The Synthesis of 1-Arylimidazoles, a New Class of Steroid Hydroxylation Inhibitors

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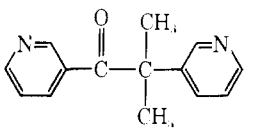
A series of new 1-arylimidazoles has been synthesized and examined for the inhibition of steroid 11β-hydroxylase. Two general synthetic methods used were (a) the nucleophilic displacement of labile aromatic halogen by imidazole and (b) Marckwald's synthesis from an aryl isothiocyanate and amino acetal. The inhibition of steroid 11β-hydroxylation activity was compared with that of 2-methyl-1,2-bis(3-pyridyl)-1-propanone (metyrapone), and a correlation between structure and activity was discovered for 1-(alkyl-substituted phenyl)imidazoles. The presence of bulky *ortho* substituents increases the activity, 1-(2-*t*-butylphenyl)imidazole being four times as active as the standard compound.

The clinical testing of pituitary and adrenal cortex functions by chemical reagents has been discussed[2] as a means of diagnosing diseases such as Cushing's syndrome, adrenogenital syndrome, primary and secondary aldosteronism, and diabetes mellitus. One way in which the effectiveness of such a chemical agent can be evaluated is by its ability to prevent the hydroxylation of steroids in the 11β, 18, and 21 positions. One such compound, metyrapone, 2-methyl-1,2-bis(3-pyridyl)-1-propanone (**1**) has been evaluated extensively as a steroid hydroxylation inhibitor.[2,3] It is used as a standard for comparison with the 1-arylimidazoles (**2**) which form



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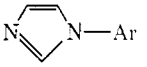

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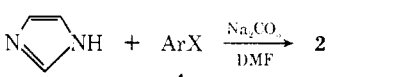
the subject of this paper. One particular group of compounds in this series shows a definite correlation between substitution pattern and biological activity. When Ar is an alkyl-substituted phenyl group, the steroid 11β-hydroxylation inhibition activity is enhanced as the size of the *ortho* substituent increases from H (relative activity 0.05) to $C(CH_3)_3$ (4.0). These results clearly demonstrate the importance of a steric effect in this activity.

Synthesis.—Two general synthetic procedures were used to prepare the 1-arylimidazoles used in the study. The first is the nucleophilic displacement of labile aromatic halogen by imidazole (**3**) using Na_2CO_3 and DMF.[4] The simplicity of this one-step procedure is offset by low yields, tedious isolation procedures, and failure when there are no electron-withdrawing substituents on the aromatic ring. The most successful



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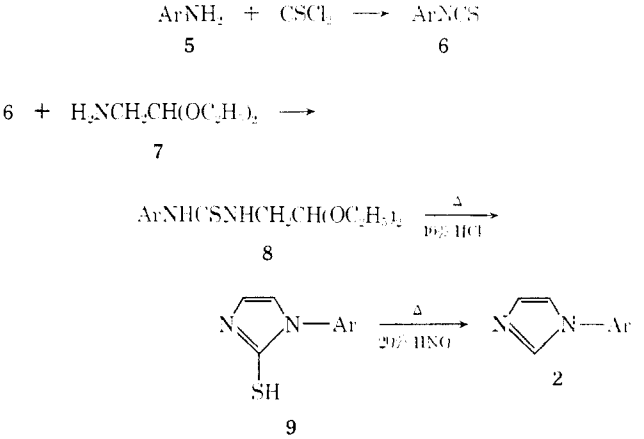
reactions occur when the aromatic halide ArX (**4**) has X = F and one or more NO_2, CN, or CO_2H functions *ortho* or *para* to X. As expected,[5] the reactivity of ArX follows the order X = F > Cl > Br. The yields can often be improved by the addition of catalytic amounts of Cu powder and KI,[6] and intractable by-products can usually be removed on Florisil. The properties of these imidazoles are summarized in Tables I and V.

The second synthetic sequence is more general and gives very satisfactory over-all yields of the desired imidazole. This is the four-step Marckwald synthesis,[7] in which the starting materials are the readily available aryl isothiocyanates (**6**) and amino acetal (**7**). The isothiocyanates **6** can be prepared by the reaction of thiophosgene with the corresponding anilines (**5**),[8] and the intermediate aryldiethoxyethylthioureas (**8**) are usually cyclized without purification to the crystalline 1-aryl-2-mercaptoimidazoles (**9**) using hot 10% HCl (Chart I). The mercapto group is readily oxidized with

CHART I



hot 20% HNO_3,[9] and the over-all yields of 1-arylimidazoles are usually 50% or better. The properties of the compounds prepared by this synthesis are summarized in Tables II–V.

(1) (a) Author to whom inquiries should be addressed. (b) E. I. du Pont de Nemours and Company. (c) Syntex Research.

(2) J. J. Chart and H. Sheppard, *J. Med. Pharm. Chem.*, **1**, 407 (1959).

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(7) (a) A. Wohl and W. Marckwald, *Ber.*, **22**, 568, 1353 (1889); (b) W. Marckwald, *ibid.*, **25**, 2354 (1892).

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(9) M. Engelhardt, U. S. Patent 2,005,538 (1935).

Table I

1-Arylimidazoles (2) Prepared by Nucleophilic Displacement of Aryl Halides with Imidazole

No.	ArX[a]	Reaction temp, °C	Reaction time, hr	Yield, %	Recrystn solvent	Mp, °C	Formula[d]
13	2,6-$(NO_2)_2C_6H_3Cl$	100	2	72	5:1 C_6H_6–C_6H_{14}	160–161	$C_9H_6N_4O_4$
2a	2-CNC_6H_4F	120	40	70	C_6H_6	146.8–147.1	$C_{10}H_7N_3$
2c	2-CN-4-$CF_3C_6H_3Cl$[b]	120	40	39	1:10 C_6H_6–C_6H_{14}	68–69	$C_{11}H_6F_3N_3$
		120	40	68			
14	2-NO_2-4-ClC_6H_3Cl[c]	Reflux	24	21	C_6H_6	94.1–94.9	$C_9H_6ClN_3O_2$
2b	2-CN-4-FC_6H_3F[c]	120	40	29	1:1 C_6H_6–C_6H_{14}	132–134	$C_{10}H_6FN_3$
		120	40	62			
15	2-NO_2-4-BrC_6H_3Br[b,c]	Reflux	20	9	2:5 C_6H_6–C_6H_{14}	113–115	$C_9H_6BrN_3O_2$
		Reflux	20	43	C_6H_6	119–120	
16	3-NO_2-2-$C_{10}H_6Br$[b]	100	20	15	C_6H_6	180–181.2	$C_{13}H_9N_3O_2$
17	2-CO_2H-4-BrC_6H_3Br[b]	100	20	60	EtOH	236–239	$C_{10}H_7BrN_2O_2$
18	2-NO_2-4-$CF_3C_6H_3Cl$[b,c]	100	20	76	C_6H_6	93–95	$C_{10}H_6F_3N_3O_2$
19	$C_6H_5CH_2Cl$	100	2	42	Subl 95° (0.1 mm)	69–71	$C_{10}H_{10}N_2$
20	2-$NO_2C_6H_4F$	165	18	61	CH_2Cl_2–C_6H_{14}	94.7–97.2	$C_9H_7N_3O_2$
21	4-$NO_2C_6H_4F$	100	18	64	Me_2CO, C_6H_6	204.4–205.2	$C_9H_7N_3O_2$
22	2,4-$(NO_2)_2C_6H_3F$	100	4	25	Me_2CO, C_6H_6	144.2–145.6	$C_9H_6N_4O_4$
23	2-NO_2-4-$CH_3C_6H_3Cl$	165	72	12	C_6H_6–C_6H_{14}	84.7–85.2	$C_{10}H_9N_3O_2$
24	5-NO_2-2-C_5H_3NCl	100	4	56	C_6H_6	218.5–219.9	$C_8H_6N_4O_2$
25	2-NO_2-4-FC_6H_3F	100	24	26	C_6H_6–C_6H_{14}, CCl_4	84.8–85.7	$C_9H_6FN_3O_2$

[a] Halogen X undergoing replacement is italicized. The residue corresponds to Ar in formula **2**. [b] Cu–KI added. [c] Florisil used. [d] All compounds analyzed for C, H, N.

Table II

Aryldiethoxyethylthioureas (8)

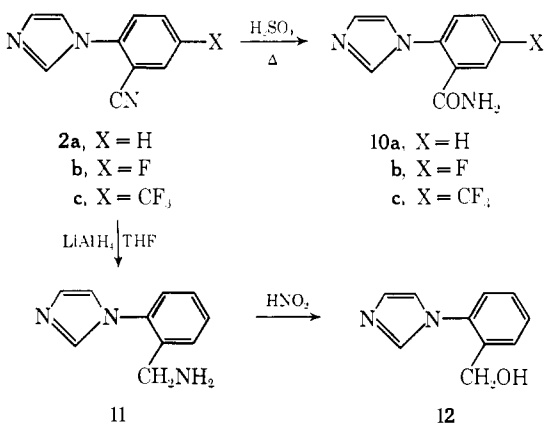
$ArNHCSNHCH_2CH(OC_2H_5)_2$

No.	Ar	Recrystn solvent, ml/g	% yield	Mp, °C	Formula[a]
26	C_6H_5	50% EtOH (6)	87	87.5–88.5	$C_{15}H_{24}N_2O_2S$
27	1,4-C_6H_4	EtOH extraction	95	198.5–199.5	$C_{20}H_{34}N_4O_4S_2$
28	2,4,6-$(CH_3)_3C_6H_2$	50% EtOH (24)	90	122–123	$C_{18}H_{28}N_2O_2S$
29	1-$C_{10}H_7$	EtOH(4)		115–116	$C_{17}H_{22}N_2O_2S$

[a] All compounds analyzed for C, H, N.

Five other compounds can be prepared from the readily available 1-(2-cyanoaryl) imidazoles (**2a–c**). H_2SO_4 hydrolysis of the nitrile group to a carboxamide group was used to prepare the three amides **10a–c** (Chart II). LAH reduction of 1-(2-cyanophenyl)-imidazole (**2a**) to 1-(2-aminomethylphenyl)imidazole (**11**), followed by deamination to 1-(2-hydroxymethylphenyl)imidazole (**12**) gives only fair yields of these two products.

Chart II



Spectral Data.—The ir bands at 1550, 1492, 1451 cm^{-1} in the spectrum of imidazole[10] cannot be clearly distinguished in our compounds because of the aromatic substituent. In general, for both the 1-aryl-2-mercaptoimidazoles and the 1-arylimidazoles we observe several bands in the 1650–1300-cm^{-1} region, which are caused by the ring-stretching modes of both the benzenoid and imidazole rings.

The effects of substitution on the benzenoid ring are readily seen from the uv data for both the 1-aryl-2-mercaptoimidazoles and the 1-arylimidazoles.[11] In the mercaptans **9**, there are commonly two absorption bands in the regions of 278–297 mμ (ε 5400–10,200) and 216–252 mμ (ε 8550–21,900), but when the aryl group bears an *ortho* substituent the band is located almost exclusively at 260–265 mμ (ε 9150–14,200). In unhindered imidazoles **2**, there is commonly a single band at 229–246 mμ (ε 7850–16,700), but when the aryl group is *ortho* substituted there are two bands near 265–272 mμ (ε 256–1650) and 261–265 mμ (ε 350–1175). The expected chromophoric shifts are observed in both series of compounds when groups such as NO_2, CH_3O, and CN are present.

The benzenoid and imidazole protons can usually be distinguished in the nmr spectra of the free imidazoles **2** and their 2-mercapto derivatives **9**. The use of

(10) D. Garfinkel and J. T. Edsall, *J. Am. Chem. Soc.*, **80**, 3807 (1958).

(11) *Cf.* (a) H. Heath, A. Lawson, and C. Rimington, *J. Chem. Soc.*, 2217 (1951), reported $\lambda_{max}^{H_2O}$ 258 mμ (log ε 4.16) for 2-mercaptoimidazole; (b) literature values for imidazole are (i) $\lambda_{max}^{C_2H_5OH}$ 210 mμ (ε 5000), 250 mμ (ε 60) [E. A. Braude, *Ann. Rept. Progr. Chem.*, **42**, 105 (1945)]; (ii) $\lambda_{max}^{C_2H_5OH}$ 207–208 mμ (log ε 3.70) [G. Leandi, A. Mangini, F. Montanari, and R. Passerini, *Gazz. Chim. Ital.*, **85**, 769 (1955)]; (iii) no λ_{max}^{THF} 200–300 mμ [H. A. Staab, *Chem. Ber.*, **89**, 1927 (1956)]; (c) L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3875 (1948).

TABLE III

1-ARYL-2-MERCAPTOIMIDAZOLES (9)

No.	Aromatic substd	Recrystn solvent	% yield	Mp, °C	Formula[c]
30	C_6H_5[7]	H_2O	74	174–176	$C_9H_8N_2S$
31	3-$NO_2C_6H_4$	EtOH	91	223–224	$C_9H_7N_3O_2S$
32	3-FC_6H_4	EtOH	92	161–162.5	$C_9H_7N_2FS$
33	C_6F_5	67% EtOH	67	188–191	$C_9H_3N_2F_5S$
34	4-$CH_3C_6H_4$[7]	50% EtOH	78	205–206.5	$C_{10}H_{10}N_2S$
35	2-$CH_3C_6H_4$[7]	33% EtOH	73	243–245	$C_{10}H_{10}N_2S$
36	4-BrC_6H_4	EtOH[a]	48	244–246 dec	$C_9H_7BrN_2S$
37	4-$CH_3OC_6H_4$[9]	EtOH	89	216–217	$C_{10}H_{10}N_2OS$
38	2-$CF_3C_6H_4$	EtOH	87	236–237.5	$C_{10}H_7F_3N_2S$
39	3-$CF_3C_6H_4$	30% EtOH	92	157–159	$C_{10}H_7F_3N_2S$
40	4-$CF_3C_6H_4$	55% EtOH	75	194–196	$C_{10}H_7F_3N_2S$
41	2,3-$(CH_3)_2C_6H_3$	EtOH	84	263–265	$C_{11}H_{12}N_2S$
42	2-$C_{10}H_7$	EtOH	69	204–205	$C_{13}H_{10}N_2S$
43	3-BrC_6H_4	EtOH	87	192.5–194	$C_9H_7BrN_2S$
44	4-CNC_6H_4	EtOH[a]	84	266–270 dec	$C_{10}H_7N_3S$
45	2-FC_6H_4	EtOH	74	187.5–189	$C_9H_7N_2FS$
46	4-FC_6H_4	EtOH	71	207.5–209.5	$C_9H_7N_2FS$
47	2-$NO_2C_6H_4$	EtOH	60	234–236	*b*
48	2-NO_2-4-$CH_3C_6H_3$	EtOH[a]	55	222–223.5	$C_{10}H_9N_3O_2S$
49	2-NO_2-4-ClC_6H_4	EtOH	31	188–192 dec	*b*
50	2-NO_2-4-$CH_3OC_6H_4$	EtOH[a]	40	228–229 dec	*b*
51	1,4-C_6H_4	EtOH[a]	95	>400 dec	$C_{12}H_{10}N_4S_2$
52	2,6-$(CH_3)_2C_6H_3$	EtOH[a]	72	303–304.5	$C_{11}H_{12}N_2S$
53	2-$(CH_3)_2CHC_6H_4$	EtOH	68	225–226.5	$C_{12}H_{14}N_2S$
54	2-$C_2H_5C_6H_4$	EtOH	87	200–201	$C_{11}H_{12}N_2S$
55	2,6-$(C_2H_5)_2C_6H_3$	EtOH	57	194–195	$C_{13}H_{16}N_2S$
56	3-$CH_3C_6H_4$	50% EtOH	82	147–149	$C_{10}H_{10}N_2S$
57	2,4,6-$(CH_3)_3C_6H_2$	EtOH	38	273–275	$C_{12}H_{14}N_2S$
58	1-(5,6,7,8-H_4)$C_{10}H_7$	EtOH	87	212–214	$C_{13}H_{14}N_2S$
59	2,6-$[(CH_3)_2CH]_2C_6H_3$	EtOH	82	243–245 dec	$C_{15}H_{18}N_2S$
60	2,4-$(C_2H_5)_2C_6H_3$	50% MeOH	70	155–157 dec	$C_{13}H_{16}N_2S$
61	2,4-$(CH_3)_2C_6H_3$	EtOH	58	188–190	$C_{11}H_{12}N_2S$

[a] Soxhlet extraction. [b] Converted directly to the imidazole. [c] All compounds analyzed for C, H, N.

$(CD_3)_2SO$ as the nmr solvent for the mercaptans did not allow the SH proton to be detected. With 1-phenyl-2-mercaptoimidazole, the SH proton was identified at 700 cps downfield of TMS in $CDCl_3$ solution. In the mercaptans in which both types of protons could be distinguished, the benzenoid protons were downfield of the imidazole 4,5-protons. The benzenoid protons were in the range of 487–420 cps downfield of TMS with splitting determined by the substitution pattern of the aryl group. The imidazole 4,5-protons were 409–447 cps downfield of TMS, and in many cases appeared as a doublet (J = 2–18 cps) each member of which could be split further (J = 1.5–3.0 cps), depending upon the particular substituent.

With increasing field strength, the chemical shifts of the protons in the imidazoles **2**, in $CDCl_3$ solution, follow the order imidazole 2-proton, benzenoid protons, imidazole 4,5-protons. Typically, the imidazole 2-proton resonance appears 488–448 cps downfield of TMS, the benzenoid protons at 502–432 cps, and the imidazole 4,5-protons at 450–415 cps. As with the mercaptans, the splitting of the aromatic signals depends upon the substitution pattern of the aryl group. The imidazole 2-proton resonance is commonly a triplet (J = 0.5–1.0 cps) while the imidazole 4,5-protons appear as a doublet (J = 3–10 cps), each member of which may be split further (J = 0.5–1.0 cps), depending upon the aryl substituent.

Biological Evaluation.—*In vitro* studies of the steroid hydroxylation inhibition activity of the new imidazoles **2** were made following published procedures.[12] In Table V the steroid 11β-hydroxylation inhibition activities of our 1-arylimidazoles are compared to metyrapone (**1**). In the alkyl-substituted phenylimidazoles a clear correlation exists between the size of the *ortho* substituent on the benzene ring and this activity. When other substituents such as NO_2 and CN are present, the results are not as simply interpreted.

Experimental Section[13]

1-Arylimidazoles (2) by Nucleophilic Displacement of Labile Aromatic Halogen.—A mixture of imidazole (**3**) (6.8 g, 0.1 mole), anhydrous Na_2CO_3 (11.0 g, 0.103 mole), aryl halide (**4**) (0.1 mole), and DMF (60 ml) was stirred for several hours[4] at 50–165°. In some cases the reaction was promoted by the addition of Cu powder (0.5 g) and KI (0.5 g).[6] The crude product was isolated by pouring the reaction mixture onto ice (500 g), filtering the precipitate, rinsing it with ice water, and drying it by suction. In the more difficult reactions, the crude 1-arylimidazole (**2**) was filtered through Florisil (50 g) using various mixtures of $CHCl_3$ and C_6H_6 (500–750 ml) as the eluent. The purification was completed by recrystallization. The experimental and analytical de-

(12) (a) G. W. Liddle, H. L. Eisen, J. W. Kendall, Jr., W. C. Williams, Jr., and A. W. Townes, *J. Clin. Endocrinol. Metab.*, **19**, 875 (1959); (b) D. C. Sharma, E. Forchielli, and R. I. Dorfman, *J. Biol. Chem.*, **238**, 572 (1963); (c) D. C. Sharma and R. I. Dorfman, *Biochemistry*, **3**, 1093 (1964).

(13) Melting points (uncorrected) were determined in capillary tubes in a Mel-Temp apparatus; ir spectra in KBr or solution media were determined on a Perkin-Elmer 221 instrument. Uv spectra in solution were determined in 1-cm cells in a Cary Model 14 spectrophotometer, and nmr spectra on a Varian Associates A-60 instrument; where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Table IV

1-Arylimidazoles (2) Prepared by Marckwald's Synthesis

No.	Aromatic subst	Bp, °C (mm)	Mp, °C	% yield	Formula[a]
62	C_6H_5	100 (0.5)		91	$C_9H_8N_2$
63	3-FC_6H_4	80 (0.1)		84	$C_9H_7FN_2$
64	4-$CH_3C_6H_4$	95 (0.05)	45–48	42	$C_{10}H_{10}N_2$
65	2-$CH_3C_6H_4$	75 (0.05)		75	$C_{10}H_{10}N_2$
66	4-BrC_6H_4[6]		118–120.5[b]	81	$C_9H_7BrN_2$
67	4-$CH_3OC_6H_4$[9]	120 (0.1)	63–64.5	37	$C_{10}H_{10}N_2O$
68	2-$CF_3C_6H_4$	75 (0.025)	43–45	83	$C_{10}H_7F_3N_2$
69	3-$CF_3C_6H_4$	70 (0.1)		85	$C_{10}H_7F_3N_2$
70	4-$CF_3C_6H_4$	90 (0.05)	66–68	78	$C_{10}H_7F_3N_2$
71	2,3-$(CH_3)_2C_6H_3$	80 (0.01)	53.5–56.5	71	$C_{11}H_{12}N_2$
72	3-$NO_2C_6H_4$		107.5–108[c]	90	$C_9H_7N_3O_3$
73	2-$C_{10}H_7$	100 (0.02)	119.5–120.5	82	$C_{13}H_{10}N_2$
74	3-BrC_6H_4	115 (0.25)		81	$C_9H_7BrN_2$
75	4-CNC_6H_4		151–152[d]	92	$C_{10}H_7N_3$
76	2-FC_6H_4	72 (0.03)		86	$C_9H_7FN_2$
77	4-FC_6H_4	80 (0.03)		88	$C_9H_7FN_2$
20	2-$NO_2C_6H_4$		95–96[e]	83	$C_9H_7N_3O_2$
23	2-NO_2-4-$CH_3C_6H_3$		79–81[f]	20	$C_{10}H_9N_3O_2$
14	2-NO_2-4-ClC_6H_3		94–95[f]	76	$C_9H_6ClNO_2$
78	2-NO_2-4-$CH_3OC_6H_3$		97–98[c]	80	$C_{10}H_9N_3O_3$
79	1,4-C_6H_4	180 (0.1)	202–204	87	$C_{12}H_{10}N_4$
80	C_6F_5	55 (0.025)	66–69	53	$C_9H_3F_5N_2$
81	2,6-$(CH_3)_2C_6H_3$	80 (0.1)	82–82.5	90	$C_{11}H_{12}N_2$
82	2-$(CH_3)_2CHC_6H_4$	80 (0.1)	67–68	91	$C_{12}H_{14}N_2$
83	2-$C_2H_5C_6H_4$	100 (0.25)		91	$C_{11}H_{12}N_2$
84	2,6-$(C_2H_5)_2C_6H_3$	95 (0.1)	72.5–74	78	$C_{13}H_{16}N_2$
85	3-$CH_3C_6H_4$	80 (0.1)		62	$C_{10}H_{10}N_2$
86	2,4,6-$(CH_3)_3C_6H_2$	100 (0.1)	106–109	67	$C_{12}H_{14}N_2$
87	2-$(CH_3)_3CC_6H_4$	80 (0.01)		69	$C_{13}H_{16}N_2$
88	1-(5,6,7,8-H_4)$C_{10}H_7$	90 (0.5)	68–70	79	$C_{13}H_{14}N_2$
89	2,6-$[(CH_3)_2CH]_2C_6H_3$	105 (0.1)	123–125	80	$C_{15}H_{18}N_2$
90	2,4-$(C_2H_5)_2C_6H_3$	90 (0.1)	65–66	59	$C_{13}H_{16}N_2$
91	1-$C_{10}H_7$	120 (0.2)		33	$C_{13}H_{10}N_2$
92	2,4-$(CH_3)_2C_6H_3$	105 (0.2)		91	$C_{11}H_{12}N_2$

[a] All compounds analyzed for C, H, N. [b] Recrystallized from 50% EtOH. [c] Recrystallized from C_6H_6. [d] Recrystallized from C_6H_6–C_6H_{14} (15:1). [e] Recrystallized from CH_2Cl_2–C_6H_{14} (1:2). [f] Recrystallized from C_6H_6–C_6H_{14} (1:1).

Table V

Comparison of 1-Arylimidazoles with Metyrapone in Steroid Hydroxylation Inhibition

No.	Ar	Potency/ metyrapone potency	No.	Ar	Potency/ metyrapone potency
87	$(CH_3)_3CC_6H_4$	4.0	65	2-$CH_3C_6H_4$	0.33
88	1-(5,6,7,8-H_4)$C_{10}H_7$	2.0	23	2-NO_2-4-$CH_3C_6H_3$	0.36
89	2,6-$[(CH_3)_2CH]_2C_6H_3$	2.0	14	2-NO_2-4-ClC_6H_3	0.32
84	2,6-$(C_2H_5)_2C_6H_3$	2.0	85	3-$CH_3C_6H_4$	0.3
82	2-$(CH_3)_2CHC_6H_4$	2.0	2c	2-CN-4-$CF_3C_6H_3$	0.25
90	2,4-$(C_2H_5)_2C_6H_4$	1.2	50	2-NO_2-4-$OCH_3C_6H_3$	0.2
91	1-$C_{10}H_7$	1.2	15	2-NO_2-4-BrC_6H_4	<0.1
92	2,4-$(CH_3)_2C_6H_3$	1.2	22	2,4-$(NO_2)_2C_6H_3$	~0.1
86	2,4,6-$(CH_3)_3C_6H_2$	1.0	62	C_6H_5	
83	2-$C_2H_5C_6H_4$	1.0	17	2-CO_2H-4-BrC_6H_3	
81	2,6-$(CH_3)_2C_6H_3$	1.0	18	2-NO_2-4-$CF_3C_6H_3$	
71	2,3-$(CH_3)_2C_6H_3$	1.0	10a	2-$H_2NCOC_6H_4$	
25	2-NO_2-4-FC_6H_3	1.0	64	4-$CH_3C_6H_4$	All <0.05
2a	2-CNC_6H_4	1.0	21	4-$NO_2C_6H_4$	
16	2-NO_2-3-$C_{10}H_6$	0.45	67	4-$CH_3OC_6H_4$	
80	C_6F_5	0.40	10c	2-H_2NCO-4-$CF_3C_6H_3$	
79	1,4-C_6H_4	0.33	19	$C_6H_5CH_2$	

tails for individual compounds prepared by this method are given in Table I.

Aryl Isothiocyanates (6).—The general applicability of the reaction of $CSCl_2$ with anilines (5) according to Dyson[8] was used exclusively to prepare aryl isothiocyanates which were not commercially available. The dithiocarbamate synthesis[14] was not found to be useful.

(14) F. B. Dains, R. Q. Brewster, and C. P. Olander, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p 447.

Aryldiethoxyethylthioureas (8).—The appropriate aryl isothiocyanate **6** (0.1 mole) was added slowly to a stirred solution of amino acetal **7** (13.3 g, 0.1 mole) in EtOH (100 ml) at room temperature. After the addition was complete, the solution was heated under reflux for 30 min, then the EtOH was evaporated to leave a heavy colorless oil of crude thiourea (**8**) which was usually processed directly to the 1-aryl-2-mercaptoimidazole **9**. Table II contains the details of aryldiethoxyethylthioureas which were more fully characterized.

1-Aryl-2-mercaptoimidazoles (9).—The crude aryldiethoxy-

ethylthiourea **8** was stirred with 10% HCl (200 ml) at reflux for 30 min. The mixture was cooled to 0°, and the crude crystalline **9** was isolated by filtration. The pure compounds were obtained by recrystallization with Darco G-60 treatment. In a few cases the mercaptan was dissolved in 10% aqueous NaOH, filtered, and reprecipitated with 10% HCl before recrystallization. Table III lists the compounds prepared and their physical properties.

1-Arylimidazoles (2). The recrystallized 1-aryl-2-mercaptoimidazole (**9**) (25 g) was slurried with 20% HNO_3 (100 ml) in a 2-l. erlenmeyer flask. When this mixture was warmed on a steam bath behind a shield in the hood, a brief, vigorous reaction produced large amounts of NO_2. The mixture was kept at 100° for 5 min, before it was cooled and basified to ~pH 8 with 15% aqueous NH_3 (~400 ml).[15] The imidazole was extracted with three 25-ml portions of $CHCl_3$ and usually purified by short-path distillation or sublimation. Tables IV and V give the experimental details for these compounds.

1-(2-Carbamoylphenyl)imidazole (10a). 1-(2-Cyanophenyl)-imidazole (**2a**) (22.5 g) was dissolved in concentrated H_2SO_4 (120 ml) and heated on a steam bath for 10 min. The crude, crystalline amide was isolated by pouring the reaction mixture into ice water (500 ml), basifying to pH 8 with 28% NH_3 solution, and cooling to 0°. Recrystallization of the crude product from H_2O (120 ml) with Darco G-60 treatment gave colorless plates of **10a** (21.2 g, 81%), mp 177.5–178.5°. *Anal.* ($C_{10}H_9N_3O$) N.

1-(2-Carbamoyl-4-fluorophenyl)imidazole (10b). The above procedure gave, with 1-(2-cyano-4-fluorophenyl)imidazole (**2b**) (1.59 g) and concentrated H_2SO_4 (8 ml), after recrystallization from water (5 ml), 0.40 g (22%) of **10b**, mp 146–147°. *Anal.* ($C_{10}H_8FN_3O$) N.

1-(2-Carbamoyl-4-trifluoromethylphenyl)imidazole (10c). The above procedure gave, with 1-[2-cyano-4-(trifluoromethyl)-phenyl]imidazole (**2c**) (25.0 g) and concentrated H_2SO_4 (125 ml), after recrystallization from 33% EtOH (150 ml) with Darco G-60 treatment, 22.8 g (85%) of colorless **10c**, mp 192–193.5°. *Anal.* ($C_{11}H_8F_3N_3 \cdot H_2O$) N.

1-(2-Aminomethylphenyl)imidazole (11). An extractor thimble was charged with **2a** (42.2 g, 0.25 mole), and a THF suspension of LAH (20 g, 0.525 mole/500 ml) was heated under reflux until 2 hr after the extraction was complete. The mixture was cooled, decomposed with 20% HCl (400 ml), stripped free of THF, diluted with H_2O, filtered, and extracted with $CHCl_3$ (400 ml). The $CHCl_3$ layer was discarded, and the H_2O layer was basified with 28% NH_3 solution and extracted continuously with $CHCl_3$. The dried extracts were evaporated to leave a brown, oily residue of crude product which was distilled in a short-path still at 80–95° (0.02 mm), yield 15.55 g (36%) of **11**. A further distillation at 85° (0.1 mm) gave colorless product, mp 49.5–52°. *Anal.* ($C_{10}H_{11}N_3$) N.

1-(2-Hydroxymethylphenyl)imidazole (12). A solution of **11** (17.0 g, 0.098 mole), in a mixture of HOAc (10 ml, 0.23 mole) and H_2O (100 ml) was cooled to 0° and treated at once with a precooled solution of $NaNO_2$[16] (6.9 g, 0.1 mole) in H_2O (25 ml). The mixture was stirred at 25° for 2 hr, then basified with 28% NH_3, and continuously extracted with $CHCl_3$. The extract was dried, concentrated and filtered through Florisil (50 g) using 600 ml of $CHCl_3$ as the eluent. The gum left on evaporation of the $CHCl_3$ was sublimed at 130° (0.1 mm) to produce 9.20 g (54%) of **12**. After a further sublimation this product melted at 101.5–102.5°. *Anal.* ($C_{10}H_{10}N_2O$) C, H, N.

(15) NaOH will open the imidazole ring, see E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 205.

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The Syntheses and Substrate Specificity for Mammalian Dihydroxyphenylalanine Decarboxylase of 3-, 4-, 5-, and 6-Methyl-2-hydroxyphenylalanines and the Substrate Specificity of 3-, 5-, and 6-Methyl-2,4-dihydroxyphenylalanines for the Enzyme[1]

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Nuclear monomethyl-substituted *o*-tyrosines have been prepared from the corresponding azlactones *via* the benzamidocinnamic acids and the benzoylamino acids or by direct conversion to the amino acids. The 3-, 4-, and 6-methyl-*o*-tyrosines could serve as substrates while the 5-methyl-*o*-tyrosine was inert for mammalian DOPA decarboxylase. The prevention of enzyme binding by the 5-Me group led to a study of the substrate specificity of the nuclear monomethyl-substituted 2,4-dihydroxyphenylalanines. The 3- and 6-methyl-2,4-dihydroxyphenylalanines could serve as substrates while 5-methyl-2,4-dihydroxyphenylalanine was inert for mammalian DOPA decarboxylase.

The finding by Fellman and Devlin[2] in 1958 that 2-hydroxyphenylalanine (*o*-tyrosine) occurs normally in the mammalian adrenal gland makes its metabolism of interest. Armstrong, *et al.*,[3] and Nishimura and Gjessing[4] showed that *o*-tyrosine is normally decarboxylated in the human to *o*-tyramine which in turn is oxidized to *o*-hydroxyphenylacetic acid. They found that *o*-tyramine and *o*-hydroxyphenylacetic acid are excreted in the urine of normal humans in quantities ranging from 0.3 to 1.0 μg and 0.1 to 0.4 g/g of creatinine, respectively. Since it had been shown by Blaschko[5] that *o*-tyrosine could serve as a substrate for mammalian dihydroxyphenylalanine (DOPA) decarboxylase, it seemed reasonable to suspect that this enzyme is responsible for the decarboxylation observed *in vivo*, and a study of some aspects of its substrate specificity for *o*-tyrosine appeared to be of interest.

We chose to investigate the influence of the incorporation of a single CH_3 as a steric barrier into each of the

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