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Anorectic Agents. 2. Structural Analogs of 5-(*p*-Chlorophenyl)-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol

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A variety of structural modifications of the anorectic agent 5-*p*-chlorophenyl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (1a) was prepared and evaluated for anorectic activity. All of the modifications resulted in complete or considerable loss of activity relative to 1a.

In the preceding paper[1] from our laboratories it was reported that 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols (1) represent a novel class of anorectic agents. From this group of substances the *p*-chlorophenyl analog 1a (mazindol, Sanorex) was found to be an effective and potent appetite suppressant in humans.[2]

In an attempt to determine some of the structural features that are needed for anorectic activity in 1 we have prepared a series of compounds where ring A has been modified by (a) the introduction of a second double bond (3), (b) enlargement to a six- (8) and seven- (9) membered ring, and (c) an additional ring fused at the 2,3 position (12).

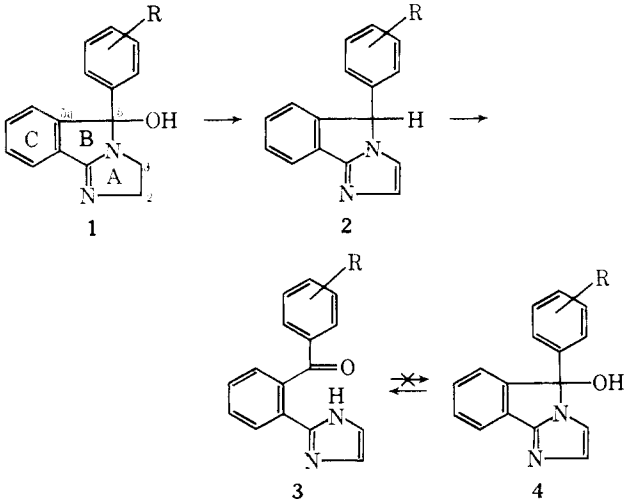
Two additional modifications, **14b** and **15b**, where the C_5–C_{5a} bond in 1 was opened and the aroyl group in 3 transferred to the imidazole N atom were also prepared and evaluated for anorectic activity.

Chemistry. The synthesis of the compounds needed for this study is described below.

Treatment of 1 with refluxing acetic acid resulted in the expected dehydration[3] to the 5-aryl-5*H*-imidazo[2,1-*a*]isoindoles **2**. Conversion of **2** to its sodium salt by sodium hydride in DMF followed by oxygenation[4] resulted in the formation of the 2-(2-imidazol-2-yl)benzophenones 3 rather than the tautomeric 5-aryl-5*H*-imidazo[2,1-*a*]isoindol-5-ols 4 (Scheme I). The structure of **3a** and **3b** was confirmed by ir, nmr, and the presence of a characteristic benzophenone uv maximum[5] at 258 and 260 mμ, respectively (Table I).

The condensation of a 2-aroylbenzoic acid with 1,3-di-

Scheme I



Scheme II

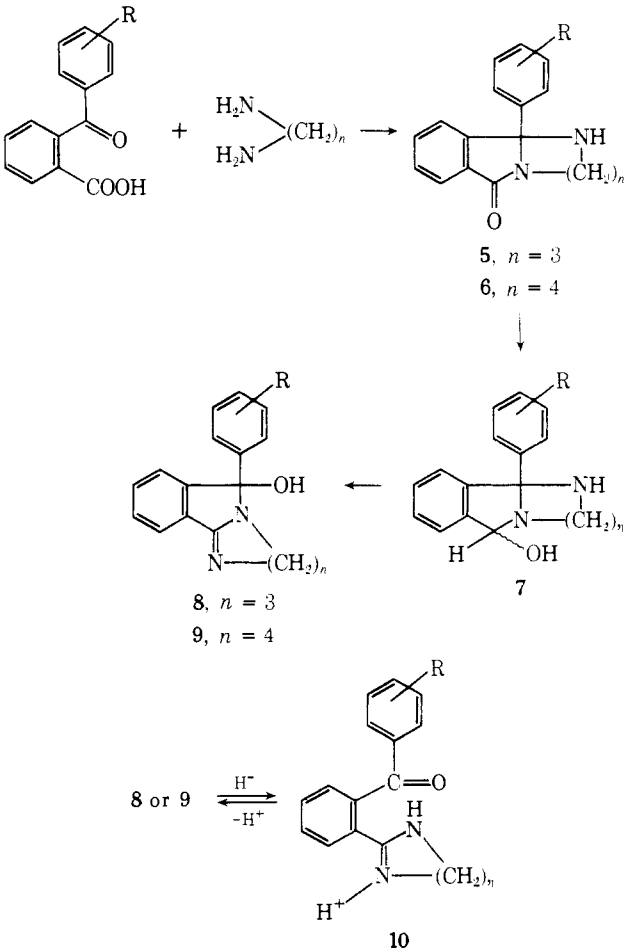


Table I. Ultraviolet Spectral Data[a]

No.	Maxima, mμ(ε) 95% EtOH	95% EtOH–HCl
3a	258 (23,000)	241 (14,730)
		266 (18,900)
3b	260 (18,500)	243 (16,500)
		265 (14,300)
8a	238 (13,195)	240 (14,625)
	270 sh (4,465)	268 (4,265)
8b	225 (26,485)	226 (22,050)
	275 sh (5,300)	243 sh (14,000)
		273 sh (4,800)
8c	230 sh (21,580)	234 (16,800)
	270 sh (4,890)	268 (4,200)
	282 (2,655)	282 (1,800)
9a	225 (18,500)	229 (16,200)
	271 (4,700)	273 (4,400)
9b	226 (25,500)	228 (21,900)
	269 sh (4,700)	241 sh (11,000)
		270 sh (4,100)
12a	227 (15,700)	223 (12,800)
	269 (4,880)	266 (13,500)
	276 (4,760)	

[a]See Experimental Section for details.

aminopropane or 1,4-diaminobutane in refluxing xylene gave the 10b-aryl-1,3,4,10b-tetrahydropyrimido[2,1-*a*]isoindol-6(2*H*)-ones **5**[6] and the 11b-aryl-1,2,3,4,5,11b-hexahydro-7*H*-[1,3]-diazepino[2,1-*a*]isoindol-7-ones **6**,[6] respectively (Scheme II). Following the procedure[1] used to prepare 1 compounds **5** and **6** were treated with $LiAlH_4$ in THF to give the labile alcohols **7**. A solution of these compounds in THF–MeOH was treated with a stream of air (O_2) to give the 6-aryl-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ols[7] and the 7-aryl-2,3,4,5-tetrahydro-7*H*-diazepino[2,1-*a*]isoindol-7-ols[7,8] (Scheme II). The structures of **8** and **9** were established by ir, nmr, and uv in 95% EtOH (Table I). The uv spectra of **8** and **9** in 95% EtOH–HCl (Table I) are very similar to those in 95% EtOH indicating that these compounds have little tendency to form the protonated benzophenone tautomer **10** (n = 3 or 4). In contrast, compounds **1** have been shown[1] to exist as the protonated benzophenone tautomer **10** (n = 2) in the same solvent.

Following the same procedure given in Scheme II the *trans*-4b-aryl-4b,5,5a,6,7,8,9,9a-octahydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ones **11** were converted to the *trans*-11-aryl-5a,6,7,8,9,9a-hexahydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ols **12** (Scheme III). Inspection of the uv spectrum of **12a** (R = H) in 95% EtOH and 95% EtOH–HCl (Table I) revealed that this compound also did not form the protonated benzophenone tautomer **13** in any significant amount.

Compounds **14** and **15** were prepared from 2-phenylimidazole or 2-phenylimidazoline and the requisite benzyl or aroyl halide in refluxing THF.

Pharmacology. The anorexic activity in rats, as determined by the free-feeding method of Randall,[9] is given in Table II. In comparison with the standard 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols **1a** and **1b** all the modifications listed above resulted in complete or considerable loss of activity at the doses used for testing.

These findings suggest that any modification of ring A or disruption of the C_5–C_{5a} bond in **1** would lead to substances with weak or no anorectic activity.

Table II. Anorexic Activity in Rats

No.	R	mg/kg po[a]	Food consumption, % controls[a] 1 hr	4 hr	LD_{50}, mg/kg po[a]
1a	4′-Cl	25	13.0	38.5	>400
1b	3′,4′-Cl_2	25	32.2	58.7	353
3a	4′-Cl	50		91.8	600
3b	3′,4′-Cl_2	50	82.9	100.3	>400
8a	H	25	85.7	100.5	
8b	4′-Cl	25		112.8	
8c	3′,4′-Cl_2	25	102.2		>400
9a	H	25		122.9	
9b	4′-Cl	25	88.5	124.3	
9c	3′,4′-Cl_2	25		66.9	305
12a	4′-Cl	50	63.7	79.5	
12b	3′,4′-Cl_2	25	68.7	65.0	
14a		50	80.8	100.0	>400
14b		50	99.3	97.3	>400
15a		50	64.8	78.8	>400
15b		50	91.1	95.4	>400

[a]See pharmacology testing in the Experimental Section for details.

Experimental Section

Chemical Synthesis. Melting points were determined in a Thomas-Hoover capillary melting point apparatus and have not been corrected. For all compounds listed in Table III pmr spectra were obtained on a Varian Associates A-60 spectrometer in $CDCl_3$ or DMSO-d_6 and ir spectra (KBr) were determined using a Perkin-Elmer Infracord. In all cases the spectra were consistent with the assigned structure. The uv spectra for a selected group of compounds (Table I) were obtained in 95% EtOH or 95% EtOH–2 *N* HCl (9:1) solvent on a Cary Model 15 spectrophotometer. Thin-layer chromatography (tlc) were carried out on compounds

Scheme III

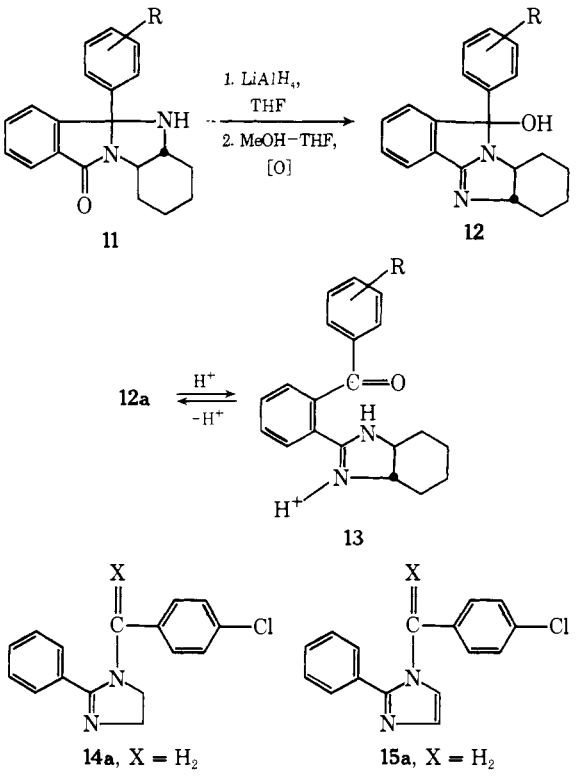


Table III. Physical Properties

No.	R	Mp, °C (recrystn solvent)[a]	Procedure,[b] % yield	Empirical formula	Analyses[c]
2a	4′-Cl	107–108 (A)	A, 85	$C_{15}H_{11}ClN_2$	C, H, Cl, N
2b	3′,4′-Cl_2	112–114 (B)	A, 65	$C_{15}H_{10}Cl_2N_2$	C, H, Cl, N
3a	4′-Cl	175–176 (C)	B, 74	$C_{15}H_{11}ClN_2O$	C, N, Cl, N
3b[d]	3′,4′-Cl_2	291–293 (C)	B, 70	$C_{15}H_{11}Cl_2N_2O$	C, H, Cl, N
5a	H	181–183 (D)[e]	C, 87	$C_{17}H_{16}N_2O$	
5b	4′-Cl	152–154 (D)	C, 70	$C_{17}H_{15}ClN_2O$	C, H, Cl
5c	3′,4′-Cl_2	188–190 (D)	C, 65	$C_{17}H_{14}Cl_2N_2O$	C, H, Cl, N
6a	H	180–182 (A)[f]	C, 75	$C_{18}H_{18}N_2O$	
6b	4′-Cl	138–140 (D)	C, 65	$C_{18}H_{17}ClN_2O$	C, H, Cl
6c	3′,4′-Cl_2	193–195 (E)	C, 28	$C_{18}H_{16}Cl_2N_2O$	C, H, Cl
8a	H	228–230 (F)[g]	D, 47	$C_{17}H_{16}N_2O$	C, H, N, O
8b	4′-Cl	254–255 (G)	D, 45	$C_{17}H_{15}ClN_2O$	C, H, Cl, N
8c	3′,4′-Cl_2	245–248 (H)	D, 25	$C_{17}H_{14}Cl_2N_2O$	C, H, Cl, N
9a	H	224–226 (I)[h]	D, 29	$C_{18}H_{18}N_2O$	C, H, N, O
9b	4′-Cl	241–243 (J)	D, 29	$C_{18}H_{17}ClN_2O$	C, H, Cl, N
9c	3′,4′-Cl_2	246–247 (K)	D, 35	$C_{18}H_{16}Cl_2N_2O$	C, H, Cl, N
11a	4′-Cl	183–185 (A)	C, 35	$C_{20}H_{19}ClN_2O$	C, H, N
11b	3′,4′-Cl_2	181–183 (A)	C, 45	$C_{20}H_{18}Cl_2N_2O$	C, H, Cl, N
12a	4′-Cl	189–192 (H)	D, 15	$C_{20}H_{19}ClN_2O$	C, H, Cl, N
12b	3,4′-Cl_2	227–230 (H)	D, 25	$C_{20}H_{18}Cl_2N_2O$	C, H, Cl, N
14a[d]		218–220 (N)	E, 63	$C_{16}H_{16}Cl_2N_2$	C, H, Cl, N
14b		109–111 (O)	E, 71	$C_{16}H_{13}ClN_2O$	C, H, Cl, N
15a		90–92 (A)	E, 78	$C_{16}H_{13}ClN_2$	C, H, Cl, N
15b		149–151 (P)	E, 73	$C_{16}H_{11}ClN_2O$	C, H, Cl, N

[a] Recrystallization solvents: A, Et_2O–pentane; B, Et_2O–hexane; C, Et_2O–THF; D, EtOH; E, CH_2Cl_2–Et_2O; F, Et_2O–MeOH; G, MeOH; H, Et_2O–MeOH–THF; I, MeOH–THF; J, MeOH–*i*-PrOH; K, $CHCl_3$–THF; L, EtOH–H_2O; M, EtAc; N, DMF–Et_2O; O, pentane; P, $CHCl_3$–pentane. [b] See Experimental Section. [c] Unless otherwise stated the analyses are within ±0.4% of the theoretical values. [d] This is the HCl salt. [e] Lit.[6b] mp 181–183°. [f] Lit.[6b] mp 180–182°. [g] Lit.[7b] mp 227–230° dec. [h] Lit.[7b] mp 216–218° dec.

listed in Table II using glass plates coated with silica gel HF-254 (E. Merck AG) with the solvent system $CHCl_3$–MeOH (9:1) for the purpose of establishing homogeneity.

Pharmacology Testing. Acute Toxicity. The studies were carried out with paired male Royal Hart Wistar rats, 136–160 g, placed in 7 × 7 × 14 in. wire cages. The LD_{50} values (Table II) were obtained 72 hr post-administration of compounds using 20 rats per substance and estimated by probit analysis.

Appetite Suppression in Rats. Food consumption was determined using a modification of the free-feeding method described by Randall.[9] Male Royal Hart Wistar rats, 280–380 g, were individually housed in a room artificially illuminated 7 a.m. to 7 p.m. daily. The animals were chronically trained on a 4-hr feeding and 2-hr fasting schedule and prior to testing were deprived of food for 20 hr but allowed water *ad libitum*. Following oral administration of the substance a predetermined amount of ground food (Purina Lab Chow) was presented in a weighed ground food cannister. The changes in food consumption for the control and treated animals were determined 1 and 4 hr after presentation. In all studies groups of ten rats were used per dose level.

Procedure A. 5-Aryl-5*H*-imidazo[2,1-*a*]isoindoles (2). A solution containing 10 g of 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ol (1) and 100 ml of HOAc was stirred and refluxed for 8 hr. The mixture was then concentrated *in vacuo* and the residue was treated with 50 ml of 2 *N* NaOH and then 100 ml of C_6H_6. The C_6H_6 layer was washed with H_2O, dried with anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo*. The residue was crystallized to give **2** (Table III).

Procedure B. 2-(2-Imidazol-2-yl)benzophenones (3). To a flask equipped with a gas inlet tube and a $CaCl_2$ drying tube there was added 100 ml of dry DMF, 1.53 g (0.0057 mol) of **2a**, and 0.30 g (0.006 mol) of NaH as a 53% dispersion in mineral oil. The pale yellow solution was stirred and dry air was bubbled through the solution for *ca.* 48 hr. The pale green solution was concentrated *in vacuo* and treated with H_2O and then $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried with anhydrous $MgSO_4$, filtered, and then concentrated *in vacuo* to give **3a**. In a similar manner **3b** was prepared from **2b** (Table III).

Procedure C. Condensation of 2-Aroylbenzoic Acids with Diamines. The appropriate 2-aroylbenzoic acid (0.10 mol), diamine (0.20 mol; ethylenediamine, 1,3-diaminopropane, or *trans*-1,2-diaminocyclohexane), 0.5 g of *p*-toluenesulfonic acid, and 250 ml of xylene were placed in a flask equipped with a stirrer and a Dean-Stark water separator. The mixture was stirred and refluxed until the level of the "H_2O layer" (mixture of H_2O and diamine) in the side arm remained constant (5–24 hr). The reaction was allowed to cool to room temperature and the resultant solid was removed by filtration. If a solid was not obtained on cooling the solvent was removed *in vacuo* and the resultant residue crystallized from the appropriate solvent to give compound **5**, **6**, or **11** listed in Table III.

Procedure D. 6-Aryl-2,3,4,6-tetrahydropyrimido[2,1-*a*]isoindol-6-ols (8), 7-Aryl-2,3,4,5-tetrahydro-7*H*-diazepino[2,1-*a*]isoindol-7-ols (9), and *trans*-11-Aryl-5a,6,7,8,9,9a-hexahydro-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ol (12). To a stirred mixture of 0.068 mol of $LiAlH_4$ and 250 ml of dry THF maintained under N_2 there was added dropwise a solution of 0.063 mol of **5**, **6**, or **11** in 500 ml of dry THF at such a rate that the internal temperature did not exceed 30°. The resultant mixture was stirred for *ca.* 6 hr at room temperature, then cooled in an ice bath, and treated with 5.2 ml of 2 *N* NaOH, 7.8 ml of H_2O, and anhydrous Na_2SO_4. The salts were filtered off; the filtrate was concentrated *in vacuo* to *ca.* one-half volume. About 200 ml of MeOH was added and the solution treated for *ca.* 12 hr with a stream of air at room temperature. The resultant solid was filtered off to give compound **8**, **9**, or **12** (Table III).

Procedure E. 1-*p*-Chlorobenzyl- and 1-*p*-Chlorobenzoyl-2-phenylimidazoline (14a,b)-1-*p*-Chlorobenzyl- and 1-*p*-Chlorobenzoyl-2-phenylimidazole (15a,b). A mixture of 0.10 mol of 2-phenylimidazole or 2-phenylimidazoline and 0.05 mol of *p*-chlorobenzyl bromide or *p*-chlorobenzoyl chloride in 200 ml of anhydrous THF was stirred and refluxed for *ca.* 52 hr. The resultant salts were removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from the appropriate solvent to give the above compounds (Table III).

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Neuroleptic Agents of the Benzocycloheptapyridoisoquinoline Series. 1. Syntheses and Stereochemical and Structural Requirements for Activity of Butaclamol and Related Compounds†

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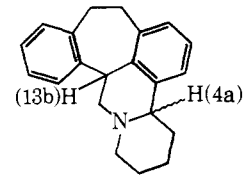
The syntheses and the structural and stereochemical requirements for antagonism of (+)-amphetamine-induced stereotypy are described for a series of benzocycloheptapyridoisoquinoline derivatives. One of these compounds, (±)-(4a,13b-*trans*)[3(OH),13b(H)-*trans*]-3-*tert*-butyl-2,3,4,4a,8,9,13b,14-octahydro-1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinolin-3-ol hydrochloride (butaclamol hydrochloride, USAN), is currently being studied in man. The relationship between structure and antiamphetamine activity in this class of compounds is discussed.

Recently, we reported[1] syntheses of the 4a,13b-cis and the 4a,13b-trans isomers of the 1*H*-benzo[6,7]cyclohepta[1,2,3-*de*]pyrido[2,1-*a*]isoquinoline 1, the trans isomer exhibiting actions characteristic of antianxiety drugs in laboratory animals.[2] One of the synthetic paths utilized in that study[1] involved the removal of oxygen from the isomeric amino ketones 2 and 3. The present report describes the synthesis and stereochemistry of a series of tertiary carbinols obtained *via* transformations of the amino ketones 2 and 3. One of these tertiary carbinols, butaclamol hydrochloride (4, USAN),‡ is a neuroleptic agent currently undergoing clinical evaluation.[3] Some pharmacological properties of 4 and related compounds will be described in this report. A detailed description of the psychopharmacological profile of butaclamol hydrochloride has recently been submitted for publication by Voith and Herr.[4]



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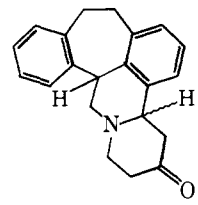
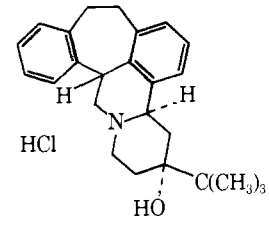


2 (4a,13b)-trans
3 (4a,13b)-cis



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Chemistry. The compounds prepared (see Table I) were obtained, in moderate yields (25–40% after purification), by the reaction of the *cis*- or *trans*-amino ketones (2, 3) with a Grignard reagent or with a hydrocarbon lithium (see Experimental Section). For those compounds derived from the 4a,13b-*trans*-amino ketone the configurations at the tertiary carbinol center were assigned on the following basis. Inspection of a molecular model of *trans*-amino ketone 2 shows that, in its most stable conformation (see Scheme I), ring A is situated on the α face of the plane formed by rings C, D, and E and is oriented to it by an angle of about 120°. Nucleophilic attack on the carbonyl group from the α face of the molecule (axial attack) is unfavorable because of the steric effect of ring A. In contrast, equatorial attack from the β face of the molecule is not subject to the influence of ring A. Experimentally, the reaction of the *trans*-amino ketone 2 with ethylmagnesium bromide afforded 6 which is consequently assigned the 3(OH),13b(H)-trans relative configuration since it is assumed to be formed by equatorial approach by the anionic species.

Hennion and O'Shea[5] have demonstrated that the small, linear acetylide anion reacts with 4-*tert*-butylcyclohexanone by axial attack to afford a product in which the *tert*-butyl and ethynyl groups bear a cis relationship. We

†Presented in part at a Symposium on Central Dopamine Receptors: Stimulants and Antagonists, during the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974, and at the 4th International Symposium on Medicinal Chemistry, Noordwijkerhout, The Netherlands, Sept 1974.

‡This compound is also known by the Ayerst code number AY-23,028.