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Iodophenyl Derivatives of α-Methylalanine and Isovaline as Potential Oral Cholecystographic Agents

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Gastrointestinal absorption as well as gall bladder accumulation are prime factors in determining the efficacy of oral cholecystographic agents. In this connection, the biological properties of α-aminoisobutyric acid (AIB; 2-methylalanine), are of particular interest. AIB is a nonmetabolizable amino acid,[1] which undergoes active intestinal transport against a concentration gradient[2] and accumulates in the liver.[3] Since the presence of iodine atoms in organic compounds markedly enhances their biliary excretion,[4] it was hoped that combination of iodinated aromatic nucleus with AIB and its homolog, isovaline, would result in new efficient oral cholecystographic agents.

Chemistry. The new iodophenyl derivatives of AIB (**22**) and of isovaline (**23-26**) were prepared as outlined in Scheme I. The requisite benzyl and phenethyl methyl ketones (**3, 5, 9, 10**) were prepared in good yields using known procedures. Thus, 3-nitrophenylacetone (**3**) was prepared by acetylation of 3-nitrophenylacetic acid (**1**), according to Smith's method,[5] *via* the enol acetate (**2a, 2b**). Nmr analysis of the enol acetate, which was isolated as a crystalline, analytically pure material, revealed the existence of two isomeric products. The major one (**2a**, 75%), 1-(3′-nitrophenyl)-2-acetoxyprop-1-ene, exhibited resonances centered at 2.14 (s, CCH_3) and 2.25 ppm (s, $COCH_3$), and the minor one (**2b**, 25%), 2-acetoxy-3-(3′-nitrophenyl)prop-1-ene, exhibited resonances centered at 2.25 (s, $COCH_3$), 3.85 (s, benzylic CH_2), and 6.00 ppm (br s, vinylic protons $=CH_2$). Acid hydrolysis of the enol acetates yielded the desired benzyl methyl ketone (**3**). 3-Methoxyphenylacetone (**5**)—a known compound[6]—was prepared in a better yield and more conveniently, by condensing 3-methoxybenzaldehyde (**4**) with nitroethane, in the presence of piperidine as a catalyst, followed by Fe-HCl reduction of the resulting 1-(3′-methoxyphenyl)-2-nitroprop-1-ene, in a procedure analogous to that described recently.[7] Aldol condensation of either 3-methoxybenzaldehyde (**4**) or 3-nitrobenzaldehyde with acetone, followed by catalytic reduction of the resulting benzalacetones (**7, 8**), afforded the phenethyl methyl ketones (**9, 10**), of which the 3-amino derivative (**9**) is a new compound. The hydantoins (**11-15**), prepared in high yields by the reaction of the corresponding ketones with sodium cyanide and ammonium carbonate, according to the Bucherer-Bergs method,[8] were hydrolyzed to give the DL-ω-phenyl-α-methyl-α-amino acids (**16-21**). Aromatic iodination of the amino acids, employing either iodine monochloride (in the case of **23**) or iodine-potassium iodide (in the case of **22, 25**) as iodinating agents, afforded the final products (**22, 23, 25**). Whereas 4-(3′-aminophenyl)isovaline (**19**) and 4-(3′-hydroxyphenyl)isovaline (**21**) reacted smoothly with the iodinating agents to yield the 2,4,6-triiodophenyl derivatives (**23, 25**), *N*-acetyl-2-methyl-3-(3′-hydroxyphenyl)alanine (**18**) yielded only the 2,4-diiodophenyl derivative (**22**), and 2-methyl-3-(3′-aminophenyl)alanine (**16**) was completely resistant to iodination under normal iodinating conditions, due to steric hindrance exerted by the 2-methylalanine side chain. Positions of the two iodine atoms in DL-2-methyl-3-(2′,4′-diiodo-5′-hydroxyphenyl)alanine (**22**) were unequivocally established by means of nmr spectra, exhibiting two distinct singlets for two separated aromatic protons at 7.02 ppm—aromatic hydrogen at position 6′—and at 8.76 ppm—aromatic hydrogen at position 3′. Acetylation of **23** with 1 equiv of Ac_2O yielded the aromatic acetamido derivative (**24**), as proved by oxidative degradation of **24** to the known 2,4,6-triiodo-3-acetamidobenzoic acid.[9] Physical constants and analytical values for the newly synthesized ketones, hydantoins, and amino acids are tabulated in Tables I-IV.

Biological Testing. Compounds **22, 23, 24,** and **25** were each tested orally in dogs and cats at 100 mg of I/kg body wt. No gall bladder visualization up to 18 hr postdose was observed. The insoluble nature of the compounds (as sodium salts), precluded any iv radiographic or toxicity studies.

Table I. Benzyl and Phenethyl Methyl Ketones

No.	Ketones	Mp (crystn solvent) or bp (mm), °C	Formula	Analyses
3	3-Nitrobenzyl methyl ketone	62 (MeOH)	$C_9H_9NO_3$	C, H, N
5	3-Methoxybenzyl methyl ketone	113-115 (1.5)[a]	$C_{10}H_{12}O_2$	C, H
9	4-(3′-Aminophenyl)-butan-2-one	58 (hexane)	$C_{10}H_{13}NO$	C, H, N
10	4-(3′-Methoxyphenyl)-butan-2-one	121-123 (1.2)[b]	$C_{11}H_{14}O_2$	C, H,

[a] Lit.[6] bp 95-97° (0.7 mm). [b] Lit.[13] bp 151-152° (10 mm).

Experimental Section†

3-Nitrobenzyl Methyl Ketone (3-Nitrophenylacetone) (3). 3-Nitrophenylacetic acid[10] (80 g, 0.44 mole) was refluxed for 4 hr under N_2 in a mixture of pyridine (180 ml) and Ac_2O (440 ml).

†All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. Ir spectra were detd either neat or in KBr disks (Perkin-Elmer 337). Nmr spectra were obtd with a Varian A-60 spectrometer (TMS). Nmr and ir spectra of new compounds were compatible with related structures and are on file with the authors. Tlc's were performed on silica gel G plates, spots detected by exposure to I_2 vapor. Paper chromatography (of the amino acids) was carried out on Whatman No. 1 paper, using *n*-BuOH–AcOH–H_2O (60:20:20) as the solvent system. Chromatograms were developed for *ca.* 22 hr at room temp, and the amino acids were detected by ninhydrin or Bromocresol Green indicator. Titrimetric analyses and molecular weights detn of the amino acids were done either in water, using NaOH and Methyl-Red as an indicator, or in glacial AcOH, using $HClO_4$ and Methyl-Violet as the indicator.

Scheme I

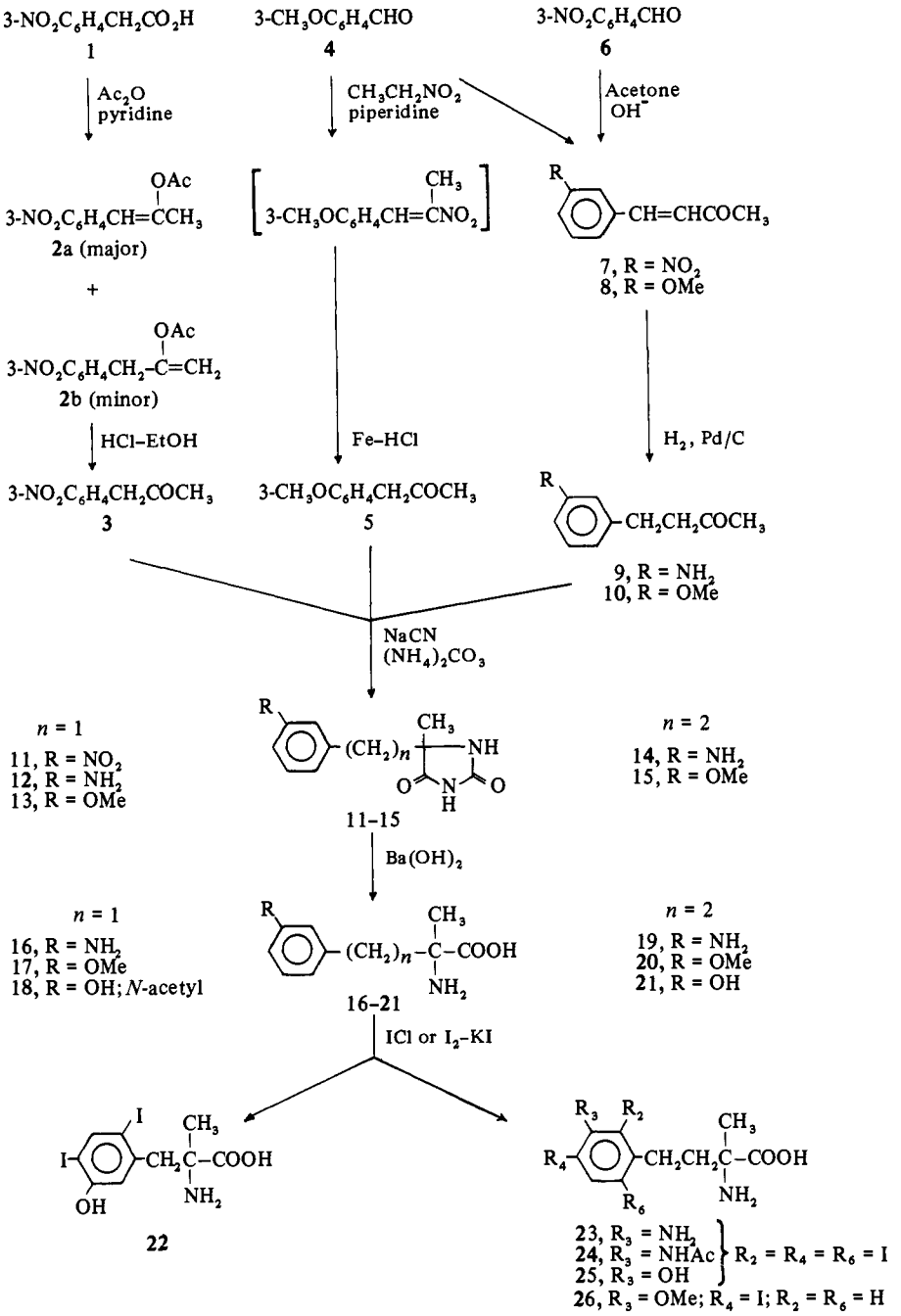

Table II. 5-Methyl-5-(substituted benzyl)hydantoins and 5-Methyl-5-(substituted phenethyl)hydantoins

No.	Substituted benzyl or substituted phenethyl	Yield, %	Mp, °C (crystn solvent)	Formula	Analyses
11	3-Nitrobenzyl	95	237 (*i*-PrOH)	$C_{11}H_{11}N_3O_4$	C, H, N
12	3-Aminobenzyl	80[a]	307–308 (dioxane)	$C_{11}H_{13}N_3O_2$	C, H, N
13	3-Methoxybenzyl	75	203–205[b] (H_2O)	$C_{12}H_{14}N_2O_3$	
14	3-Aminophenethyl	96	155 (H_2O)	$C_{12}H_{15}N_3O_2$	C, H, N
15	3-Methoxyphenethyl	95	113–115 (MeOH)	$C_{13}H_{16}N_2O_3$	C, H, N

[a] Yield of catalytic reduction of 11. [b] Lit.[6] mp 202–204°.

After evaporation of the solvents, the residue was distilled *in vacuo* to give 79 g (81% yield) of the enol acetate of 3-nitrophenylacetone (**2a, 2b**) as a pale yellow oil which solidified on cooling: bp 167–170° (1.0 mm); mp 69°; ir (neat) cm^{-1} 1755 (C=O ester), 1525 and 1350 (C-NO_2); nmr ($CDCl_3$), indicative of a mixture of the two isomeric enol acetates, **2a** (75%) δ 2.14 (s, $=CCH_3$), 2.25 (s, $COCH_3$), and **2b** (25%) δ 2.25 (s, $COCH_3$), 3.85 (s, CH_2), 6.00 (br s, $=CH_2$). *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.79; H, 5.04; N, 6.25.

The mixture of the enol acetates was hydrolyzed to the ketone by refluxing it in a mixture of EtOH (300 ml) and concd HCl (30 ml) for 1 hr, pouring the reaction mixture into water, and extracting with benzene. After evaporation of the solvent and crystn of the residue from MeOH, the product (3) was obtained in pure form (56 g, 88% yield): ir (KBr) cm^{-1} 1715 (C=O ketone), 1525 and 1355 (C-NO_2); nmr ($CDCl_3$) δ 2.30 (s, $COCH_3$), 3.91 (s, CH_2), 7.54–8.15 (m, 4 arom protons).

3-Methoxybenzyl methyl ketone (3-methoxyphenylacetone) (5)

Table III. ω-Phenyl-α-methyl-α-amino Acids

No.	Amino acid	Yield, %	Mp, °C (crystn solvent)	R_f	Formula	Analyses[d]
16	DL-Alanine, 2-methyl-3-(3'-aminophenyl)	80	279–280 dec (H_2O)		$C_{10}H_{14}N_2O_2$	C, H, N
16·HCl	HCl salt		293 dec (dil HCl)	0.62	$C_{10}H_{15}ClN_2O_2$	
17	DL-Alanine, 2-methyl-3-(3'-methoxyphenyl)	90	283 dec[a] (H_2O)	0.71	$C_{11}H_{15}NO_3$	
18	DL-*N*-Acetylalanine, 2-methyl-3-(3'-hydroxyphenyl)	58[b]	229 dec (H_2O)	0.93	$C_{12}H_{15}NO_4$	C, H, N
19	DL-Isovaline, 4-(3'-aminophenyl)	84	298 dec (H_2O)	0.43	$C_{11}H_{16}N_2O_2$	C, H, N
20	DL-Isovaline, 4-(3'-methoxyphenyl)	87	290–291 dec (H_2O)	0.82	$C_{12}H_{17}NO_3$	C, H, N
21	DL-Isovaline, 4-(3'-hydroxyphenyl)	65[c]	256–257 dec (EtOH–H_2O)	0.73	$C_{11}H_{15}NO_3$	C, H, N

[a] Lit.[6] mp 277° dec. [b] Based on demethylation of 17 followed by N-acetylation. [c] Based on demethylation of **20**. [d] Molecular weights were determined for all compounds, except 17, and agreed with the calculated values within ±0.4%.

Table IV. Iodophenyl Derivatives of 2-Methylalanine and Isovaline

No.	Amino acid	Yield, %	Mp, °C (crystn solvent)	R_f	Formula	Analyses[c]
22	DL-Alanine, 2-methyl-3-(2',4'-diiodo-5'-hydroxyphenyl)	75[a]	236 dec (H_2O)	0.84	$C_{10}H_{11}I_2NO_3$	C, H, I, N
22, *N*-Ac	DL-*N*-Acetylalanine, 2-methyl-3-(2',4'-diiodo-5'-hydroxyphenyl)	90	258–259 dec (EtOH–H_2O)		$C_{12}H_{13}I_2NO_4$	C, H, I, N
23	DL-Isovaline, 4-(3'-amino-2',4',6'-triiodophenyl)	86	258–259 dec (DMSO)	0.86	$C_{11}H_{13}I_3N_2O_2$	C, H, I, N
23·HCl	HCl salt		238–239 dec (dil HCl)		$C_{11}H_{14}ClI_3N_2O_2$	
24	DL-Isovaline, 4-(3'-acetamido-2',4',6'-triiodophenyl)	77[b]	247–248 dec (EtOH–H_2O)	0.97	$C_{13}H_{15}I_3N_2O_3$	C, H, I, N
25	DL-Isovaline, 4-(3'-hydroxy-2',4',6'-triiodophenyl)	73	256–246 dec (H_2O)		$C_{11}H_{12}I_3NO_3$	C, H, I, N
25·HCl	HCl salt		252–254 dec (HCl dil)	0.81	$C_{11}H_{13}ClI_3NO_3$	
26	DL-Isovaline, 4-(3'-methoxy-4'-iodophenyl)	90	288 dec (H_2O)	0.85	$C_{12}H_{16}INO_3$	C, H, N

[a] Total yield of iodination of 18 followed by deacetylation. [b] Yield of acetylation of **23**. [c] Molecular weights were determined for all compounds, except **26**, and agreed with the calcd values within ±0.4%.

was prepared by condensation of 3-methoxybenzaldehyde (**4**) with nitroethane in toluene, with piperidine as a catalyst, followed by reduction of the resulting 1-(3'-methoxyphenyl)-2-nitroprop-1-ene with Fe and HCl, in a procedure analogous to that described recently.[7] The product was extracted from the reduction mixture with benzene and distilled *in vacuo* (60% yield): nmr ($CDCl_3$) δ 2.07 (s, $COCH_3$), 3.60 (s, CH_2), 3.71 (s, OCH_3), 6.75–7.18 (m, 4 arom protons).

4-(3'-Aminophenyl)butan-2-one (9). 3-Nitrobenzalacetone (7) was prepd in 70% yield by condensation of 3-nitrobenzaldehyde (**6**) with acetone as described previously:[11] nmr ($CDCl_3$) δ 2.43 (s, $COCH_3$), 6.82 (d, =CHCO) and 7.54 (d, C_6H_5CH=) AB quartet (J_{AB} = 16.5 Hz). Catalytic reduction of 7 in AcOEt over Pd/C (10%) afforded 9 in 94% yield: ir (KBr) cm^{-1} 3345 and 3425 (C-NH_2), and 1705 (C=O ketone); nmr ($CDCl_3$) δ 2.11 (s, $COCH_3$), 2.74 (m, CH_2CH_2), 3.54 (br s, NH_2, disappears upon exchange with D_2O), 6.52–7.05 (m, 4 arom protons).

4-(3'-Methoxyphenyl)butan-2-one (10). 3-Methoxybenzalacetone (**8**) was prepared in 80% yield from 3-methoxybenzaldehyde (**4**) and acetone as described previously:[12] nmr ($CDCl_3$) δ 2.32 (s, $COCH_3$), 3.77 (s, OCH_3), 6.65 (d, =CHCO), and 7.43 (d, C_6H_5CH=) AB quartet, (J_{AB} = 16.0 Hz). Catalytic hydrogenation of 8 in AcOEt over PtO_2 afforded **10** in 95% yield: nmr ($CDCl_3$) δ 2.06 (s, $COCH_3$), 2.67 (t, CH_2), 2.75 (t, CH_2), 3.71 (s, OCH_3), 6.70–7.12 (m, 4 arom protons).

General Procedures for the Preparation of the Hydantoins (11, 13, 14, 15, Table II) and the Corresponding ω-Phenyl-α-methyl-α-amino Acids (16, 17, 19, 20, Table III). A solution of the ketone (0.4 mole), NaCN (1.0 mole), and $(NH_4)_2CO_3$ (3.0 mole) in 1.500 ml of a 50% EtOH–H_2O mixture was stirred for 12 hr at 55–60°. The reaction mixture was then concentrated *in vacuo* to about one-half of its original volume, diluted with an equal volume of water, and cooled in an ice bath. Filtration gave the desired product which was recrystallized from an appropriate solvent.

Typical nmr spectrum of 5-(3'-aminobenzyl)-5-methylhydantoin (**12**), prepd by catalytic hydrogenation of 11 over Pd/C, was (CF_3COOH) δ 1.54 (s, CH_3), 3.08 and 3.16 (dd, CH_2 two nonequivalent benzylic hydrogens, adjacent to an asymmetric center, C_5, J_{AB} = 3.5 Hz), 7.30–7.90 (m, 4 arom protons).

The 5,5-disubstituted hydantoins (0.1 mole) were hydrolyzed to the corresponding amino acids by $Ba(OH)_2 \cdot 8H_2O$ (0.3 mole), in aqueous solution (500 ml), following *ca.* 50-hr reflux. After dilution of the reaction mixture with water, CO_2 was bubbled through until pH 6 was reached, and then the mixt was filtered hot. The filtrate was evapd, and the residue—the product—crystallized from an appropriate solvent. The phenolic amino acids (**18, 21**) were obtained from the corresponding methoxy derivs (**17, 20**) by demethylation using 48% HBr.

The typical nmr spectrum of DL-2-methyl-3-(3'-aminophenyl)-alanine (**16**), as the HCl salt, was (D_2O) δ 1.94 (s, CH_3), 3.45 and 3.64 (dd, CH_2 two nonequivalent benzylic hydrogens, adjacent to an asymmetric center, C_2, J_{AB} = 14 Hz), 7.45–8.45 (m, 4 arom protons).

Typical Iodinating Procedures. DL-2-Methyl-3-(2',4'-diiodo-5'-hydroxyphenyl)alanine (22). To a stirred solution of 18 (23.7 g, 0.1 mole) in 25% aqueous CH_3NH_2 (300 ml), was added slowly a 1 *M* solution of I_2 in aqueous KI (220 ml, 0.22 mole). Stirring was continued, after completion of the addition, for another 2 hr; the solution was evapd *in vacuo* to about half of its original volume, diluted with water, and acidified with dil HCl. Excess of I_2 was destroyed by bubbling SO_2 through the solution, and the yellow product which precipitated, DL-2-methyl-3-(2',4'-diiodo-5'-hydroxyphenyl)-*N*-acetylalanine (**22**, *N*-Ac), was filtered and crystallized from AcOH or aqueous EtOH: nmr (pyridine-d_5) δ 1.69 (s, CCH_3), 1.79 (s, $COCH_3$), 3.86 and 4.05 (dd, CH_2 two nonequivalent benzylic hydrogens, J_{AB} = 14 Hz). The *N*-acetyl compound (**22**, *N*-Ac), (10 g), was refluxed in 6 *N* HCl (300 ml) until all the solid dissolved. Evaporation of the solution and crystallization of the residue from 25% HCl yielded **22** as the HCl salt (8.5 g, 86% yield), mp 218–220° dec. The free amino acid (**22**) was obtained from its HCl salt, by dissolving the salt in dilute NaOH and neutralizing with AcOH: nmr (5% NaOD in D_2O) δ 1.83 (s, CCH_3), 3.48 (overlapping dd), δ_A 3.42 and δ_B 3.54 (two nonequivalent benzylic hydrogens CH_2, J_{AB} = 15 Hz), 7.02 (s, arom H at position 6'), 8.76 (s, arom H at position 3').

DL-4-(3'-Amino-2',4',6'-triiodophenyl)isovaline (23). 4-(3'-Aminophenyl)isovaline (**19**) (7 g, 0.033 mole) was suspended in H_2O (250 ml) and dissolved in minimal amount of dil HCl. The solution was warmed to 60°, and a 3 *M* solution of ICl in concd HCl was added slowly with stirring, so that the rate of addition equaled the rate of disappearance of the ICl, as checked by KI–starch paper. After the addition of about 2 equiv of ICl, a yellow precipitate formed, and the reaction rate slowed down. The addition of 3 equiv of ICl lasted for about 5 hr. The reaction mixture was then left in the refrigerator overnight, filtered, and washed with acetone, to give the HCl salt of the iodinated amino acid (**23**·HCl): 18 g, 86% yield; nmr of the free iodinated amino acid (**23**) (CF_3COOH) δ 1.89 (s, CCH_3), 2.22 (m, CH_2C), 3.35 (m, benzylic CH_2), 8.45 (s, 1 arom proton).

Acetylation of **23** with 1 equiv of Ac_2O in AcOH yielded **24**, which upon oxidative degradation with alkaline $KMnO_4$ at 50°

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°).

Acknowledgment. We wish to thank Dr. George Brook Hoey of Mallinckrodt, St. Louis, Mo., for screening the iodoamino acids in dogs.

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Preparation and Antitumor Properties of Analogs of Acronycine

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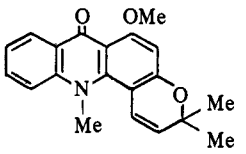
Acronycine (**1**), also known as acronine, one of a group of alkaloids isolated from the bark of an Australian tree, has been shown to have broad spectrum antitumor activity against experimental neoplasms in laboratory animals.[1] Acronycine, possessing an acridone system fused to a *gem*-dimethyldihydropyran 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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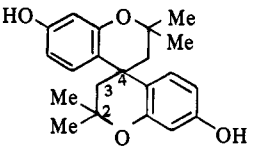
Chemistry. If the cyclic oxygen atom in acronycine is replaced with nitrogen, the ring system which results is a derivative of 1,7-phenanthroline. Four 1,7-phenanthrolines were prepared, following modified literature procedures. 5-Amino-1,7-phenanthroline (**2**) was prepared in 60% yield by Raney nickel 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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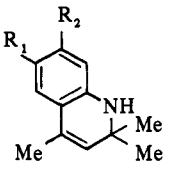
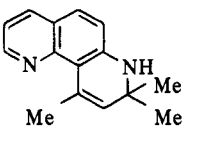
and mass spectroscopy. The nmr spectrum clearly indicated a highly symmetrical molecule, since only one type of aromatic substitution pattern was observed, only two types of methyl groups, and no evidence of olefinic protons. The one other symmetrical spiro compound possible in addition to **6** would 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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