoyl-4-chlorophenylacetic acid# (2 g, 7.3 mmoles) and hydrazine hydrate (0.4 g, 8 mmoles) in EtOH (10 ml) were heated under reflux for 4 hr. Evaporation of EtOH gave the oily

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‡After this work was completed, Wermuth and Flammang[3] reported the synthesis of 1-phenyl derivatives of the title structure.

§Mps are uncorrected. All compds were analyzed for C, H, and N and gave results within ±0.4% of the theoretical values. Ir and nmr spectral data were consistent with the structures assigned.

#Obtained from 1-phenyl-1-hydroxy-6-chloroindan by CrO_3 oxidation according to Nizamuddin, *et al.*[6]

hydrazone (2.3 g) which was sublimed at 140–150° (5×10^{-3} mm) to yield crystalline **1** (1 g, 48%), mp 135–137°. Recrystn from EtOH afforded 0.85 g, mp 137–138°. *Anal.* ($C_{16}H_{13}ClN_2O$) C, H, N.

Similarly prepd was **2** (65% yield), mp 229–230° (from $CHCl_3$–EtOH) (*Anal.* ($C_{15}H_{11}ClN_2O$) C, H, N), and, using 2-benzoyl-4,5-dimethoxyphenylacetic acid,[7] 1-phenyl-3-methyl-3,5-dihydro-7,8-dimethoxy-4*H*-benzo[2,3]diazepin-4-one **(3)** (40% yield) (from MeOH), mp 160–162° (*Anal.* ($C_{18}H_{18}N_2O_3$) C, H, N), and 1-phenyl-3,5-dihydro-7,8-dimethoxy-3*H*-benzo[2,3]diazepin-4-one **(4)** (75% yield) (from MeOH), mp 200–202° (*Anal.* ($C_{17}H_{16}N_2O_3$) C, H, N).

1-Methyl-3,5-dihydro-7,8-dimethoxy-4*H*-benzo[2,3]diazepin-4-one (5) and 1-Methyl-2-amino-2,3-dihydro-3-oxo-6,7-dimethoxyisoquinoline (8). 2-Acetyl-4,5-dimethoxyphenylacetic acid[8] (7.2 g, 30 mmoles) and hydrazine hydrate (1.5 g, 30 mmoles) in EtOH (200 ml) were heated under reflux for 2 hr, the solution was left overnight and concd to give the hydrazone **10** (5.3 g, 70%), mp 170–171° dec (from $CHCl_3$). *Anal.* ($C_{12}H_{16}N_2O_4$) C, H, N. The hydrazone (7.2 g, 28 mmoles) was heated at 180° (2×10^{-2} mm) for 4 hr; the cooled product was sepd into water-soluble and -insoluble parts. The latter was crystd from EtOH to give **5** (3.2 g, 45%), mp 210–212°. *Anal.* ($C_{12}H_{14}N_2O_3$) C, H, N.

The water-soluble fraction was crystd from MeOH to give **8** (1.8 g, 25%), mp 227–229°. *Anal.* ($C_{12}H_{14}N_2O_3$) C, H, N.

1-Phenyl-3-(γ-dimethylaminopropyl)-3,5-dihydro-8-chloro-4*H*-benzo[2,3]diazepin-4-one (6). A soln of **2** (0.9 g, 3.3 mmoles) in dry dioxane (25 ml) was stirred with 50% NaH suspension (0.2 g, 5 mmoles) in mineral oil at 50° for 1 hr and then treated with γ-dimethylaminopropyl chloride (0.7 g) in dioxane (10 ml). The mixture was stirred at 50° overnight and filtered, and the filtrate was stripped of solvent. The basic product was isolated through dil HCl and was obtained as an oil (0.5 g) which crystd from hexane, 0.4 g (34%), mp 84–86°. *Anal.* ($C_{20}H_{22}ClN_3O$) C, H, N.

1-Methyl-3-(β-dimethylaminoethyl)-3,5-dihydro-7,8-dimethoxy-4*H*-benzo[2,3]diazepin-4-one **(7)**, characterized as a maleate (85% yield), was prepd in a similar manner from **5**, mp 155–157° (from EtOH–Et_2O). *Anal.* ($C_{20}H_{27}N_3O_7$) C, H, N.

2-Acetyl-4,5-dimethoxyphenylacetic Acid Guanylhydrazone (11). The acid (1.45 g, 6 mmoles) and aminoguanidine hydrogen carbonate (0.8 g, 6 mmoles) in EtOH (25 ml) were heated under reflux overnight to give the guanylhydrazone (1.1 g, 63%), mp 291° dec (*Anal.* ($C_{13}H_{18}N_4O_4$) C, H, N), forming a HCl salt, mp 210–212° (from EtOH) (*Anal.* ($C_{13}H_{19}ClN_4O_4$) C, H, N).

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References

(1) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961); L. H. Sternbach, *Angew. Chem., Int. Ed. Engl.*, **10**, 34 (1971).
(2) J. O. Halford, R. W. Raiford, and B. Weissmann, *J. Org. Chem.*, **26**, 1898 (1961).
(3) C. G. Wermuth and M. Flammang, *Tetrahedron Lett.*, 4293 (1971).
(4) S. Irwin, "Animal and Clinical Pharmacological Techniques in Drug Evaluation," H. Nodine and P. S. Siegler, Ed., Yearbook Medical Publishers, Philadelphia, Pa., 1964, pp 36–54.
(5) J. David and R. S. Grewal, "Symposium on CNS Drugs," G. S. Sidhu, Ed., New Delhi, 1966, pp 44–52.
(6) S. Nizamuddin, M. Gossal, and D. M. Chaudhury, *J. Indian Chem. Soc.*, **42**, 569 (1965).
(7) H. R. Bentley, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 1763 (1952).
(8) P. M. Chakraborti, *Tetrahedron Lett.*, 1771 (1963).

Synthesis of 9-(3-Deoxy-3-fluoro-β-D-arabinofuranosyl)adenine

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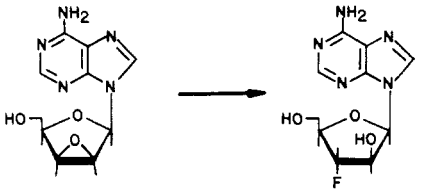
Modifications in the carbohydrate moiety of nucleosides that occur in the nucleic acids have led to structural analogs that possess important and useful biological properties. A significant example is 9-β-D-arabinofuranosyladenine (ara-A)[1] which has demonstrated significant antiherpes virus activity.[2,3] It was, therefore, of interest to prepare an ara-A analog (3-deoxy-3-fluoro-β-D-arabinofuranosyladenine, **2**) with a subtle modification in the carbohydrate moiety, in the hope that the antiviral activity might be maintained or increased with added selectivity.

The ring opening of the epoxide, 9-(2,3-anhydro-β-D-lyxofuranosyl)adenine **(1)**, seemed to provide the best approach



1 2

to the synthesis of **2**, since highly stereoselective scission of carbohydrate epoxides to the corresponding fluorohydrins has been observed[4-6] with KHF_2. Goodman and coworkers[7-9] have found, however, that 9-(2,3-anhydro-β-D-pentofuranosyl)adenines react with many nucleophiles to furnish mixtures of 2′- and 3′-substituted nucleosides. Treatment of **1** with KHF_2 in ethylene glycol at reflux gave a 41% yield of **2** as the single nucleoside product. As a result of the strenuous conditions required for displacement, there was considerable decomposition. Adenine was the only other isolable product; no other nucleosides were detected.

Exclusive opening of the epoxide at C-3 by fluoride ion was confirmed by elemental and chromatographic analysis as well as pmr spectral data for **2** which showed H-3′ as a pair of triplets ($J_{F,3'}$ = 53 Hz, $J_{3',4'}$ and $J_{2',3'}$ = 3.5 Hz) and H-1′ as a broadened doublet (fine splitting with fluorine) instead of a wide quartet ($J_{F,1'} \sim 18$ Hz), which would be expected if the fluorine were at C-2.[10] The mass spectral data indicated[11] from the presence of a *m/e* 178 (base + 44) peak, that the substituent at C-2 was a hydroxy group instead of fluorine.

Antiviral Evaluation.† *In vitro* cell culture experiments with herpes virus indicated that **2** possessed no significant antiviral activity, which suggests that the enzymatic site of action of ara-A[12] is extremely sensitive to changes in the carbohydrate moiety at C-3.

Experimental Section‡

9-(3-Deoxy-3-fluoro-β-D-arabinofuranosyl)adenine (2). A mixture of **1** (3.00 g, 12 mmoles) and KHF_2 (9.00 g) in ethylene glycol (45 ml) was heated to refluxing temperature for 55 min. The reaction mixture was cooled and applied directly on a column prepacked with silica gel (Merck 7734, 600 g) in EtOAc-*n*-PrOH-H_2O (4:1:2, upper phase). The product was eluted with the same solvent mixture and crystallized from water to give 1.33 g (41%) of needles: mp 261–262° dec; $[\alpha]^{25}D$ −12.7° (*c* 1.0, DMF); uv $\lambda_{max}^{pH\ 1}$ 256 nm (ε 14,800), $\lambda_{max}^{pH\ 7}$ 259 nm (ε 15,100), $\lambda_{max}^{pH\ 11}$ 259 nm (ε 15,100); pmr (DMSO-d_6) δ 8.22 (s, 2, H_2+H_8), 7.30 (s, 2, NH_2), 6.38 [d (with

†The authors wish to thank Dr. R. W. Sidwell and his staff for the antiviral evaluation.

‡Melting point was determined on a Thomas-Hoover melting point apparatus and is uncorrected. The uv spectra were recorded on a Cary 15 spectrophotometer and optical rotation was determined with a Perkin-Elmer polarimeter 141. The infrared spectrum was recorded with a Perkin-Elmer 257 (KBr); nmr spectra were recorded with a Hitachi Perkin-Elmer R-20A nmr spectrometer (DSS); and the mass spectrum was recorded with a Perkin-Elmer 270 mass spectrometer. Satisfactory analytical data (C, H, N, F within ±0.4% of theoretical values) were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn.