New Compounds: Synthesis of *para*-Substituted Nortropanyl Benzoates

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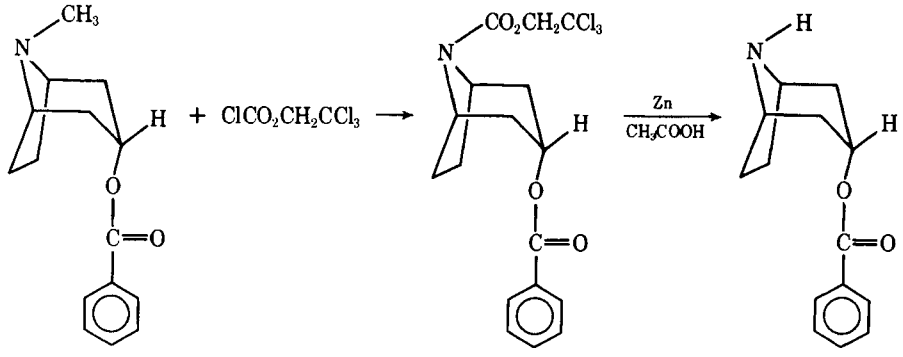
Abstract □ The syntheses of the *p*-methyl-, *p*-*tert*-butyl-, *p*-chloro-, *p*-cyano-, *p*-amino-, and unsubstituted benzoate esters of nortropine are reported. These compounds were characterized by their NMR, IR, and mass spectra and analytical data.

Keyphrases □ Nortropanyl benzoate—*para*-substituted derivatives, synthesis, NMR, IR, and mass spectral characterization □ Tropanyl esters—demethylation to yield nortropanyl esters for comparison of kinetic data

To investigate the role of the tropanyl *N*-methyl group in the substrate specificity of rabbit serum atropin esterase, a series of nortropanyl benzoate esters was required. Specifically, the kinetic data will be compared to those obtained with the tropanyl benzoates (1). These compounds also will be useful in a continuing study of the anticholinergic properties of tropanyl benzoate (*endo*-8-azabicyclo[3.2.1]octan-3-yl benzoate) and its *para*-substituted methyl, methoxy, *tert*-butyl, chloro, cyano, and amino derivatives.

The most direct approach for producing the nortropanyl esters is demethylation of the corresponding tropanyl esters. Of the methods available for removal of *N*-methyl



Scheme I

Table I—Physical Data of *para*-Substituted Nortropanyl Benzoates

Substituent	Melting Point	Melting Point of Hydrochloride	Yield, %	Formula	Analysis, % Calc.	Found
H	92–93°	314–315° dec. 214–216° (4) 241–244°[a]	27	$C_{14}H_{17}NO_2$	C 72.70 H 7.41 N 6.06 O 13.83	72.53 7.44 6.06 13.58
CH_3	83–84°	343–345° dec.	47	$C_{15}H_{19}NO_2$	C 73.43 H 7.81 N 5.71 O 13.05	73.23 7.78 5.65 12.86
OCH_3	61–63°	302–303° dec.	46	$C_{15}H_{19}NO_3$	C 68.93 H 7.33 N 5.36 O 18.37	69.79 7.46 5.31 18.22
tert-Butyl	117–118°	258–265° dec.	36	$C_{18}H_{25}NO_2$	C 75.23 H 8.77 N 4.78 O 11.13	75.09 8.94 4.87 11.23
Cl	117–118°	317–318° dec.	17	$C_{14}H_{16}ClNO_2$	C 63.28 H 6.07 Cl 13.34 N 5.27 O 12.04	63.17 6.23 13.27 5.27 11.87
CN	144–145°	293–294° dec.	22	$C_{15}H_{16}N_2O_2$	C 70.29 H 6.29 N 10.93 O 12.48	70.40 6.37 10.87 12.30
NH_2	153–155°	250–252° dec.	30	$C_{14}H_{18}N_2O_2$	C 68.27 H 7.37 N 11.37 O 12.99	68.20 7.38 11.19 12.69

[a] As the picrate.

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Table II—Spectral Data of *para*-Substituted Nortropanyl Benzoates

Substituent	Molecular Ion, *m/e* (% of base peak)	IR Spectrum (Potassium Bromide), cm^{-1}	^{1}H-NMR Spectrum (Deuterochloroform), δ					
			Aromatic	H-3	H-1, H-5	H-8[a]	H-2, H-4, H-6, H-7	R
H	231 (0.7)	3400 b, 3160, 2960, 1710, 1455, 1325, 1280, 1260, 1220, 1180, 1125, 1075, 1030, 860, 710	7.27–8.10	5.28	3.52	—	1.80, 1.87, 1.95, 2.00, 2.05, 2.10, 2.15, 2.23 (sh)	—
CH_3	245 (3.6)	3400 b, 3240, 2950, 1710, 1605, 1360, 1280, 1260, 1180, 1110, 1085, 1000, 855, 760, 690	7.15–7.70	5.30	3.54	1.75	1.85, 1.87 (sh), 2.00, 2.05, 2.07, 2.17, 2.23	2.43
OCH_3	261 (1.4)	3400 b, 2940, 1695, 1600, 1570, 1500, 1420, 1280, 1260, 1170, 1115, 1100, 1035, 845, 770	6.79–8.05	5.27	3.52	—	1.70, 1.80, 1.83, 1.93 (sh), 2.00, 2.03, 2.10, 2.15, 2.23	3.82
tert-Butyl	287 (0.7)	3420 b, 3300, 2960, 1705, 1610, 1465, 1410, 1280, 1260, 1190, 1125, 970, 855, 775, 710	7.42–8.07	5.32	3.57	1.80	1.95, 2.02, 2.07, 2.15, 2.17, 2.27	1.37
Cl	265 (4.3)	3400 b, 3240, 2940, 1710, 1590, 1485, 1400, 1360, 1275, 1260, 1170, 1120, 1000, 855, 760	7.20–8.00	5.27	3.53	1.63	1.77, 1.85, 1.95, 2.02, 2.05, 2.18, 2.27	—
CN	256 (2.9)	3400 b, 3235, 2940, 2245, 1710, 1410, 1315, 1285, 1265, 1120, 1090, 1005, 855, 775, 700	6.67–8.27	5.35	3.58	1.73	1.80 (sh), 1.90, 1.98 (sh), 2.08, 2.12 (sh), 2.20, 2.27, 2.32	—
NH_2	246 (0.4)	3440, 3375, 3290, 2940, 1680, 1600, 1515, 1310, 1280, 1260, 1165, 1110, 1000, 850, 770	6.65–7.96	5.26	3.54	—	1.76, 1.80, 1.84, 1.95, 1.98, 2.03, 2.09, 2.15, 2.23	4.13

[a] These assignments were determined upon addition of deuterium oxide.

groups, the use of 2,2,2-trichloroethyl chloroformate followed by reductive cleavage by zinc in acetic acid (Scheme I) appeared to be the best procedure since it preserves the ester linkage and avoids the benzoylation of a secondary amine alcohol. This method was reported by Woodward (2) and later used (3) to obtain nortropanyl acetate. The nortropanyl esters reported here were characterized by their NMR, IR, and mass spectra and analytical data.

EXPERIMENTAL[1]

The tropanyl benzoate was dissolved in 30 ml of benzene; if a cloudy solution was obtained, the benzene–water azeotrope was distilled until the solution was clear. Potassium carbonate and distilled 2,2,2-trichloroethyl chloroformate were added, and the mixture was refluxed for 4 days. A second portion of the chloroformate, equal to the first portion, was added after 2 days. The mixture was filtered, and the solvent was removed from the filtrate.

The clear residue was dissolved in a minimum amount of acetic acid. Zinc dust was added slowly over 2 hr, with sufficient cooling to maintain room temperature, until bubbling was no longer evident. The acetic acid was removed by evaporation, and 100 ml of water was added. The slurry was made basic with sodium hydroxide, which produced a copious white precipitate. This mixture was extracted with ethyl acetate. The extract was dried over magnesium sulfate, and the solvent was removed. The resulting free base was purified by recrystallization of its hydrochloride salt in ethanol. Analytical samples were sublimed (Table I).

[1] Mass spectra were obtained on a DuPont Dimaspec 321 gas chromatograph–mass spectrometer with a DuPont 320 data system using solid-probe introduction and ionization at 70 ev. NMR spectra were determined in deuterochloroform with a Varian Associates EM-390 NMR spectrometer using tetramethylsilane as the internal standard. IR spectra were recorded on a Beckman Acculab 6 spectrometer. Melting points were obtained using an Electrothermal apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The 2,2,2-trichloroethyl chloroformate was obtained from Aldrich Chemical Co.

RESULTS AND DISCUSSION

All of the esters furnished the expected NMR spectra. They were comparable to those of the previously reported tropanyl benzoates except that the bridgehead protons appeared ~0.4 ppm downfield. The mass spectra base peak for all of the compounds was *m/e* 110, corresponding to the nortropanyl ion. In all spectra, there were peaks at *m/e* 68, 80, and 126. The substituted benzoyl and phenyl fragments were detected in all cases except for the *p-tert*-butyl compound. The molecular ion peaks were observed and were of low relative intensity compared to the tropanyl benzoates (1). A summary of these data appears in Table II.

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