9-Nitro-1,2,3,4-tetrahydrophenanthrene (XII).—A mixture of XI (0.05 g, 0.18 mmole), copper (0.075 g, electrolytic metal, Fisher), and quinoline (8 ml) was heated for 15 min at reflux temperature. The dark brown solution was cooled, dissolved in $CHCl_3$, and filtered free of copper. The $CHCl_3$ solution was extracted four times with 10% HCl, twice with saturated $NaHCO_3$, twice with water, and dried (Na_2SO_4). The $CHCl_3$ was evaporated under reduced pressure to leave a brown oily residue (0.046 g) which was dissolved in a minimum amount of Skellysolve B and chromatographed on 1.5 g of Merck alumina in Skellysolve B. The second 10-ml fraction eluted with Skellysolve B yielded 0.024 g (61%) of yellow crystalline material (XII), mp 75.5–76.5°, $\lambda_{max}^{CHCl_3}$ 6.63 and 7.46 μ, which was used as such for reduction.

9-Acetylamino-1,2,3,4-tetrahydrophenanthrene (X).—A mixture of 0.027 g (0.12 mmole) of XII, 0.080 g (1.2 g-atoms) of zinc dust, and acetic acid (3.5 ml) was refluxed for 1.5 hr. The suspension was filtered hot, and the resulting yellow filtrate was diluted with water and the solution was evaporated to dryness under reduced pressure. The residue (0.023 g) was taken up in $CHCl_3$ and dried (Na_2SO_4). Evaporation of the $CHCl_3$ under reduced pressure left a semisolid brown residue which was dissolved in a minimum amount of benzene and chromatographed on 1.0 g of Merck alumina in benzene. Fractions (10 ml) were collected, and fractions 3, 4, and 5, eluted with 5% ether in benzene, yielded light yellow material. These fractions were combined, dissolved in benzene, and rechromatographed on 1.0 g of Davison silica gel in benzene. The fractions eluted with 10% ether in benzene yielded crystalline residues; these were combined and recrystallized from ethanol–water with Norit to afford colorless fine needles (2 mg): mp 192.5–193°; λ_{max} 3.04 (s), 3.26 (w) (NH of amide), 6.05 μ (s) ("amide-I band"). The latter physical data supported characterization of the material as X (lit.[11] mp 191–192° from ethanol).

9-Amino-1,2,3,4-tetrahydrophenanthrene (IX).—The nitro compound XII was reduced catalytically with Pt and hydrogen. Recrystallization of the product from Skellysolve B gave light tan crystals: mp 76–77°; λ_{max} 2.89 (s), 2.96 (w) (free NH_2 stretching), 6.18 μ (w) (NH bending). The literature[11] reports mp 76.5–77° for IX from ethanol–methanol.

New Compounds

A Direct Synthesis of 1-β-D-Arabinofuranosyl-5-fluorocytosine[1]

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The interesting cancer chemotherapeutic agent, 1-β-D-arabinofuranosyl-5-fluorocytosine (1), has recently been synthesized[2] by an application of the Fischer-Helferich procedure[3] in a seven-step sequence. The Hilbert-Johnson[4] method when applied to the synthesis of this compound has resulted in a more direct synthesis of 1 and 1-β-D-arabinofuranosyl-5-fluorouracil (**2**).[2,3,5,6]

An unusual feature of the nmr spectra of the nucleosides in the 5-fluoropyrimidine series was the appearance of a pair of doublets for the anomeric hydrogen rather than the expected doublet which is attributed to an apparent long-range coupling effect of the 5-fluoro group on the C_1' proton[7] (see Table I). The effect is also evident in the very recently published nmr spectra of α- and β-5-fluoro-2-deoxyuridine,[8] wherein the pattern for the anomeric proton appears as a split triplet (multiplet of six) and a split pair of doublets (multiplet of eight) in the β and α anomers, respectively, rather than the normal patterns consisting of a triplet (pseudo-triplet) or a pair of doublets (multiplet of four) expected in the nonfluorinated compounds.[9,10]

TABLE I

60-MC NMR SPECTRA OF $C_1'H$ IN 1-β-D-ARABINOFURANOSYLPYRIMIDINES

Base	τ[d]	Description	J, cps
5-Fluorouracil (**2**)	4.02[a]	Pair of doub	4, 2
2′,3′,5′-Tri-O-acetate of **2**	3.72[b]	Pair of doub	4.5, 2
5-Fluorocytosine (**1**)	3.98[a]	Pair of doub	4, 2
5-Fluoro-4-methoxy-1H-pyrimidin-2-one (**3**)	3.99[a]	Pair of doub	4, 2
4-Methoxy-5-methyl-1H-pyrimidin-2-one	3.94[a]	Doub	4
Cytosine	3.88[c]	Doub	4.5
Uracil 2′,3′,5′-tri-O-acetate	3.64[b]	Doub	4
Thiouracil 2′,3′,5′-tri-O-acetate	3.66[b]	Doub	4

[a] In DMSO-d_6. [b] In $CDCl_3$. [c] In D_2O. [d] Relative to TMS internal standard for organic solvents and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) for D_2O.

Experimental Section

1-(β-D-Arabinofuranosyl)-5-fluoro-4-methoxy-1H-pyrimidin-2-one (3).—2′,3′,5′-Tri-O-benzyl-1-(*p*-nitrobenzoyl)-D-arabinofuranose[11] (28.5 g, 0.05 mole) was added to dry methylene chloride (350 ml) which had been saturated with HCl at 0°. The solution was allowed to stand at 0° for 2 hr while bubbling in a slow stream of anhydrous HCl. The *p*-nitrobenzoic acid which had separated in nearly quantitative yield was removed by rapid filtration through a sintered-glass funnel. The filtrate was concentrated to dryness *in vacuo* (bath 40°) and evacuated (0.1 mm) for 16 hr (25°). The residual chloro sugar was dissolved in dry CH_2Cl_2 (320 ml) and 2,4-dimethoxy-5-fluoropyrimidine[12] (7.9 g, 0.05 mole) in CH_2Cl_2 (80 ml) was added along with molecular sieves[13] (20 g). The mixture was stirred for 3 days at ambient temperature protected by a drying tube. The mixture was filtered (Celite) and the filtrate and a CH_2Cl_2 wash were combined and concentrated *in vacuo* to a pale yellow syrup (29.2 g). The syrup was dissolved in dry CH_3OH (400 ml) and hydrogenated in two batches each using freshly prereduced $PdCl_2$ (3 g) and an initial hydrogen pressure of 3 atm. Reduction was complete in 15 min and the systems were bled free of hydrogen and flushed with N_2 and the mixtures were filtered from the catalyst. The catalyst was washed with CH_3OH and the filtrates and washes were neutralized by stirring with Dowex

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(2) J. J. Fox, N. Miller, and I. Wempen, *J. Med. Chem.*, **9**, 101 (1966).

(3) N. C. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky, and J. J. Fox, *J. Am. Chem. Soc.*, **83**, 4060 (1961).

(4) T. Y. Shen, H. M. Lewis, and W. V. Ruyle, *J. Org. Chem.*, **30**, 835 (1965); F. Keller, and A. R. Tyrrill, *ibid.*, **31**, 1289 (1966).

(5) E. J. Reist, J. H. Osiecki, L. Goodman, and B. R. Baker, *J. Am. Chem. Soc.*, **83**, 2208 (1961).

(6) F. Keller, N. Sugisaka, A. Tyrrill, L. H. Brown, J. E. Bunker, and I. J. Botvinick, *J. Org. Chem.*, **31**, 3842 (1966).

(7) We wish to thank Dr. E. J. Reist, Stanford Research Institute, Menlo Park, Calif., for confirming the presence of this spectral feature in anomerically pure **2** prepared by another method.[5]

(8) A. Dipple and C. Heidelberger, *J. Med. Chem.*, **9**, 715 (1966).

(9) M. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **87**, 4934 (1965).

(10) R. U. Lemieux and M. Hoffer, *Can. J. Chem.*, **39**, 110 (1961).

(11) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

(12) M. Prystas and F. Sorm, *Collection Czech. Chem. Commun.*, **30**, 1900 (1965).

(13) Linde Molecular Sieves Type 4A, 1/16-in. pellets, Linde Division, Union Carbide Corp.

2-X8 (HCO_3^-) ion-exchange resin. The neutralized solutions were filtered free of resin, the resin was washed with a small amount of methanol, and the combined filtrate and wash were concentrated *in vacuo* (35° bath) to a residual solid. The residue was dissolved in CH_3OH (50 ml) and diluted with ether (75 ml) and hexane (100 ml). The solution was seeded and stored at 5° for 16 hr to give the product as a crystalline solid (3.4 g, 0.0123 mole, 24.6%), mp 170–171.5°. Continued storage afforded a second crop (1.7 g, 34% total). The material was homogeneous by tlc (silica gel–benzene–*n*-butylamine–water, 15:5:1). An analytical sample was prepared by recrystallization from a methanol–ether mixture containing a trace of hexane: mp 172–173°, $[\alpha]^{25}D$ +178.1° (*c* 1.0, CH_3OH), λ_{max}^{EtOH} 290 mμ (ε 6500), λ_{min}^{EtOH} 244 mμ (ε 845).

Anal. Calcd for $C_{10}H_{13}FN_2O_6$: C, 43.48; H, 4.75; N, 10.14; F, 6.88. Found: C, 43.24; H, 4.76; N, 9.88; F, 7.09.

A coupling run on the same scale as above (5 days) without the addition of molecular sieves yielded only 2.4 g (17%) of **3**.

1-β-D-Arabinofuranosyl-5-fluorocytosine (1).—A solution of **3** (2.76 g, 0.01 mole) in a 5% solution of anhydrous NH_3 in CH_3OH (200 ml) was sealed in a glass-lined bomb which was heated in an oil bath at ~125° for 16 hr. The bomb was cooled and opened and the contents was evaporated to dryness *in vacuo*. The residue was triturated with a small amount of CH_3OH, filtered, washed, and dried *in vacuo* to give **1** (2.3 g, 88%), mp 234–235° dec. The compound moved as a single spot on tlc (silica gel–benzene–*n*-butylamine–water, 15:5:1) and was free of starting material. The material was recrystallized once from a hot CH_3OH–H_2O mixture to give pure **1**, mp 230–232° dec, $[\alpha]^{25}D$ +165.2° (*c* 0.2, H_2O) [lit.[2] mp 237–238°, $[\alpha]^{23}D$ +163 ±2° (*c* 0.18, H_2O)]. The ultraviolet and infrared spectra were identical with those of a sample prepared from **2** by the method of Fox, *et al.*[2]

1-β-D-Arabinofuranosyl-5-fluorouracil (2).—The 4-alkoxy derivative **3** (0.6 g, 2.07×10^{-3} mole) was dissolved in 1 *N* HCl in methanol (20 ml), and the tightly stoppered solution was stored for 72 hr at ambient temperature. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in a minimum of absolute EtOH, seeded, and stored at ~5° to give **2** (0.35 g, 65%) in two crops: mp 187–189, 184–185°. The combined crops were recrystallized once from hot absolute EtOH to give pure **2**, mp 186–188°, $[\alpha]^{24.5}D$ +116.7° (*c* 0.2, H_2O) [lit.[3] mp 187–188°, $[\alpha]^{24}D$ +128° (*c* 0.21, H_2O)]. The ultraviolet and infrared spectra were in good agreement with those of an authentic sample.

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Terpene Compounds as Drugs. III. Terpenylketoximes

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The report[1] that some oximes of aliphatic ketones are endowed with interesting hypnotic and anticonvulsant properties and our interest in the terpene field have led us to synthesize the oximes of geranylacetone, nerylacetone, and farnesylacetone and to study their pharmacological properties. However, none of the three compounds displayed hypnotic and anticonvulsant activity of any interest. By contrast, geranylacetone oxime and nerylacetone oxime revealed a marked and unexpected hyperglycemic activity in rats and rabbits.

Experimental Section

Geranylacetone Oxime.—Geranylacetone[2] (4.6 g, 0.0237 mole), hydroxylamine hydrochloride (2.47 g, 0.0355 mole), and $NaHCO_3$ (2.98 g, 0.0355 mole) were poured into 10 ml of water, and the mixture was stirred for 24 hr at room temperature. An emulsion formed which was then extracted with ether, the ethereal solution was washed with water and dried (Na_2SO_4), and the solvent was removed. The residue was distilled *in vacuo* to yield a colorless oil (4.1 g, 83%), bp 107–108° (0.05 mm), $n^{20}D$ 1.4897, lit.[3] $n^{20}D$ 1.4894.

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.58; H, 11.07; N, 6.69. Found: C, 74.74; H, 11.06; N, 6.51.

Nerylacetone oxime was similarly prepared from nerylacetone[2] with an 84% yield, bp 112–114° (0.12 mm), $n^{20}D$ 1.4890.

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.58; H, 11.07; N, 6.69. Found: C, 74.55; H, 11.18; N, 6.49.

Farnesylacetone oxime was derived from farnesylacetone[2] in an 81% yield, bp 142–143° (0.07 mm), $n^{20}D$ 1.4974.

Anal. Calcd for $C_{18}H_{31}NO$: C, 77.92; H, 11.26; N, 5.05. Found: C, 77.75; H, 11.05; N, 4.90.

(1) F. Hanschild, 2nd Conferentia Hungarica pro Therapia et Investigatione in Pharmacologia, Budapest, Oct 2–7, 1962.

(2) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957).

(3) M. F. Carroll, *J. Chem. Soc.*, 704 (1940).

(4) O. Isler, R. Rüegg, L. H. Chopard-dit-Jean, A. Wintersteiner, and D. Wiss, *Helv. Chim. Acta*, **41**, 786 (1958).

Formation of 4-Amino-3,5-di(3-indolylmethyl)-s-triazole from Indole-3-acetonitrile and Hydrazine

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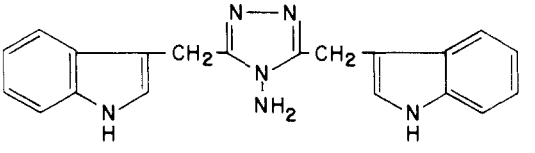
During investigations of the chemistry of indolic compounds and possible routes to tryptamines, indole-3-acetonitrile was treated with anhydrous hydrazine. Analytical data obtained together with consideration of reactions reported in the Experimental Section led to the structural assignment as 4-amino-



3,5-di(3-indolylmethyl)-s-triazole for the compound obtained.

Experimental Section

Mass spectroscopy was performed by the Morgan Schaffer Corp., Montreal 26, Quebec, Canada. Nmr spectra was done by Nuclear Magnetic Resonance Specialties, Inc., New Kensington, Pa.

Indole-3-acetonitrile (5.0 g, 0.032 mole) was refluxed with 25.0 ml of anhydrous hydrazine for 18 hr. Most of the hydrazine was removed under vacuum and the residual solution was poured into water resulting in the precipitation of 6.1 g (58% yield) of light yellow product, mp 224–226. Three crystallizations from ethanol–water gave a cream-colored compound, mp 227–228° (cor).

Anal. Calcd for $C_{20}H_{18}N_6$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.42; H, 5.52; N, 24.22.

Chromatography on thin layer silica on glass in 9:1 $CHCl_3$–CH_3OH produced one spot at R_f 0.1 giving a positive xanthydrol reaction for indoles, negative ninhydrin reaction, and weak fluorescence under uv light. The compound was insoluble in water, but soluble in dilute HCl. Mass spectroscopic analysis gave 342 as the parent peak and therefore molecular weight. The infrared absorption spectrum (KBr) showed the presence of the N–H stretching band at 2.95 μ. The uv spectrum (in

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