Synthesis of Compounds Structurally Related to Poison Ivy Urushiol. 4.[1a] 3-(1-Alkyl)alkylcatechols of Varying Side-Chain Shape and Flexibility[1b]

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Received July 3, 1970

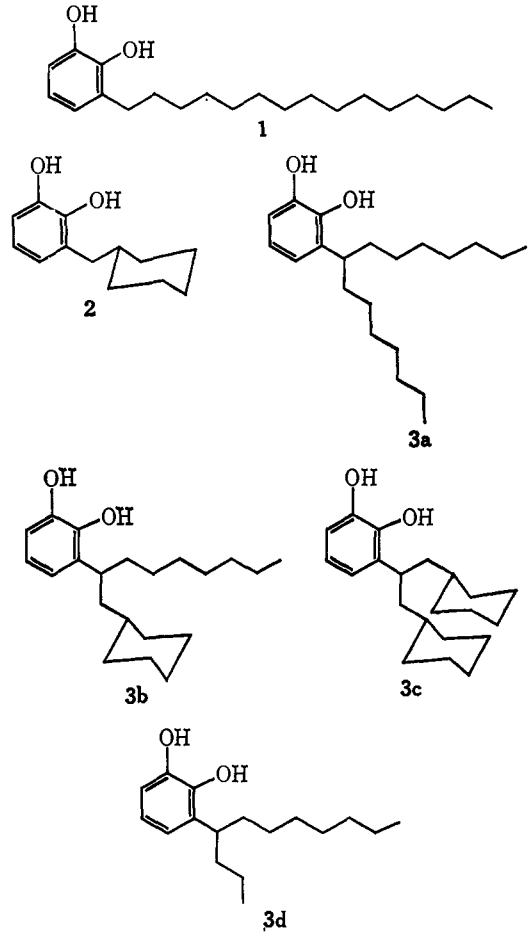
As part of a continuing study to elucidate the role of the side chain in the activity of 3-alkylcatechols as allergic agents (poison ivy dermatitis), five side-chain analogs of the saturated component of poison ivy urushiol, 3-*n*-pentadecylcatechol (3-*n*-PDC), have been synthesized. 3-Cyclohexylmethylcatechol was synthesized by converting the product of the Grignard reaction between cyclohexylmagnesium bromide and *o*-veratraldehyde to the corresponding 3-alkylcatechol by means of a dehydration, hydrogenation, methyl ether cleavage sequence. Side-chain analogs of 3-*n*-PDC bearing side chains symmetrically branched at the 1 position, 3-*n*-(1-*n*-heptyl)octylcatechol and 3-(1-cyclohexylmethyl)cyclohexylethylcatechol, were synthesized by an analogous route following the reaction of the appropriate Grignard reagent with Me *o*-veratrate. Side-chain analogs of 3-*n*-PDC bearing side chains unsymmetrically branched at the 1 position, 3-*n*-(1-*n*-propyl)octylcatechol and 3-*n*-(1-cyclohexylmethyl)octylcatechol, were synthesized also by an analogous route following reaction of the appropriate Grignard reagent with, respectively, 3-*n*-propanoylveratrole and 3-*n*-octanoylveratrole. The alkyl aryl ketones were prepared by the reaction of the appropriate R_2Cd with *o*-veratroyl chloride. Biological evaluation of these 5 branched-chained catechols together with several unbranched analogs of 3-*n*-PDC demonstrated that a remarkable antigenic specificity exists for the shape and flexibility as well as the overall size of the side chain of a 3-alkylcatechol in the function of these agents as sensitizers and elicitors of delayed contact dermatitis.

Biological studies,[2] reported elsewhere,[3] on the variances in the several modes of dermatological activity of a 3-alkylcatechol with side-chain *length*[1a] indicated that the side chain of such compounds has a twofold role in their potencies as allergic agents: (1) the side chain is a determinant of the facility of skin transport, depending on its length (lipophilicity of the compound); (2) the side chain is a specific antigenic determinant (cross-reactivity was optimum for compounds bearing side chains most similar in length).[4]

In the present phase of our continuing investigations of the role of the side chain, **2** and **3a–3d** (see Scheme I) were conceived as a group to provide analogs of 3-*n*-pentadecylcatechol (3-*n*-PDC, **1**), the saturated component of poison ivy urushiol, which on complete and systematic biological evaluation[2] (with several of the straight-chained analogs whose synthesis has been reported separately[1a]) would provide data elucidating the aforementioned two roles.

Since 3-cyclohexylmethylcatechol (**2**) is nearly isomeric with 3-*n*-alkylcatechols having linear side chains 5–8 CH_2 units in length,[1a] it was presumed to have approximately equal lipophilicity and thereby similar properties of transport through the skin and/or other systems involved in the passage of lipophilic molecules. However, if flexibility and steric character of the side chains of such compounds are important factors in their roles as antigenic determinants, it was anticipated

SCHEME I



that **2** would not be completely cross-reactive with the straight-chained analogs.

Similarly, **3a**, **3b**, **3c**, and 3-*n*-PDC (**1**) are isomeric (C_{15}) and thereby should have approximately equal lipophilicity and transport properties. A biological evaluation, therefore, of the relative potencies of 3-*n*-(1-*n*-heptyl)octylcatechol (iso-PDC, **3a**), 3-*n*-(1-cyclohexylmethyl)octylcatechol (isomonocyclo-PDC, **3b**),

(1) (a) Previous paper in the series (3): A. P. Kurtz and C. R. Dawson, *J. Med. Chem.*, **14**, 729 (1971), describes synthesis of straight-chain analogs and includes details pertinent to work described in the present paper; (b) taken from the Ph.D. Dissertation of A. P. Kurtz, Columbia University, 1968; these investigations were supported by Contract PH-43-64-76 with the Division of Biologics Standards of the National Institutes of Health; (c) National Institutes of Health Predoctoral Fellow, 1965–1968.

(2) Biological evaluations of the compounds described herein and in the previous paper[1a] were carried out by Dr. Harold Baer and associates of the Division of Biologics Standards of the National Institutes of Health, Bethesda, Md.

(3) (a) H. Baer, R. C. Watkins, A. P. Kurtz, J. S. Byck, and C. R. Dawson, *J. Immunol.*, **99**, 365 (1967); (b) *ibid.*, **99**, 370 (1967).

(4) (a) See ref 16 of companion paper.[1a] (b) Details on these and other studies, including a detailed review of pertinent immunochemical theory and terminology, are presented in the Ph.D. Dissertation of A. P. Kurtz, Columbia University, 1968.

3-(1-cyclohexylmethyl)cyclohexylethylcatechol (isodicyclo-PDC, **3c**), and 3-*n*-PDC (**1**) as homologous and cross-reactive elicitors of contact dermatitis[4a] was planned to elucidate further the steric and conformational requirements of the side chain of a 3-alkylcatechol as an antigenic determinant.

If an ordered series comprising 3-*n*-octylcatechol,[1a] **3d**, **3a**, and **3b** is visualized, a group of 3-*n*-(1-alkyl)-octylcatechols is realized in which the size and steric requirements of a side-chain branch are increased from H to cyclohexylmethyl.

For overall cross-reactivity evaluations, **2**, **3a–3d**, and the linear side-chained catechols varying in side-chain length from 5 to 15 C atoms[1a] were anticipated to provide biological data which might elucidate which side chains are capable of "fit" and intimate lipophilic "binding" in cell-fixed immunochemical reactive sites[4b] of varying shape, size, and topology.

Recently completed biological evaluation[2] of these compounds has provided data in conformity with those expectations. These results, described in detail in the literature of immunology,[5] are summarized later in this report.

Chemistry.—As previously described,[1a] 3-*n*-alkylcatechols of chain length n can be synthesized by a Grignard, hydrogenation, pyridinium chloride cleavage sequence starting with *o*-veratraldehyde (**4**) and an *n*-alkyl bromide of chain length $n - 1$. Strict application of this route proved impractical for the syntheses of the branched-chained catechols, however, since the 3-alkylveratrole carbinol precursors of catechols (**2**,**3**) proved resistant to direct catalytic hydrogenolysis of the side-chain OH function, presumably due to steric interference. Modification of the synthesis developed for the linear-chained 3-*n*-alkylcatechols[1a] to include a dehydration step prior to side-chain hydrogenation easily afforded the catechols **2** and **3** after synthesis of appropriate precursor intermediates. The required precursor 3-(1-hydroxy)alkylveratroles were secured by simple Grignard addition to *o*-veratraldehyde (**4**) in the case of the synthesis of **2**, and by routes outlined in Scheme II in the case of the synthesis of **3a–3d**.

Cyclohexanemethanol was converted to the corresponding bromide in 57% yield by conventional means.[6]

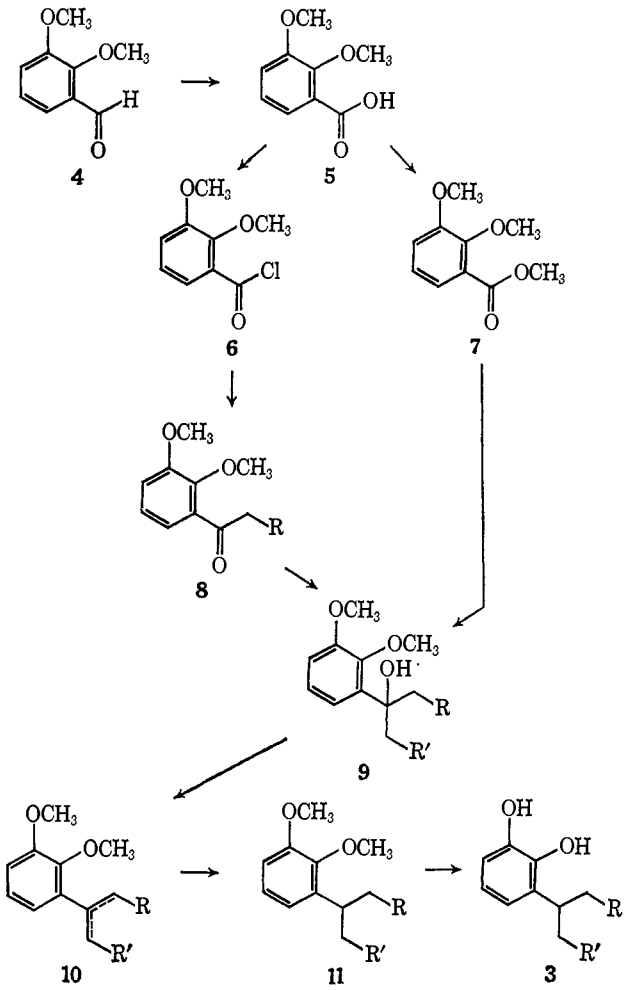
o-Vanillin was methylated conventionally[7] with Me_2SO_4 to *o*-veratraldehyde (**4**).

Side chains unbranched at the 1 position can be constructed by single Grignard addition to **4**. Thus, 3-(1-hydroxy)cyclohexylmethylveratrole was obtained.

Synthesis of the symmetrically branched iso-PDC (**3a**) and isodicyclo-PDC (**3c**) required double Grignard addition to an ester of *o*-veratric acid (**5**). The Me ester **7** was obtained by oxidation of **4** and subsequent esterification[8] (overall yield, 65%).

Synthesis of the unsymmetrically branched isomonocyclo-PDC (**3b**) and isoundecylcatechol (**3d**) required single addition of the appropriate Grignard reagents to, respectively, 3-*n*-octanoylveratrole (**8b**) and 3-*n*-propanoylveratrole (**8d**).[9] The acid **5** was converted conventionally to the acid chloride **6**. The ketones **8b** and **8d** were obtained from **6** by dialkylcadmium synthesis[10] in yields of, respectively, 41 and 85%.

SCHEME II



a, R = R′ = *n*-hexyl
b, R = *n*-hexyl; R′ = cyclohexyl
c, R = R′ = cyclohexyl
d, R = ethyl; R′ = *n*-hexyl

Data for the preparation (*via* 1′-hydroxy intermediates) of the precursor 3-(1-dehydro)alkylveratrole and 3-alkylveratrole (saturated side chain) precursors to catechols (**2**, **3a–3d**) by Grignard addition with the appropriate alkyl halide to the appropriate carbonyl intermediate, $KHSO_4$ dehydration, and side-chain saturation (see Scheme II) are presented in Table I.

Each 3-alkylveratrole was smoothly cleaved to the corresponding catechol using pyridinium chloride[11] according to the method described previously.[1a] Pertinent data for this cleavage and the catechol products thereof are given in Table II.

(5) (a) H. Baer, C. R. Dawson, and A. P. Kurtz, *J. Immunol.*, **101**, 1243 (1968); (b) H. Baer, C. R. Dawson, J. S. Byck, and A. P. Kurtz, *ibid.*, **104**, 178 (1970).

(6) G. S. Hiers and R. Adams, *J. Amer. Chem. Soc.*, **48**, 2385 (1926).

(7) G. Barger and R. Silberschmidt, *J. Chem. Soc.*, 2919 (1928).

(8) J. D. Edwards, Jr., and J. L. Cashaw, *J. Org. Chem.*, **20**, 847 (1955).

(9) While it is theoretically possible to derive the structure of **3d** from **8b**, thus obviating the necessity of preparing **8d**, **8d** is the route of choice to **3d** since after dehydration and saturation, the product of the reaction of PrMgBr with **8b** was nearly impossible to efficiently separate from contaminant derivatives of unreacted **8b**. See ref 4b for details.

(10) (a) H. Gilman and J. F. Nelson, *Rec. Trav. Chim. Pays-Bas*, **55**, 518 (1936); (b) J. Cason, *Chem. Rev. (London)*, **40**, 15 (1947); (c) J. Cason, *J. Amer. Chem. Soc.*, **68**, 2078 (1946); (d) D. A. Shirley, *Org. React.*, **8**, 28 (1954).

(11) The modification (procedure B) of the procedure of E. Wenkert, E.-M. Loeser, S. N. Mahapatra, F. Schenker, and E. M. Wilson, *J. Org. Chem.*, **29**, 435 (1964), is described in the accompanying paper.[1a]

TABLE I

PRECURSORS TO 3-ALKYLVERATROLES

Precursors to compd	1′-Dehydroalkylveratroles		Alkylveratroles					
	Compd	Bp (mm), °C	Compd	Bp (mm), °C	% yield	Formula	Anal.[a]	Purity (vpc), %
2	1′-Dehydro-dimethyl-2	120–122 (0.65)	Dimethyl-2	142–145 (1.0)	63[b]	$C_{15}H_{22}O_2$		99+[c]
3a	10a	191–193 (0.45)	11a	169–170 (0.35)	66[d]	$C_{23}H_{40}O_2$		
3b	10b	150–152 (0.15)	11b	153–154 (0.2)	45[e]	$C_{23}H_{38}O_2$		99.5+[f]
3c	10c	167–170 (0.20)	11c	156–160 (0.12)	42[d,g]	$C_{23}H_{36}O_2$	C, H	99.5+[f]
3d	10d	130–132 (0.5)	11d	126–128 (0.1)	42[e]	$C_{19}H_{32}O_2$	C, H	98[h]

[a] Microanalyses for selected compds, where made, agreed with theory to within ±0.4%. [b] From **4**. [c] QF-1, 150°. [d] From **7**. [e] From the ketone precursor. [f] SE-30, 11**b**: 180°; 11**c**: 200°. [g] Lower yield for 11**c** compared to yield for 11**a** presumably due to steric hindrance of second Grignard addition. A low-boiling forerun obtained during the distn of **10c** contd material which, if assigned the structure cyclohexylmethylveratryl ketone or derivatives, corresponded to a 35% yield from **7**. See ref 4b. [h] SE-30 (150°): <2% impurity which by retention time data was neither *n*-C_3-veratrole or *n*-C_8-veratrole.

TABLE II

3-ALKYLCATECHOLS

Compd	Bp (mm), °C	% yield from carbonyl precursor	% yield from 11	Mp, °C[a]	Anal.[b]	Vpc, %	Formula
2		53	84	115.1–116.5	C, H	98+[c]	$C_{13}H_{18}O_2$
3a	185–187 (0.08)	63	95	43.7–45.2	C, H	97.5[d]	$C_{21}H_{36}O_2$
3b	171–173 (0.45)	36	80	43.5–46.0	C, H	98+[e]	$C_{21}H_{34}O_2$
3c		32	76	92.2–93.7	C, H	98+[f]	$C_{21}H_{32}O_2$
3d		32	76	53.0–55.0[g]	C, H	99+[h]	$C_{17}H_{28}O_2$

[a] Mp of catechol at final stage of purity; samples used for microanalysis and biological evaluation. [b] Microanalyses agreed with theory to within ±0.4%. [c] QF-1, 150°. [d] SE-30, 200°: <0.5% possible contamination with *n*-C_8-catechol. [e] SE-30, 150 and 190°: <0.1% possible contamination with *n*-C_8-catechol. [f] SE-30, 150 and 190°: <0.1% possible contamination with 3-cyclohexylethylcatechol. [g] Purified by vacuum sublimation. [h] SE-30, 150°: <0.1% contamination with 3-*n*-butylcatechol.

Biological Results.—The 5 branched-chained 3-alkylcatechols have been evaluated and compared with several members of the straight-chained series[1a] for activity as sensitizers and elicitors[4a] of poison ivy dermatitis. Details have been presented in the immunologic literature.[5]

The role of the side chain of an alkylcatechol as an antigenic determinant of remarkable specificity was confirmed. Optimum cross-reactivity was realized when the antigenic determinant of a challenge agent (side chain) was capable of "fit" into the reactive site corresponding to sensitization with a particular compound and when, while being able to fit, the challenging antigenic determinant (side chain) could conform intimately to the topography of the reactive site permitting the optimum number of lipophilic interactions.

The following data[5a] are illustrative. When a guinea pig was sensitized with the linear side-chained 3-*n*-PDC (**1**), the geometric mean dermatitis-eliciting dose (GM) for the homologous challenge agent, 3-*n*-PDC, was 0.0029 μmole. On animals sensitized with 3-*n*-PDC, however, isodicyclo-PDC (**3c**) and 3-cyclohexylmethylcatechol (**2**) were nonreactors. The data suggested that the side chain of **3c** is too bulky for cross-reactivity with an immunochemical reactive site compatible with the 3-*n*-PDC side chain while the small rigid structure of the side chain of **2** cannot conform with the topology of the 3-*n*-PDC reactive site. However, 3-*n*-PDC (GM = 0.024 μmole) reacted nearly as well as the homologous allergen, isodicyclo-PDC (**3c**) (GM = 0.014 μmole), on animals sensitized with the latter, while **2** was again a nonreactor. Thus, 3-*n*-PDC could "follow the contours" of the immunochemical reactive site compatible with **3c** while **2**, again, could not unwind for intimate conformation. Similarly, while 3-*n*-octylcatechol[1a] (GM = 0.016 μmole) reacted as well as **2** (GM = 0.019 μmole) on animals sensitized with the latter, **2** (GM = 0.58 μmole) was a poor reactor on animals sensitized with 3-*n*-octylcatechol; on such animals, 3-*n*-octylcatechol had GM = 0.0008 μmole.

Certain of the physical properties for these alkylcatechols point to effects of side-chain structure on inter- and intramolecular interactions.

The melting points for the isomeric C_{15} catechols may be listed in increasing order as follows: iso-PDC (**3a**), mp 43.7–45.2°; isomonocyclo-PDC (**3b**), mp 43.5–46.0°; 3-*n*-PDC (**1**), mp[1a] 59.2–60.0°; isodicyclo-PDC (**3c**), mp 92.2–93.7°. Further, 3-cyclohexylmethylcatechol has mp 115.1–116.5° while nearly isomeric 3-*n*-alkylcatechols have lower melting points as follows:[1a] *n*-C_5, mp 40.4–42.2°; *n*-C_8; mp 38.2–39.2°. High melting points presumably reflect low side-chain structural entropy, rigidity, and ordered packing in the crystal lattice. The high melting point of 3-cyclohexylmethylcatechol relative to the *n*-C_5 or *n*-C_8 catechols and the high melting point of isodicyclo-PDC relative to the isomeric PDC's probably reflect the fact that in the cyclic-chained compounds, the "*tert*-butylcyclohexane" character of portions of the side chain enhances intermolecular packing relative to compounds with more flexible side chains. Such *tert*-butyl-

cyclohexane order is disrupted by the presence of the linear branch in isomonocyclo-PDC and does not even exist in iso-PDC and the linear-chained compounds. 3-Cyclohexylmethylcatechol **3b**, and **3c** were poor challenge allergens on animals sensitized, respectively, with 3-*n*-octylcatechol and 3-*n*-PDC while the reverse cross-reactivity was excellent.[5a] Such specificity points to an *immunochemical* incompatibility based on side-chain rigidity and bulk.

Of additional interest is the similarity in melting points for iso-PDC and the linear-chained C_5 and C_8 compounds. The melting point of 3-*n*-PDC is 17–22° higher than the melting points of these shorter-chained compounds, presumably reflecting the fact that the melting point of a long-chain 3-alkylcatechol is related to the number of intermolecular lipophilic binders (CH_2 units) in the side chains of members of a homologous series. If iso-PDC is considered to bind to itself *intramolecularly*, the number of intermolecular "binders" remaining would not be significantly different from the number of intermolecular "binders" of the *n*-C_5 or the *n*-C_8 catechols. Thus, the similarity in melting points for iso-PDC and the short-chained catechols may reflect the fact that from an intermolecular point of view, they are not very different. There is no strong intramolecular side-chain binding in the other iso-PDC's since in these compounds, the presence of the *tert*-butylcyclohexane moiety(ies) probably inhibits such binding. Iso-PDC may possess an immunochemical binding site about as efficient as the C_8 compound but inferior to 3-*n*-PDC due to intramolecular binding of each C_7 side-chain branch to the other.

Experimental Section

General details pertinent to these preparations are given at the beginning of the Experimental Section of the previous paper.[1a] Microanalyses, where performed, were within ± 0.4% of theory.

***o*-Veratraldehyde (4).**—*o*-Vanillin was methylated by the method of Barger and Silberschmidt[7] in 89% yield as described in the previous paper.[1a]

***o*-Veratric acid (5)** was prepared from **4** according to the method of Edwards and Cashaw[8] in 79% yield: mp 120–122.5° (lit.[8] mp 120–122°).

Cyclohexylmethyl Bromide (Hexahydro-α-bromotoluene).—Cyclohexanemethanol was converted to the bromide in 57% yield by a variation of the procedure of Hiers and Adams:[6] bp 73–75° (14 mm) [lit.[6] bp 76–77° (26 mm)]; ir and nmr consistent with the desired structure. *Anal.* ($C_7H_{13}Br$) C, H, Br.

***o*-Veratroyl Chloride (6).**—**5** was conventionally converted to **6** by refluxing neat with $SOCl_2$ and distilling *in vacuo*: 85% yield; vpc (SE-30, 100°), 90% **6**, 10% **5**;[12] bp 150–150.5° (9 mm); mp 54.5–56.0° (lit.[13] mp 54–55°); the ir showed no OH bands and the nmr was consistent with structure.

3-*n*-Octanoylveratrole (8b).—The Grignard reagent from 32.3 g (0.18 mole) of *n*-heptyl bromide[14] and 0.2 mole of Mg in a total of 100 ml of Et_2O was prepared in the conventional manner.[1a] The soln was dild with 150 ml of Et_2O and cooled to 0°. To the cooled stirring soln was gradually added 18.35 g (0.1 mole) of anhyd $CdCl_2$ over a period of 1 min. The white slurry was brought to reflux for 30 min at which time the Gilman[15] test for the presence of Grignard reagent, carried out on an aliquot, proved negative. The slurry was cooled again to 0°, and a soln of 36.1 g of *o*-veratroyl chloride (**6**; vpc, 90% RCOCl, 10% acid; 0.162 mole of RCOCl) in 100 ml of Et_2O[16] was added over 15 min. At the end of the addn, the system was stirred at reflux for 3 hr and at room temp for 18 hr.[17] Conventional work-up[10] and distn gave 24.3 g of the product ketone **8b**, bp 134–135° (0.3 mm); vpc (SE-30, 175°) 17% high mol wt impurities. Spinning-band distn of this yield combined with 28.6 g from another run of the prepn gave a fraction: 38.55 g; bp 114–115° (0.1 mm); vpc, less than 1% impurities; yield from **6**, 41%.[17] The ir spectrum confirmed structure: (C=O, 5.95); nmr: τ 3.00 (s, 3 H, arom), 6.17 and 6.21 (two s, 6 H, MeO), 7.14 (t, J = 7 cps, 2 H, CH_2 α to C=O), 8.1–9.3 (broad envelope, 13 H, C_6H_{13}). *Anal.* ($C_{16}H_{24}O_3$) C, H.

3-*n*-Butanoylveratrole (8d).—As outlined for the prepn of **8b**, 0.146 mole of **6** was treated with the Pr_2Cd prepd from 0.232 mole of *n*-PrBr.[4] Work-up and distn gave **8d**; 26.0 g (85% yield),[17] bp 108–110° (0.35 mm); vpc (SE-30, 110°), <1% impurities. The ir and nmr spectra confirmed structure and were analogous to that reported above for **8b**. *Anal.* ($C_{12}H_{16}O_3$) C, H.

3-Cyclohexylmethylveratrole and 3-(1-Alkyl)alkylveratroles (11a–11d) *via* 1′,2′-Dehydro Analogs.—3-(1-Hydroxy)cyclohexylmethylveratrole was prepd by conventional[1a,4b] addn of the Grignard reagent (1.3 moles/mole of aldehyde) from bromocyclohexane[14] to *o*-veratraldehyde (**4**). Attempts at direct hydrogenolysis of the product gave only mixts of materials difficult to vacuum distill due to concomitant dehydration.

Conventional[1a,4b] addn of the Grignard reagents (2.4 moles/mole of ester) from *n*-heptyl bromide and cyclohexylmethyl bromide to the ester **7** gave, respectively, the carbinols **9a** and **9c**. Reactions[1a,4b] of the Grignard reagents (1.2 moles/mole of ketones) from *n*-heptyl bromide and *n*-PrBr[14] with the ketones, respectively, **8b** and **8d** afforded the carbinols **9b** and **9d**.

Ir spectra of all crude carbinols were consistent with desired structures. Dehydration was performed without further characterization.

Each 1′-hydroxyalkylveratrole was dehydrated according to the following critical procedure. A 50- to 100-ml flask, equipped with a side arm into which a thermometer was sealed, was attached to a Vigreux distn apparatus equipped for vacuum fractionation of the product oil. The carbinol and $KHSO_4$ (powdered, 10 g/0.1 mole of carbinol) were introduced into the pot and the system was evacuated to 10 mm, the contents of the flask being agitated by N_2 bubbling through a bleed-in capillary. Heating and gradual evacuation were increased until dehydration commenced, and in each case, after about 15 min, the dehydration was complete allowing further evacuation and direct vacuum distn from the pot. 3-(1-Hydroxy)cyclohexylmethylveratrole dehydrated at 175° (760 mm); dehydration for **9a–9d** occurred at 80–140° (0.35–0.1 mm). Purity and structure for each olefinic veratrole were checked prior to hydrogenation by ir and spectral analysis (ir, loss of OH). The nmr spectrum for **10c** is representative of this group of compounds: τ 2.8–3.6 (m, 3 H, arom), 4.77 (d, J = 10 cps, 1 H, vinyl), 6.24 and 6.33 (two s, 6 H, MeO), 7.0–7.8 (broad envelope, 3 H, allylic), 7.8–9.5 (broad envelope, 21 H, C_6H_{11} and C_6H_{10}).

Each (1′,2′-dehydro)alkylveratrole was hydrogenated in soln with EtOAc containing 10% Pd/C and a trace of H_2SO_4 at 3.87 kg/cm² (room temp) using a Parr apparatus. *In vacuo* distn followed conventional work-up. **Dimethyl-2** and **11a–11d** were characterized by ir and nmr spectra and by the data presented in Table I. The nmr spectrum for **11a** is representative of this group of compds: τ 2.9–3.5 (m, 3 H, arom), 6.24 and 6.27 (two s, 6 H, MeO), 6.5–7.5 (envelope, 1 H, benzylic), 8.75 (broad s), 8.95–9.32 (distorted t); τ 8.0–9.4 signals integrated for 30 H.

Cleavage of Alkylveratroles to Alkylcatechols (2, 3a–3d).—Each alkylveratrole was cleaved using pyridinium chloride and HCl gas as previously described.[11] Each catechol was purified by distn and/or recrystn from hexane. Ir and nmr spectral data supported assigned structure in each case. The nmr spectrum for **3c** is representative of this group of compds: τ 3.44 (s, 3 H,

(12) Since the acid contaminant did not seriously interfere with subsequent reactions, no attempt was made to improve purity of **6**.

(13) F. K. Beilstein, "Handerbuch der Organischen Chemie," Vol. 10, 1941, p 249.

(14) Eastman Organic Chemicals, Rochester, N. Y.

(15) H. Gilman, "Organic Chemistry," 2nd ed, Vol. I, Wiley, New York, N. Y., 1943, p 496.

(16) A preliminary experiment had shown that there was little advantage and considerable technical difficulty in replacing Et_2O with PhH[10d] prior to the addition of the acid chloride in this R_2Cd ketone preparation.

(17) The reaction progress was monitored by vpc analysis of hydrolyzed aliquots periodically removed from the reacting mixt. Maximum ketone (74%) was present at 4 hr from the time of addn of the acid chloride in the prepn of **8b**. A reaction time of 3 hr rather than 18 hr was used therefore in the preparation of **8d**.

arom), 4.70 (s, 2 H, OH), 6.80 (q, J = 7 cps, 1 H, benzylic), 7.8–9.5 [broad envelope, 26 H, $(C_6H_{11}CH_2)_2$]. Further characterization and yield data for the catechols are presented in Table II.

Acknowledgment.—We are pleased to acknowledge the able technical assistance of Mr. Stephen G. Rice, Columbia College, 1967.

Synthesis and Antihypertensive Properties of Some *N*-(Guanidinoalkyl)pyrrolidines

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Received October 13, 1970

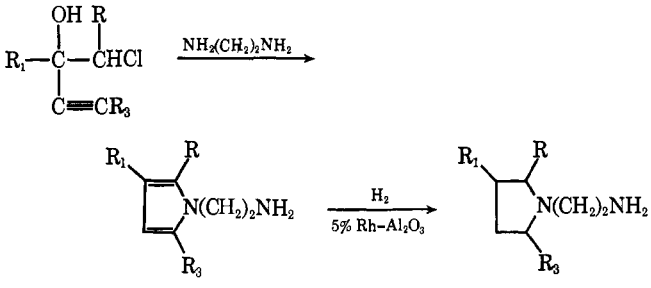
The synthesis of 21 *N*-(guanidinoalkyl)pyrrolidines is described. Some of these, **7a**, **7b**, **10**, **11**, **12**, **12a**, **12b**, **13**, and **21**, exhibited an antihypertensive activity similar to that of guanethidine when tested in renal hypertensive rats. Structure–activity relationships are discussed.

Since the discovery of the antihypertensive action of guanethidine,[1] many related compounds have been synthesized and several have been found to be active antihypertensives[2] which, like guanethidine, mediate their effect *via* adrenergic neurone blockade. This paper describes the preparation and pharmacological properties of a series of *N*-(guanidinoalkyl)pyrrolidines.[3] Details and antihypertensive activities of these compounds are shown in Table I.

Chemistry.—The majority of the compounds listed in Table I were prepared by treating the appropriate *N*-(aminoalkyl)pyrrolidine with *S*-methylpseudothiouronium sulfate in aq EtOH and then neutralizing with 5 *N* H_2SO_4 (method A). Compounds **16–18** were prepared as described in the Experimental Section.

The *N*-(aminoalkyl)pyrrolidine precursors to **1–4**, **7a**, **8**, **9**, **12–14**, and **16–20**, were synthesized as outlined in Schemes I and II. The first step of these syntheses

SCHEME I

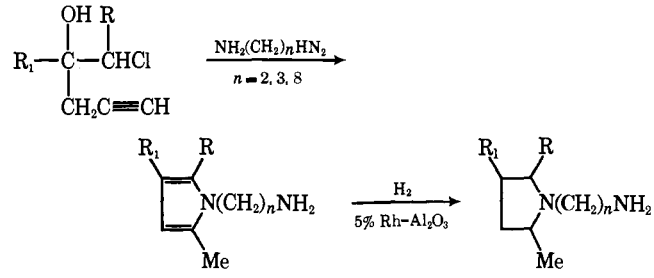


involved the formation of pyrroles from acetylenic carbinols in a manner suggested by the work of Perveev and others.[4,5]

The precursor to **5** was obtained by catalytic hydrogenation of 1-(2-aminoethyl)-3-phenylpyrrole.

When the pyrrole ring carried substituents on 2 or more C atoms, the catalytic hydrogenation step of

SCHEME II



Schemes I and II yielded *N*-(aminoalkyl)pyrrolidines as mixtures of stereoisomers. Usually no attempt was made to separate these isomers. In the case of the precursor to **12**, however, the cis and trans isomers of the *N*-(aminoalkyl)pyrrolidine were separated by preparative glpc and converted to the *N*-(guanidinoalkyl)-pyrrolidines **12a** and **12b**, respectively. The configurational assignments were made from the pmr spectra on the basis of the mutual shielding effect of Me groups in close proximity. Compound **12a** was also isolated by fractional crystallization of a mixture of the isomeric *N*-(guanidinoalkyl)pyrrolidine sulfate salts.

In the case of **7a**, the catalytic hydrogenation step of Scheme II gave predominantly the cis isomer of the *N*-(aminoalkyl)pyrrolidine intermediate as shown by glpc. The cis configuration of the Me substituents was confirmed by X-ray crystallographic analysis of the *N*-brosyl derivative.[6] However, synthesis of the *N*-(aminoalkyl)pyrrolidine as outlined in Scheme III, followed by purification as described in the Experimental Section, gave predominantly the trans isomer. Guanylation of this isomer mixture gave **7b**.

The precursor to **21** was obtained from a mixture of isomeric branched-chain compounds.

The precursor to **15** was obtained by catalytic hydrogenation of 2,4-dimethyl-1-(2-methylaminoethyl)-pyrrole which was prepared as described in the Experimental Section.

The *N*-(2-aminoethyl)pyrrolidine intermediates for **6**, **10**, and **11** were synthesized as outlined in Scheme IV.

(1) R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniel, *J. Pharmacol. Exp. Ther.*, **128**, 22 (1960).

(2) R. P. Mull and R. A. Maxwell, "Antihypertensive Agents," E. Schlittler, Ed., Academic Press, New York, N. Y., 1967, p 115.

(3) Many of these compds are described by D. Miller and C. S. Fake in British Patent 1,185,080 (1970) and other patents.

(4) F. Ya. Perveev and E. M. Kuznetsova, *Zh. Obshch. Khim.*, **28**, 2360 (1958); *Chem. Abstr.*, **53**, 3190 (1959).

(5) E. R. Catlin, Ph.D. Thesis, Oxford, England (1964).

(6) Professor G. Sim, University of Sussex, Sussex, England, unpublished work.