pharmacokinetic parameters, which might have been impacted directly by the physiological changes. There were significant decreases in the cardiac index (41%), hepatic blood flow (31%), renal blood flow (44%), and GI tract blood flow (60%) in older animals. These changes may account for the decreased renal clearance (68%), total clearance (67%), volume of distribution (57%), and bioavailability (25%). The renal clearance values were 3.9 and 2.4 times larger than the respective renal blood flow in young-adult and middle-aged rats indicating a significant active renal secretion of *N*-acetylprocainamide, consistent with previous findings (9). The nonrenal clearance values were 82 and 52 times larger than the respective hepatic blood flow in young-adult and middle-aged rats, indicating a combination of active biliary secretion and biotransformation of the drug in the liver. The decrease in the volume of distribution might have been due also to a change in body composition in the older animals. While the fatty tissue and skin account for a larger percentage of the body weight in older animals, the percentages of lean body mass and body water decrease.

The distribution of *N*-acetylprocainamide in the liver and kidneys was also affected by age. The liver–plasma and kidney–plasma concentration ratios increased with age (86 and 44%, respectively). This elevation of the drug level in the organs seems to be inversely proportional to the decrease in liver and kidney blood flow (31 and 44%, respectively) in the older rats. The drug accumulation in the organs of the older rats probably is caused by: (*a*) higher plasma levels of *N*-acetylprocainamide (initial concentrations of 19 and 46 μg/ml in 3- and 12-month-old animals, respectively); (*b*) the diminution in the blood flow to the organs (the redistribution of *N*-acetylprocainamide from the tissues was affected to a greater extent by this than by the actual distribution of the drug in the organs); and (*c*) changes in the composition of the liver and kidney tissues which favored a larger drug uptake. Interestingly, with the minor change in heart blood flow (12%), the heart–plasma concentration ratio did not change much with age.

In conclusion, the data show an age-dependent reduction in the bioavailability of orally administered *N*-acetylprocainamide solution in rats. The elimination of the drug, however, is impaired to a greater extent with age, which results in significant accumulations in the plasma and tissues after chronic administration. This finding indicates that in long-term toxicity testings of this and other drugs which show age-dependent pharmacokinetics, an adjustment in the chronically administered dose is essential.

REFERENCES

(1) A. D. Bender, *J. Am. Geriat. Soc.*, **13**, 192 (1965).

(2) M. S. Yates and C. R. Hiley, *Experientia*, **35**, 78 (1979).

(3) D. L. Schmucker, *Am. Pharmacol. Exp. Ther.*, **30**, 445 (1979).

(4) K. Wilson and J. Hanson, *Methods Find. Exp. Clin. Pharmacol.*, **2**, 303 (1980).

(5) P. G. Harms and S. R. Ojeda, *J. Appl. Physiol.*, **36**, 391 (1974).

(6) C.-M. Lai, B. L. Kamath. Z. M. Look, and A. Yacobi, *J. Pharm. Sci.*, **69**, 982 (1980).

(7) A. Yacobi, H. F. Stampfli, C.-M. Lai, and B. L. Kamath, *Drug. Metal. Dispos.*, **9**, 193 (1981).

(8) B. L. Kamath, A. Yacobi, S. D. Gupta, H. Stampfli, M. Durrani, and C.-M. Lai, *Res. Commun. Chem. Pathol. Pharmacol.*, **32**, 299 (1981).

(9) B. L. Kamath, C.-M. Lai, S. D. Gupta, M. J. Durrani, and A. Yacobi, *J. Pharm. Sci.*, **70**, 299 (1981).

(10) E. J. Triggs, R. L. Nation, A. Long, and J. J. Ashley, *Eur. J. Clin. Pharmacol.*, **8**, 55 (1975).

(11) L. Penzes, G. Simon, and M. Winter, *Exp. Gerontol.*, **3**, 607 (1968).

(12) L. Penzes and M. Boross, *Exp. Gerontol.*, **9**, 253 (1974).

(13) L. Penzes and M. Boross, *Exp. Gerontol.*, **9**, 259 (1974).

(14) J. Klimas, *J. Gerontol.*, **23**, 529 (1968).

(15) D. F. Davies and N. W. Shock, *J. Clin. Invest.*, **29**, 496 (1950).

(16) S. A. Friedman, A. E. Raizner, H. Rosen, N. A. Solomon, and W. Sy, *Ann. Intern. Med.*, **76**, 41 (1972).

Synthesis and Antiallergenic Properties of 3-*n*-Pentadecyl- and 3-*n*-Heptadecylcatechol Esters

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Received February 12, 1982, from the *Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677.* Accepted for publication June 11, 1982.

Abstract □ A synthetic procedure is described for the preparation of 3-*n*-pentadecyl- and 3-*n*-heptadecylcatechols and their acetate and alaninate esters. The Wittig reagent prepared from 2,3-dimethoxybenzyltriphenylphosphonium bromide (III) was coupled with 1-tetradecanal or 1-hexadecanal to give the olefins IV and V, respectively. Catalytic reduction of IV and V followed by demethylation with boron tribromide afforded VIII and IX. The acetates were prepared using acetic anhydride and pyridine, while the alaninates were prepared using *N*-(*tert*-butoxycarbonyl)-L-alanine and dicyclohexylcarbodiimide followed by removal of the *tert*-butoxycarbonyl group with hydrogen chloride gas. The esters were active in guinea pigs in the production of tolerance and desensitization or hyposensitization to poison ivy-type contact dermatitis.

Keyphrases □ Synthesis—3-*n*-pentadecyl- and 3-*n*-heptadecylcatechols, acetate and alaninate esters □ Urushiols—poison ivy and poison oak, synthesis of saturated congeners □ 3-*n*-Pentadecylcatechol—synthesis, acetate and alaninate esters □ 3-*n*-Heptadecylcatechol—synthesis, acetate and alaninate esters

Poison ivy (*Toxicodendron radicans*), poison oak (*T. diversilobum*), and poison sumac (*T. vernix*) are the primary cause of occupational dermatitis in the United States. Other genera of the plant family Anacardiaceae with dermatogenic constituents include *Anacardium* (cashew nuts), *Semicarpus* (india ink tree), *Metopium* (poison wood), and *Mangifera* (mango). The allergenic components in most of these plants are 3-*n*-alk-(en)-yl catechols with C-15 or C-17 side chains and different degrees of unsaturation (0–3 olefinic bonds) (1–5).

Extracts of poison ivy, poison oak, and poison sumac have been used for diagnosis and prophylactic treatment of poison ivy, oak, and sumac dermatitis (6–8). However, the efficacy of these extracts in producing desensitization is questionable (9). Kligman (10) found that, in humans, only hyposensitization was possible by oral or intramuscular injection of either poison ivy oleoresin or pentadecylcatechol. Oleoresin produced hyposensitization after intramuscular injection of 2–2.5 g or after oral administration of 3.5–4.0 g in multiple doses. The hyposensitization was temporary, and the individuals regained their original sensitivity within 6–10 months after cessation of the treatment.

A previous publication (11) reported a new method for

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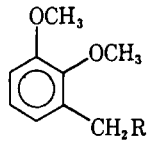
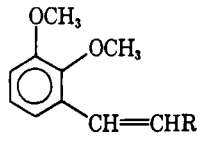
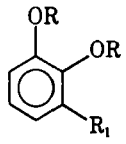


I: R = OH
II: R = Br
III: R = $\overset{+}{P}$—$(C_6H_5)_3\bar{B}r$



IV: R = $C_{13}H_{27}$
V: R = $C_{15}H_{31}$



VI: R = CH_3, R_1 = $C_{15}H_{31}$
VII: R = CH_3, R_1 = $C_{17}H_{35}$
VIII: R = H, R_1 = $C_{15}H_{31}$
IX: R = H, R_1 = $C_{17}H_{35}$
X: R = $COCH_3$, R_1 = $C_{15}H_{31}$
XI: R = $COCH_3$, R_1 = $C_{17}H_{35}$
XII: R = $COCH(CH_3)NHCO_2C(CH_3)_3$, R_1 = $C_{17}H_{35}$
XIII: R = $COCH(CH_3)NH_2 \cdot HCl$, R_1 = $C_{17}H_{35}$
XIV: R = $COCH(CH_3)NHCO_2C(CH_3)_3$, R_1 = $C_{15}H_{31}$
XV: R = $COCH(CH_3)NH_2$ HCl, R_1 = $C_{15}H_{31}$

the induction of tolerance to poison ivy and oak urushiol in guinea pigs by intravenous injection of pentadecylcatechol-associated autologous red blood cells 2 weeks prior to attempted contact sensitization. It was also reported (12) that intravenous administration of the esterified urushiol (poison ivy or poison oak urushiol acetate) was effective in producing immune tolerance in naive guinea pigs and desensitization or hyposensitization in already sensitized animals. This paper reports the improved synthesis of the saturated congeners of poison ivy and poison oak urushiol acetates (diacetyl-3-*n*-pentadecylcatechol and diacetyl-3-*n*-heptadecylcatechol), and their efficacy in the production of tolerance and hyposensitization. In addition, the synthesis and activity of a water-soluble ester of heptadecylcatechol (heptadecylcatechol-dialaninate dihydrochloride) is described.

EXPERIMENTAL[1]

Synthesis—*2,3-Dimethoxybenzyl Bromide (II)*—A solution of 25 g (148.8 mmoles) of 2,3-dimethoxybenzyl alcohol (I) in 400 ml of dry ether was stirred at room temperature for 2.5 hr with 8 ml of phosphorus tribromide. The organic layer was washed with water, dried (anhydrous sodium sulfate), and the solvent removed at reduced pressure to give 33.7 g of II (98% yield); IR: ν_{max} (liquid film) 2940, 2830, 1585, and 1480 cm^{-1}; UV: λ_{max} (log ϵ) 219 (4.10) and 286 (3.24) nm; ^{1}H-NMR: δ 7.03–6.72 (3, m), 4.53 (2, s), 3.97 (3, s), and 3.80 (3, s) ppm; mass spectrum: *m/z* (%): 230 (35), 232 (M^+ +2, 34), 151 (88), and 136 (100).

2,3-Dimethoxybenzyltriphenylphosphonium Bromide (III)—A solution of 28 g of II (120 mmoles) in 500 ml of benzene containing 32 g (121 mmoles) of triphenylphosphine was allowed to reflux for 5 hr, whereupon a copious white precipitate formed. The precipitate was removed by filtration, washed with benzene, and dried to give 59 g (99% yield) of III; mp 233–234°; IR: ν_{max} (KBr) 2940, 2830, 2780, 1580, 1480, 1470, and 1430 cm^{-1}; UV: λ_{max} (log ϵ) 225 (4.46), 265 (sh, 3.61), 268 (3.67), 275 (3.66), and 282 (sh, 3.37) nm; ^{1}H-NMR: δ 8.00–7.50 (15, m), 7.00–6.60 (3, m), 5.13 (2, br, d, J = 14 Hz), 3.77 (3, s), and 3.50 (3, s).

2,3-Dimethoxy-$\Delta^{1'}$-pentadecenylbenzene (IV)—A dispersion of 5 g (10 mmoles) of the aforementioned phosphonium salt (III) in 100 ml of tetrahydrofuran (dried over sodium hydride) was stirred under nitrogen while 6 ml (10.2 mmoles) of a 1.7 *M* solution of *n*-butyllithium in hexane was added slowly. After 10 min the solution developed a deep-red color, at which time a solution of 2.65 g (10 mmoles) of 80% tetradecyl aldehyde[2] in 10 ml of tetrahydrofuran was added in a dropwise manner. The mixture slowly turned yellow and was stirred at room temperature for 2 hr. The mixture was refluxed for 16 hr and then cooled to room temperature. TLC (hexane–ethyl acetate, 95:5) on silica gel showed one spot (R_f 0.90) and no starting aldehyde (R_f 0.75). The solvent was removed under reduced pressure, and the residue was added to ethyl acetate (150 ml) and water (50 ml). The organic phase was washed with water (50 ml) and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 7.0 g of a pale amorphous solid which was filtered through 15 g of silica gel-60 (hexane–ethyl acetate, 97:3) to yield 3.3 g of a colorless solid. GC (2% OV-17) showed two peaks (*cis* and *trans* isomers of IV in a 2:3 ratio, respectively). GC/MS analysis showed the following ions: *cis m/z* 346 (M^+, 91%), 177 (100%), and 151 (83%); *trans m/z* 346 (M^+, 100%), 177 (90%), and 151 (70%).

2,3-Dimethoxy-pentadecylbenzene (VI)—The *cis* and *trans* isomeric mixture of IV (3.3 g) was dissolved in 40 ml of *tert*-butyl alcohol and 640 mg of 10% palladium-on-carbon was added. The mixture was hydrogenated on a Parr hydrogenator at 1.41 kg/cm^2 for 16 hr. Filtration of the product through diatomaceous earth[3] followed by evaporation of the solvent resulted in 3.3 g of VI as a white solid, mp 35–36°; IR: ν_{max} (liquid film) 2920, 2855, 1597, 1583, 1478, 1272, 1087, 1015, and 747 cm^{-1}; UV: λ_{max} (log ϵ) 207 (3.99), 213 (sh, 3.84), 270 (3.01), and 276 (3.00) nm; ^{1}H-NMR: δ 0.90 (3, t, J = 5 Hz), 1.28 (26, br, s), 2.62 (2, t, J = 6 Hz), 3.80 (6, s), and 6.82–6.46 (3, m) ppm; mass spectrum: *m/z* 348 (M^+, 40%), 151 (100%), and 136 (90%).

3-n-Pentadecylcatechol (VIII)—A solution of 2,3-dimethoxy-pentadecylbenzene (VI) (500 mg, 1.44 mmoles) in 30 ml of methylene chloride was cooled to 0° under nitrogen. A solution of boron tribromide in methylene chloride (1.1 ml of 12% v/v) was added and the mixture was allowed to slowly come to room temperature. After standing for 90 min, 3 ml of water was added followed by sodium bicarbonate (until no more gas evolution was noticeable). The organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to yield a light brown residue (408 mg). Crystallization from hexane–isooctane yielded colorless needles of VIII, mp 55–56°; IR: ν_{max} 3400, 2910, 2840, 1615, 1590, 1475, 1285, 1055, 942, 827, and 725 cm^{-1}; UV: λ_{max} (log ϵ) 278 (3.23) and 230 (3.19) nm; ^{1}H-NMR (FT): δ 0.90 (3, t, J = 5 Hz), 1.26 (26, br, s), 2.55 (s, t, J = 6 Hz), 5.10 (2, br, s, exchangeable with D_2O), and 6.72 (3, br, s) ppm; mass spectrum: *m/z* 320 (M^+, 4%) and 123 (base peak).

Diacetyl-3-n-pentadecylcatechol (X)—Acetylation of VIII was carried out by stirring 400 mg with 1 ml each of acetic anhydride and pyridine at room temperature for 4 hr. The mixture was poured onto ice, and then extracted with chloroform (3 × 30 ml). The combined chloroform extract was washed successively with 20 ml of ice water, 20 ml of chilled 10% H_2SO_4, 20 ml of water, saturated sodium bicarbonate solution, and then 30 ml of water. The chloroform layer was dried over anhydrous sodium sulfate, and the solvent was evaporated to give a white solid (502 mg). Recrystallization from chloroform–ethanol afforded rosette crystals of X, mp 51–52°; IR: ν_{max} 2910, 2840, 1770, 1760, and 1470 cm^{-1}; UV: λ_{max} (log ϵ) 278 (sh, 1.65), 258 (2.45), and 210 (4.11) nm; ^{1}H-NMR: δ 7.30–7.00 (3, m), 2.50 (2, t, J = 6 Hz), 2.28 (3, s), 2.22 (3, s), 1.27 (26, br, s), and 0.88 (3, t, J = 6 Hz) ppm; mass spectrum: *m/z* 404 (M^+, 0.3%), 320 (48%), and 123 (100%).

2,3-Dimethoxy-$\Delta^{1'}$-heptadecenylbenzene (V)—Compound V was prepared from 5 g (10 mmoles) of the phosphonium salt (III) and 2.8 g (11.6 mmoles) of *n*-hexadecylaldehyde[4] following the same procedure used for the synthesis of IV. The reaction was filtered, the filtrate evaporated under reduced pressure, and the residue partitioned between chloroform (150 ml) and water (3 × 30 ml). The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was dissolved in 15 ml of hexane, filtered, and the filtrate chromatographed on silica gel-60 (50 g, hexane–ethyl acetate, 95:5) to yield 3.6 g of a colorless solid. GC and GC/MS examination showed a mixture of *cis* and *trans* isomers (2:3, respectively); mass

[1] Melting points are uncorrected and were determined on a Thomas-Hoover Unimelt apparatus. The UV absorption spectra were obtained in methanol using a Beckman-Acta Model IV recording spectrophotometer. IR absorption spectra were recorded using a Perkin-Elmer 281B infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL Model C-60 HL spectrometer. Fourier transform ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL NJM-FX60 spectrometer. Chemical shifts were reported in δ units with tetramethylsilane as the internal standard and deuterochloroform as the solvent. Mass spectral analyses were performed on a Finnigan 3200 GC/MS/DS. GC analyses were performed on a Beckman GC-65 using a 3% OV-17 or 5% OV-225 column and FID detector with 30 ml/min carrier gas (nitrogen).

[2] Aldrich Chemical Co., Milwaukee, Wis.

[3] Celite.

[4] Prepared from palmitic acid following the procedure described in Ref. 13.

Table I—^{13}C-NMR Chemical Shifts (ppm) for Compounds I–XI [a]

Carbon Number	Compound										
	I	II	III[b]	IV[c] *trans*	IV[c] *cis*	VI	VII	VIII	IX	X[d]	XI[e]
1	152.6	152.8	152.4	153.2	153.0	152.9	152.9	143.3	143.2	142.8	142.8
2	147.2	147.8	147.8	146.7	147.6	147.6	147.7	142.1	142.0	140.8	140.9
3	135.1	131.8	123.8	132.3	132.4	136.8	136.8	129.8	129.7	136.8	136.9
4	124.1	124.0	123.7	124.3	124.4	123.6	123.6	122.3	122.3	127.2	127.2
5	120.8	122.6	114.1	123.8	123.8	122.2	122.2	120.4	120.3	126.0	126.1
6	112.5	113.4	120.8	110.0	111.6	110.5	110.5	113.2	113.1	120.9	120.9
1-OCH_3	55.9	55.8	56.3	55.9	55.8	55.7	55.7				
2-OCH_3	60.6	60.6	60.3	60.6	60.3	60.4	60.7				
1′	60.6	28.1		132.5	133.6	30.9	30.9	29.8	29.8	29.7	30.2
2′				118.4	122.4	30.0	30.0	29.8	29.8	29.7	29.8
3′				33.5	33.5	29.8	29.8	29.8	29.8	29.7	29.8
4′-11′				29.8	29.8	29.8	29.8	29.8	29.8	29.7	29.8
12′				29.4	29.4	29.5	29.8	29.4	29.8	29.4	29.8
13′				32.0	32.0	32.0	29.8	32.0	29.8	32.0	29.8
14′				22.7	22.7	22.7	29.5	22.7	29.4	22.7	29.8
15′				14.1	14.1	14.0	32.0	14.1	32.0	14.0	32.0
16′							22.7		22.7		22.7
17′							14.0		14.0		14.1

[a] ^{13}C-NMR data on the alaninate derivatives are provided in *Experimental*. [b] In the proton-decoupled spectrum, the benzylic methylene carbon appeared at δ 25.7 ppm as a doublet (J = 48.8 Hz) as a result of coupling with phosphorus. The aromatic carbons of the triphenylphosphine residue of III also appeared as doublets at δ 135.1, 134.1, 130.2, and 118.1. We have also observed long-range coupling between phosphorus and carbons 1, 2, 3, 5, and 6. [c] The *trans* isomer of IV was separated by column chromatography; ^{13}C-NMR was recorded on the mixture and on the *trans* isomer. The data obtained on the *cis* isomer was by subtraction. No attempt was made to separate the *trans* isomer of V. [d] The carbonyl carbon atoms of the acetate groups were observed at δ 168.0 and 167.9 ppm while the methyl signals were observed at δ 20.5 and 20.1 ppm. [e] The carbonyl carbon atoms of the acetate groups were observed at δ 168.1 ppm (double intensity) and the methyl signals were observed at δ 20.6 and 20.2 ppm.

spectrum: *cis* m/z 374 (M^+, 56%), 177 (100%), and 151 (78%); *trans* m/z 374 (M^+, 61%), 177 (100%), and 151 (58%). The ^{1}H-NMR spectrum of the mixture showed peaks at δ 0.90 (3, t, J = 6 Hz), 1.30 (26, br, s), 2.48–2.10 (2, br, d), 3.88, 3.85 and 3.83 (6, 3s), and 5.48–7.15 (5, m).

2,3-Dimethoxy-heptadecylbenzene (*VII*)—Catalytic hydrogenation of V (3.6 g) was carried out as outlined for the preparation of VI to give a quantitative yield of VII as a colorless solid, mp 44–46°; IR: ν_{max} 1595, 1580, 1470, 1270, 1083, 1013, 737, and 717 cm^{-1}; UV: λ_{max} (log ε) 231 (3.16), 271 (3.03), and 276 (3.02) nm; ^{1}H-NMR: δ 0.90 (3, t, J = 5 Hz), 1.30 (30, br, s), 2.18 (2, t, J = 6 Hz), 3.85 (3, s), 3.83 (3, s), and 6.62–7.00 (3, m); mass spectrum: m/z 376 (M^+, 50%), 151 (97%), and 136 (100%).

3-n-Heptadecylcatechol (*IX*)—2,3-Dimethoxy-heptadecylbenzene (VII), 3.01 g, was demethylated with boron tribromide, following the procedure described for the preparation of VIII, to give 2.16 g (78% yield) of a colorless solid. Recrystallization from hexane–isooctane gave fine needles of IX, mp 63–64°; IR: ν_{max} 3380, 2920, 2847, 1617, 1592, 1475, 1468, 1282, 1190, and 720 cm^{-1}; UV: λ_{max} (log ε) 230 (3.19) and 275 (3.21) nm; ^{1}H-NMR: δ 0.89 (3, t, J = 6 Hz), 1.26 (30, br, s), 2.63 (2, t, J = 6 Hz), 4.99 (1, s, exchangeable with D_2O), 5.09 (1, s, exchangeable with D_2O), and 6.72 (3, s); mass spectrum: m/z 348 (M^+, 30%) and 123 (base peak).

Diacetyl-3-n-heptadecylcatechol (*XI*)—Compound XI was prepared by acetylation of IX following the same procedure as used for preparation of X. Crystallization from chloroform–ethanol afforded rosettes, mp 56–57°; IR: ν_{max} 2930, 2855, 1785, 1770, and 1480 cm^{-1}; UV: λ_{max} (log ε) 276 (sh, 1.64), 257 (2.47), and 210 (4.08) nm; ^{1}H-NMR: δ 7.30–7.00 (3, m), 2.50 (2, t, J = 6 Hz), 2.28 (3, s), 2.22 (3, s), 1.26 (30, br, s), and 0.88 (3, t, J = 5 Hz); mass spectrum: m/z 432 (M^+, 0.2%), 348 (15%), and 123 (100%).

3-n-Heptadecylcatechol-dialaninate Dihydrochloride (XIII)—A solution of dicyclohexylcarbodiimide (2.11 g, 10.2 mmoles) in 120 ml of acetonitrile was cooled in an ice bath for 10 min and then 1.94 g (10.3 mmoles) of *N*-(*tert*-butoxycarbonyl)-L-alanine was added. This solution was stirred in an ice bath for 30 min during which time a cloudy white precipitate appeared. Two portions of IX were then added (618 mg and 1.22 g) and the mixture was stirred at room temperature for 2 hr after each addition. TLC analysis of the reaction product using 2% methanol in chloroform showed some starting material (R_f 0.3, blue black with ferric chloride) an appreciable amount of the diester (XII) (R_f 0.75, yellow with chlorine tolidine reagent), and some monoester (R_f 0.70, yellow with chlorine tolidine reagent). Therefore, 1.03 g (5 mmoles) of dicyclohexylcarbodiimide in 30 ml of acetonitrile (cooled to 0°) and 950 mg (5 mmoles) of *N*-(*tert*-butoxycarbonyl)-L-alanine was stirred in an ice bath for 20 min and then was added to the above mixture. After stirring overnight, the reaction was filtered, and the solvent was removed by evaporation. The residue was chromatographed on 50 g of silica gel-60 (chloroform) to yield 3.25 g (4.7 mmoles) of XII as an oil (94% yield); $[\alpha]_D^{22°}$ − 19° (c 0.59, $CHCl_3$); UV: λ_{max} (log ε) 257 (2.40) and 220 (3.40) nm; IR: ν_{max} ($CHCl_3$); 3440, 3370, 2915, 2860, 1770, 1705, and 1500 cm^{-1}; ^{1}H-NMR: δ 1.30 (30, br, s), 1.50 (18, s), 2.70 (2, br, t, J = 6 Hz), 4.60–4.50 (2, br, s), 5.50 (1, br, s), 5.63 (1, br, s), and 7.10–7.00 (3, m); ^{13}C-NMR: δ 14.0 (q), 17.9 (q), 18.1 (q), 22.7 (t), 28.5 (q), 29.4 (t), 29.7 (t), 32.0 (t), 49.5 (d), 49.8 (d), 79.9 (s), 120.7 (d), 126.2 (d), 127.3 (d), 136.9 (s), 140.5 (s), 142.7 (s), 155.6 (s), 170.8 (s), and 171.0 (s) ppm.

Conversion of XII to XIII—A solution of XII (2.75 g) in ethyl acetate (50 ml) was chilled at 0° for 25 min, and then was saturated with hydrogen chloride for 3 min. The mixture was stirred for 20 min at 0° and then the solvent was evaporated to yield 1.81 g of XIII, mp 204–205° (dec); $[\alpha]_D^{25}$ + 107° (c 0.52, $CHCl_3$); UV: λ_{max} (log ε) 264 (2.54) and 210 (4.04) nm; IR: ν_{max} (KBr) 3420, 2920, 2840, 1790, and 1600 cm^{-1}; mass spectrum: m/z 419 (3%), 348 (23%), 136 (10%), and 123 (100%). Due to the insolubility of the material, the ^{1}H and ^{13}C-NMR spectra were not obtained.

3-n-Pentadecylcatechol-dialaninate Dihydrochloride (XV)—Reaction of VIII with *N*-(*tert*-butoxycarbonyl)-L-alanine in the manner previously described for the preparation of XIII afforded XIV; UV: λ_{max} (log ε) 280 nm (sh, 2.02), 258 (2.47), and 219 (3.40) nm; IR: ν_{max} ($CHCl_3$) 3440, 3370, 2930, 1770, 1700, and 1500 cm^{-1}; ^{1}H-NMR: δ 7.22–7.17 (3, m), 5.70 (1, br, s), 5.55 (1, br, s), 4.63 (2, br, q, J = 6 Hz), 2.60 (2, t, J = 6 Hz), 1.50 (18, s), 1.28 (26, br, s), and 0.92 (3, t, J = 6 Hz); ^{13}C-NMR: δ 171.1 (s), 170.8 (s), 155.5 (s), 142.6 (s), 140.5 (s), 136.9 (s), 127.3 (d), 126.3 (d), 120.7 (d), 80.0 (s), 49.8 (d), 49.4 (d), 32.0 (t), 30.1 (t), 30.0 (t), 29.7 (t), 29.5 (t), 29.4 (t), 28.5 (q), 22.7 (t), 18.1 (q), 17.9 (q), and 14.0 (q). The *tert*-butyloxycarbonyl protecting groups of XIV were removed with hydrogen chloride in ethyl acetate in the aforementioned manner to yield the dialaninate dihydrochloride XV.

Biological Studies—*Animals*—Female Hartley line-bred guinea pigs weighing 450–500 g were used; guinea pig food and water supplemented with vitamin C were offered *ad libitum*. Groups of 6–12 animals were used, and in all cases a sensitive control group was administered the vehicle only. Sensitization and skin testing were carried out using procedures previously described (11, 12).

Dosing—Doses of 1 or 10 mg of 3-*n*-pentadecylcatechol diacetate (X) per animal were administered intravenously. Emulsions containing the acetates were prepared using polyoxyethylene (20), sorbitan monostearate, and sorbitan monooleate[5] in saline as previously described (12). For tolerance studies, the drug was given to the animals 2 weeks prior to the attempted sensitization. Emulsions of either X or XI were given orally after sensitization of the guinea pigs for desensitization studies. The water-soluble ester (XIII) was given in aqueous solution. The animals were given a cumulative dose equivalent to 52.5 mg of the free catechols (VIII or IX) in the ester form over a period of 3 weeks as follows: (*a*) three doses of 2.5 mg each given on alternate days during the first week; (*b*) three doses of 5 mg each during the second week; and (*c*) three doses of 10 mg each during the third week. The animals were sensitized and skin

[5] Atlas Chemical Industries Inc., Wilmington, Del.

tested prior to dosing, and their sensitivity was measured again the week after the last dose.

RESULTS AND DISCUSSION

Poison ivy dermititis is a major problem among outdoor workers in the U.S. It is estimated that over 1.5 million cases of poison ivy dermatitis are encountered every year with a loss of over 152,000 work days in the United States[6].

In our search for ways to control contact dermatitis caused by the urushiols of poison ivy, oak, and sumac, two successful procedures were developed in this laboratory using guinea pigs as the animal model (11, 12). Of particular interest was the discovery that the esterified urushiol (urushiol acetate) had the ability to block the development of sensitivity in guinea pigs if administered prior to the attempted sensitization (tolerance induction), as well as the ability to desensitize or hyposensitize already sensitive animals (12). This study described the synthesis of the saturated congeners of poison ivy and poison oak urushiols and the ability of their esters to induce tolerance and desensitization or hyposensitization. The synthesis of VIII and IX (the saturated components of poison ivy and oak urushiols, respectively) have been previously described (14–17). These methods involved initially a Grignard reaction of the appropriate alkylmagnesium halide with either 2,3-dimethoxybenzaldehyde or 2,3-dimethoxybenzyl chloride. In addition, the reaction of the Grignard reagent with the phenolic aldehyde was investigated (18).

However, these procedures provided inconsistent results, and the final products were difficult to purify. Use of the Wittig reaction afforded high yields of products which were easy to purify. The Wittig reagent was prepared from 2,3-dimethoxybenzyl halide since the long-chain alkyl halide failed to form the phosphonium salt. The use of boron tribromide in methylene chloride for the demethylation was superior to previously used reagents such as hydrochloric acid, hydroiodic acid, or pyridinium chloride. Demethylation took place in two steps *via* the monomethyl ether, with demethylation of the more sterically hindered group occurring first.

In addition to the acetate esters, the water-soluble dialaninate ester dihydrochlorides (XIII and XV) were prepared. Spectral data are given in *Experimental*. Table I shows the ^{13}C-NMR data on compounds I–XI.

The synthetic compounds were tested for their ability to induce tolerance or desensitization to poison ivy and poison oak urushiols. Guinea pigs were used as the animal model, and immune tolerance was produced by a single- or 10-mg iv dose of X. Over 90% of the animals treated with X were completely tolerant (not reactive to ≤ 3.2-μg test doses of VIII for 6 weeks); none of the control animals were tolerant to VIII. The esters X, XI, and XIII were tested orally (gastric gavage) for their ability to desensitize or hyposensitize guinea pigs which were previously sensitized to poison ivy or oak urushiol. The dosage schedule consisted of consecutive escalating doses for 3 weeks: an amount of the ester equivalent to 2.5 mg of the parent catechol 3 times a week for the first week, doubling each week thereafter. The animals were tested with poison ivy or oak urushiol the week following the last dose and again 4 weeks later. Thity-eight percent of the guinea pigs receiving X were desensitized to 3-μg doses of poison ivy urushiol. There was also significant reduction of the sensitivity (hyposensitization) of the remaining animals as judged by the Driaze method (19) of evaluating skin erythema and edema. Compounds XI and XIII were also found to hyposensitize guinea pigs to poison oak urushiol.

A more detailed comparison of the toxicity and efficacy of free urushiols and their corresponding esters will be published[7].

[6] These figures were obtained from the Public Health Service for 1969, the last year for which there are figures available.

[7] E. S. Watson *et al.*, submitted for publication to *J. Invest. Dermatol.*

REFERENCES

(1) W. F. Symes and C. R. Dawson, *J. Am. Chem. Soc.*, **76**, 2959 (1954).

(2) S. V. Sunthankar and C. R. Dawson, *J. Am. Chem. Soc.*, **76**, 5070 (1954).

(3) K. H. Markiewitz and C. R. Dawson, *J. Org. Chem.*, **30**, 1610 (1965).

(4) M. D. Corbett and S. Billets, *J. Pharm. Sci.*, **64**, 1715 (1975).

(5) S. Billets, J. C. Craig, M. D. Corbett, and J. F. Vickery, *Phytochemistry*, **15**, 533 (1976).

(6) C. H. Ducan, *N.Y. Med. J.*, **104**, 901 (1916).

(7) G. A. Gellin, C. R. Wolf, and H. Milby, *Arch. Environ. Health*, **2**, 280 (1971).

(8) H. S. Mason and A. Lada, *J. Invest. Dermatol.*, **22**, 457 (1975).

(9) F. A. Stevens, *J. Am. Med. Assoc.*, **127**, 912 (1945).

(10) A. M. Kligman, *Arch. Dermatol.*, **78**, 47 (1958).

(11) E. S. Watson, J. C. Murphy, P. W. Wirth, M. A. ElSohly, and P. Skierkowski, *J. Pharm. Sci.*, **70**, 785 (1981).

(12) E. S. Watson, J. C. Murphy, C. W. Waller, and M. A. ElSohly, *J. Invest. Dermatol.*, **76**, 164 (1981).

(13) W. P. Campbell and D. Todd, *J. Am. Chem. Soc.*, **64**, 928 (1942).

(14) H. S. Mason, *J. Am. Chem. Soc.*, **67**, 1538 (1945).

(15) B. Loev and C. Dawson, *J. Am. Chem. Soc.*, **78**, 1180 (1956).

(16) A. P. Kurtz and C. Dawson, *J. Med. Chem.*, **14**, 729 (1971).

(17) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **33**, 2451 (1968).

(18) B. Loev and C. R. Dawson, *J. Am. Chem. Soc.*, **78**, 4083 (1956).

(19) J. H. Draize, G. Woodward, and H. O. Calvery, *J. Pharmacol. Exp. Ther.*, **82**, 377 (1944).

ACKNOWLEDGMENTS

This work was supported by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

The authors are grateful to Mr. Roger Seidel for providing the mass spectral analysis and Ms. Paula Smith for her technical assistance.