gave 3-acetamido-2,4,6-triiodobenzoic acid.[9]

4-(3'-Methoxy-4'-iodophenyl)isovaline (26). Treatment of **20** with 1 equiv of ICl in concd HCl (3 *M*), followed by the usual work-up, gave 4-(3'-methoxy-4'-iodophenyl)isovaline **(26)**, in 90% yield. Para substitution by I was proved by nmr spectrum; nmr (CF_3COOH) δ 1.76 (s, CCH_3), 2.25 (m, CH_2C), 2.75 (m, benzylic CH_2), 3.75 (s, OCH_3), 6.50 (dd, 1 arom proton at position 6', J = 8.5 and 3.5 Hz), 6.78 (d, 1 arom proton at position 2', J = 4 Hz), 7.58 (d, 1 arom proton at position 5', J = 9 Hz).

Oxidative degradation of 4-(3'-methoxy-4'-iodophenyl)isovaline with alkaline $KMnO_4$ at 50° gave 3-methoxy-4-iodobenzoic acid, mp 235–236° (benzene), which reacted with CH_2N_2 to give methyl 3-methoxy-4-iodobenzoate, mp 50° (benzene–petr ether), prepared previously by iodination of 3-hydroxybenzaldehyde followed by treatment of the benzoiac acid deriv with CH_2N_2, without, however, establishing the position of the iodine substituent[14] (lit.[14] mp 49°).

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Preparation and Antitumor Properties of Analogs of Acronycine

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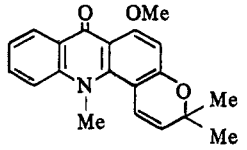
Acronycine **(1)**, also known as acronine, one of a group of alkaloids isolated from the bark of an Australian tree, has been shown to have broad spectrum antitumor activity against experimental neoplasms in laboratory animals.[1] Acronycine, possessing an acridone system fused to a *gem*-dimethyldihydropyran ring, is unique among cancer chemotherapeutic agents. It represents a new lead in chemotherapy.

Four types of chemical relatives of acronycine were synthesized in the expectation of elucidating structure-activity relationships and of finding agents possessing additional biological activity. The types were: 1,7-, 1,10-, and 4,7-phenanthrolines; 2,2-dimethylchromans; double chromans; and 2,2-dimethyl-1,2-dihydroquinolines.



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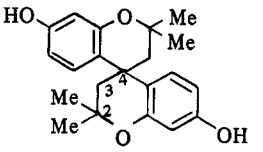
Chemistry. If the cyclic oxygen atom in acronycine is replaced with nitrogen, the ring system which results is a derivative of 1,7-phenanthroline. Four 1,7-phenanthrolines were prepared, following modified literature procedures. 5-Amino-1,7-phenanthroline **(2)** was prepared in 60% yield by Raney nickel reduction of 5-nitro-1,7-phenanthroline **(3)**, which in turn was prepared by a double Skraup synthesis on *sym*-diaminonitrobenzene.[2] 1,7-Phenanthroline-4,10-diol **(4)** and its precursor, 4,10-dihydroxy-1,7-phenanthroline-3,9-dicarboxylic acid **(5)**, were prepared according to the literature.[3]

2,2,4-Trimethyl-4-(4-hydroxyphenyl)chroman (Dianin's compound) bears a structural resemblence to acronycine and is known to be a clathrating agent, capable of forming inclusion complexes with a great variety of inorganic and organic substances.[4,5] Dianin's compound is made by condensing phenol with mesityl oxide in the presence of HCl gas. When resorcinol was employed in our laboratory in place of phenol, with ferric chloride as the catalyst, in the anticipation of obtaining a more highly ring-hydroxylated derivative, the unexpected spiro compound 2,2,2',2'-tetramethyl-7,7'-dihydroxy-4,4'-(3*H*,3'*H*)-spirobi(2*H*-1-benzopyran) **(6)** was obtained, in 26% yield. Compound **6** was identified by means of elemental analysis, ir, nmr,



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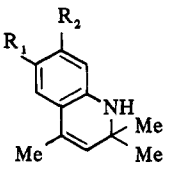
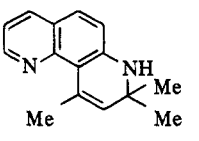
and mass spectroscopy. The nmr spectrum clearly indicated a highly symmetrical molecule, since only one type of aromatic substitution pattern was observed, only two types of methyl groups, and no evidence of olefinic protons. The one other symmetrical spiro compound possible in addition to **6** would be that isomer in which the two chroman nuclei are both joined through carbon number three (see numbering in **6**) instead of carbon four. This alternate arrangement is much less favored when one considers the actual chemical shifts of the methylene protons: in **6** the methylenes are located between two saturated carbons and appear as a singlet at *ca.* 2.05 ppm in hexadeuterioacetone. If the methylene protons were benzylic (as in the alternate structure) one would expect them to appear closer to 2.5 ppm. Structure **6** is also favored by the mechanism of formation. The mass spectrum was rationalized on the basis of structure **6**. It showed the molecular ion at *m/e* 340.1678 (calcd 340.1675) (21%), two intensely charged ions, $C_9H_{11}O_2$ (100%) and $C_{11}H_{11}O_2$ (87%), at *m/e* 151 and 175, respectively, and an intense doubly charged ion at *m/e* 155 (22%).

Three 2,2,4-trimethyl-1,2-dihydroquinolines **(7, 8, 9)** were synthesized as chemical relatives of acronycine. Relatively few dihydroquinolines of this type having substituents in the carbocycle have been reported. Compounds **8** and **9**



7, $R_1 = OCH_3$; $R_2 = H$
8, $R_1 = C_6H_5NH$; $R_2 = H$
9, $R_2 = NH_2$; $R_1 = H$



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were previously unreported. Condensation of the amine directly with mesityl oxide was accomplished, instead of generating the mesityl oxide *in situ* from acetone. Teuber and Glosauer[6] used the latter method in their synthesis of **7**. The previously unreported 8,8,10-trimethyl-7,8-dihydro-1,7-phenanthroline (**10**) was obtained by the condensation of mesityl oxide with 7-aminoquinoline; the latter was obtained by Raney nickel reduction of 7-nitroquinoline (**11**), which in turn was obtained through a Skraup reaction on *m*-nitroaniline.[7]

The double chroman 2,2,5,7,7,10-hexamethylbenzo[1,2-*b*:4,5-*b'*]dipyran (**12**) was synthesized to show the biological effect of two of the dialkylpyran moieties found in acronycine. Compound **12** was reported by Frampton[8] who isolated it as a generally uncharacterized product in a few per cent yield when 2,5-dimethyl-1,4-hydroquinone was caused to condense with isoprene in acetic acid with zinc chloride as catalyst. We prepared the compound in 84% yield using a few drops of H_2SO_4 as catalyst, as suggested by the work of Smith.[9] A phosphate ester approach to the synthesis of **12** has been reported.[10] The 2,5-dimethyl-1,4-hydroquinone was obtained in 60% yield.[11]

The preparation and reidentification of 3*H*-pyrano[3,2-*f*]-quinolin-3-one (**13**) was reported previously.[12]

Following the work of Snyder and Freier,[13] 4-hydroxy-5-methoxy-1,10-phenanthroline-3-carboxylic acid (**14**) and 4-hydroxy-5-methoxy-1,10-phenanthroline (**15**) were prepared as chemical relatives of acronycine. Compound **15** was obtained analytically pure, mp 190-192°, whereas Snyder and Freier obtained only a crude sample, mp 165-185°.

The final chemical relative of acronycine, 5-methoxy-4,7-phenanthroline (**16**), was prepared according to Eistert and Fink.[14]

Biological Results. Products were evaluated for antitumor activity by the Cancer Chemotherapy National Service Center. None of the compounds tested (**2-13**) was active against the murine L1210 lymphatic leukemia *in vivo*. It is worthwhile noting that acronycine itself fails to demonstrate activity in this system.[1a,1b,1d] Of six compounds (**2**, **6**, **7**, **12**, **15**, and **16**) evaluated against the Lieberman Plasma Cell (LPC-1) tumor system *in vivo*, only **7** was found to be active, a dosage of 400 mg/kg (dose 1 on day 13, number of daily injections 28, evaluation on day 48) resulting in a 54% increase in mean survival time (% *T/C* = 154) of tumor-bearing mice as compared with an untreated control group. The agent was administered subcutaneously in steroid suspending solution.

Experimental Section

Elemental microanalyses were performed by Galbraith Laboratories; where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points were determined in open tubes and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. Nmr spectrum was determined by Sadtler Laboratories on a Varian A-60A 60-MHz spectrometer in hexadeuterioacetone (Me_4Si). Mass spectral data were determined by Battelle Memorial Institute on an A.E.I. MS-9 double-focusing mass spectrometer.

5-Amino-1,7-phenanthroline (2). 5-Nitro-1,7-phenanthroline[2] (2.25 g) and *ca.* 2 g of W-2 Raney nickel were suspended in 200 ml of EtOH and shaken in a Parr apparatus at an initial pressure of 49 psi. The theoretical uptake of H_2 occurred in 15 min. Filtration and condensation to 40 ml yielded a faintly yellow solid: yield 1.1 g (60%). Recrystallization from EtOH did not raise the mp: mp 208-209°. The ir spectrum (KBr) showed no absorption attributable to nitro groups; amino group: 3430, 3300, 3150, 1635, and 1600 cm^{-1}. *Anal.* ($C_{12}H_9N_3$) C, H, N.

2,2,2',2'-Tetramethyl-7,7'-dihydroxy-4,4'(3*H*,3'*H*)-spirobi(2*H*-1-benzopyran) (6). Resorcinol (27.5 g), mesityl oxide (6.4 g), and ferric chloride (2.7 g) were refluxed in 100 ml of PhH for 5 hr. The still hot PhH phase was decanted from the black insolubles and was allowed to stand overnight. The PhH phase was extracted twice with hot water to remove unchanged resorcinol and the PhH phase evaporated using EtOH to remove H_2O azeotropically. An amber glass remained, which, when rubbed with $CHCl_3$, gave a solid. Filtration of the solids followed by washing with 40 ml of ice-cold $CHCl_3$ yielded a nearly colorless product, which was recrystallized twice from $CHCl_3$ to yield 5.1 g (26%) of compound: mp 199-200°, nmr (Me_2CO-d_6) ppm, singlets 1.33 and 1.56, CH_3C; singlet in DMSO-d_6) *ca.* 2.05, CCH_2C (AB pattern in acetone); meta doublet 6.14, aromatic; ortho meta doublet of doublets 6.47, aromatic; ortho doublet 7.18, aromatic; singlet 7.98, phenolic proton; ir ($CHCl_3$), nonbonded and bonded OH 3580 and 3300; ether 1090 cm^{-1}. *Anal.* Calcd for $C_{21}H_{24}O_4$: C, 74.12; H, 7.06; O. 18.82. Found: C, 74.27; H, 7.09; O, 18.59.

6-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (7). *p*-Anisidine (19.5 g), redistilled mesityl oxide (15.6 g), and iodine (0.64 g) were heated at reflux for 6 hr and allowed to stand overnight. The mixture was distilled directly, and the fraction bp 120-126° (1.3 mm) was collected: yield 4.6 g (14%). The HCl salt was prepared in the usual way from ether and HCl, being careful to avoid an excess of HCl. It was recrystallized from EtOH: mp 215-218°. The mixed mp with *p*-anisidine·HCl was 180-196°: ir (liq film) 3350 NH; 1380 and 1365 cm^{-1}, *gem*-dimethyl. *Anal.* ($C_{13}H_{18}NOCl$) C, H, Cl, N.

6-Anilino-2,2,4-trimethyl-1,2-dihydroquinoline (8). *N*-Phenyl-*p*-phenylenediamine (21.3 g) (purified by recrystallization from PhH–ligroin), mesityl oxide (13.7 g), and iodine (0.6 g) were heated at reflux for 7 hr, and allowed to stand overnight. The mixture was distilled directly, and after recovering 15.6 g of unchanged starting amine, the fraction bp 185-195° (1.0 mm) was collected as 2.7 g of viscous amber oil. The mono-HCl salt was made in the usual manner, and, when *ca.* 10% of it had been precipitated, addition of HCl in Et_2O was stopped, the salt thus precipitated was filtered off, and the addition of HCl was continued. This eliminated nearly all of the salt of unchanged starting amine. Purification was accomplished by washing with hot EtOH: yield 1.2 g (3.4%); mp 238-243°. The analytical sample was recrystallized from EtOH–MeOH (6:1) as slightly green shiny plates: mp 244-245° dec; ir ($CHCl_3$) 3400 cm^{-1}, secondary amine; 1385 and 1362, *gem*-dimethyl. *Anal.* ($C_{18}H_{21}N_2Cl$) C, H, Cl, N.

7-Amino-2,2,4-trimethyl-1,2-dihydroquinoline (9). *m*-Phenylenediamine (10.8 g) and mesityl oxide (19.6 g) were heated at reflux for 7 hr and allowed to stand overnight. Direct distillation of the mixture gave a fraction bp 140-148° (1.8 mm), amounting to 4.1 g (13%) of thick amber oil. The HCl salt was unstable. The presence of acid turned the compound brick red: ir (neat) 1380 and 1359 cm^{-1} *gem*-dimethyl. *Anal.* ($C_{12}H_{16}N_2$) C, H, N.

8,8,10-Trimethyl-7,8-dihydro-1,7-phenanthroline (10). 7-Aminoquinoline[15] (13.3 g), mesityl oxide (19.6 g), and iodine (0.4 g) were heated at reflux for 7 hr and allowed to stand overnight. Unchanged mesityl oxide was removed under reduced pressure, and the mixture distilled; all material boiling up to 170° (1.1 mm) was collected. The 14.2 g of oil so obtained was redistilled, and the fraction bp 148-154° (0.7 mm) was collected: yield 2.9 g (14%) of product, highly sensitive to acid; ir ($CHCl_3$) 3400 cm^{-1} secondary amine. *Anal.* ($C_{15}H_{16}N_2$) C, H, N.

2,2,5,7,7,10-Hexamethylbenzo[1,2-*b*:4,5-*b'*]dipyran (12). 2,5-Dimethyl-1,4-hydroquinone[11] (6.8 g) and 4.6 g of freshly fused $ZnCl_2$ were dissolved with heat in 175 ml of glacial AcOH. As this cooled to near room temp, isoprene (14 g) dissolved in 70 ml of AcOH was added. The mixture was allowed to stand at room temp for 1 hr, and, after heating at gentle reflux for 1.25 hr, two drops of 36 *N* H_2SO_4 was added. The solution was heated at reflux for an addtnl hr and cooled in ice. The white crystals (10.3 g) which were collected were purified by recrystallization from $CHCl_3$: mp 192-195° (lit[8] 193-196°). From the original filtrate, a second crop of crystals could be obtained by forcing pptn with H_2O, extracting with ligroin, removing phenols with Claisen's alkali, and evaporating the solvent: total yield 11.5 g (84%); ir ($CHCl_3$) 1386 and 1372 cm^{-1} *gem*-dimethyl. *Anal.* ($C_{18}H_{26}O_2$) C, H.

4-Hydroxy-5-methoxy-1,10-phenanthroline (15). 4-Hydroxy-5-methoxy-1,10-phenanthroline-3-carboxylic acid[13] (3.9 g) was heated dry in a butyl phthalate bath at 290-295° for 12 min and cooled. Eleven separate hot acetone extracts (12-15 ml) were made of the crude, dark reaction product. Each extract was treated with H_2O to ppt the product, all yields were combined and recrystallized from absolute EtOH using a large amount of charcoal: yield

0.90 g (27%) of yellow crystals, an analytical sample of which melted at 190–192°; ir ($CHCl_3$) 3000, 1650, 1520, 1455, 1285, 1172 cm^{-1}. *Anal.* ($C_{13}H_{10}N_2O_2$) C, H, N.

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Potential Antifertility Agents. 2. Tetrazole Derivatives of Nonsteriodal Estrogens[1]

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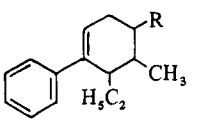
Replacement of the carboxyl group in biologically active compounds with the comparably acidic 5-tetrazoyl group has often resulted in retention of biological activity.[2] Work from these laboratories has shown that tetrazoles have retained activities of known carboxyl counterparts in the anti-inflammatory,[2,3] hypocholesterolemic,[4] and antiinfective[5] areas. We now report the tetrazole analogs (**1d** and **2d**) of the potent nonsteroidal estrogens **1a**[6,†] and **2a**.[‡] We hoped that the tetrazole derivatives might show a favorable dissociation of antifertility and estrogenic activities or a wide separation between feminizing and hypocholesterolemic properties of estrogens.

Chemistry. A sample of the acid **1a** was prepared from phenylmagnesium bromide and 2-methyl-3-ethyl-4-keto-



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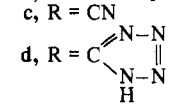
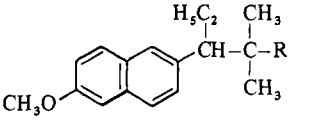
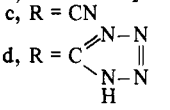
b, R = $CONH_2$
c, R = CN
d, R = 



2a, R = CO_2H
b, R = $CONH_2$
c, R = CN
d, R = 

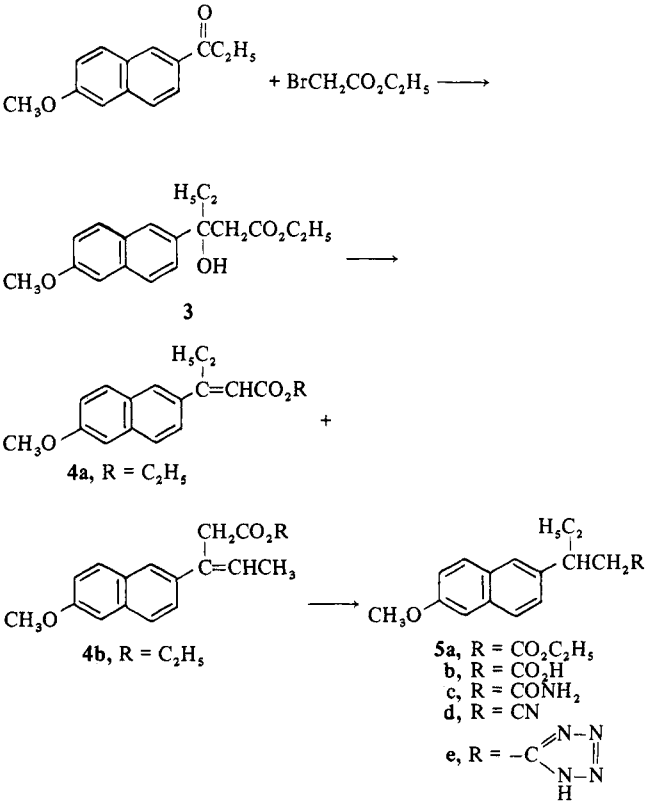
cyclohexanecarboxylic acid as described by Mebane.[6] The reported procedure was followed exactly in order to produce the same presumed mixture of diastereoisomers obtained by Mebane. Vpc analysis confirmed that **1a** (assayed as the methyl ester) is a mixture of diastereoisomers. Standard procedures were used to convert **1a**, *via* the amide (**1b**) and nitrile (**1c**), to the desired tetrazole (**1d**). The broad melting range of **1d** is suggestive of an isomeric mixture, but we have no additional evidence to confirm this. Nmr spectra confirmed that **1a–d** were the pure Δ^4 isomers with no detectable Δ^3 double bond isomer present.

A commercial sample of **2a** was similarly converted to the nitrile **2c**. The nitrile **2c** was resistant to treatment with NH_4N_3 under conditions employed with **1c**, but reaction with AlN_3 in diglyme produced the desired tetrazole **2d** in satisfactory yield.

In other series of tetrazoyl derivatives of biologically active acids, optimal activities were seen with tetrazoles which were less highly substituted than the standard drug after which they were modeled.[3,4] Because of this, we prepared the tetrazole **5e** (Scheme I) which is devoid of the crowding effect of the geminal dimethyl groups present in **2d**.

Oral Biological Activities. Methodology for assays reported herein has been previously described.[1] Compound **1d** was not contraceptive in mice in doses as high as 50 mg/kg,

Scheme I



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4a, R = C_2H_5

4b, R = C_2H_5

5a, R = $CO_2C_2H_5$
b, R = CO_2H
c, R = $CONH_2$
d, R = CN
e, R =

†Derivatives of **1a** bearing a *p*-methoxyl group on the aromatic ring were first reported as potent estrogens by Nathan and Hogg, *cf.* ref 7.

‡Vallestril; obtained from Searle Chemicals, Inc.