[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Local Anesthetics. III. Aroyl Derivatives of β-Methyl-β-monoalkylamino Propanols

BY J. STANTON PIERCE, ROBERT D. GANO AND J. M. LUKEMAN

In previous papers[2,3] from this Laboratory, the preparation of alkoxybenzoates of β-monoalkylaminoethanols, β-methyl-β-monoalkylaminopropanols and β-monoalkylaminobutanols was described. Some of the products were found to be effective as local anesthetics. It thus seemed advisable to prepare esters of the above β-secondary aminoalkanols with other aromatic acids. Therefore, we have prepared cinnamates,[4] alkoxycinnamates, hydrocinnamates and alkoxyhydrocinnamates of β-monoalkylaminoethanols, β-methyl-β-monoalkylaminopropanols and β-monoalkylaminobutanols. Usually, the derivatives of β-methyl-β-monoalkylaminopropanols proved to be more readily purified than the derivatives of the other amino alcohols, so the esters of this series were studied more thoroughly than the others and are reported in this paper. Also, phenylurethans of β-methyl-β-monoalkylaminopropanols are being prepared and will be reported in a subsequent publication.

TABLE I

AROYL INTERMEDIATES

Alkyl substituent	Alkoxybenzaldehyde B. p., °C.	Mm.	Yield, %	Alkoxycinnamic acid M. p., °C. (cor.)	Yield, %	Alkoxyhydrocinnamic acid M. p., °C. (cor.)	Yield, %	Alkoxyhydrocinnamoyl chloride B. p. °C.	Mm.	Yield, %
p-Methyl	[v]			169–170[a]	63	101–102[b]	54	165–180[c]	17	81
p-Ethyl	136–139[d]	13	39	191–192[e]	55					
p-*n*-Propyl	154–157[e]	31	60	165–166[e]	61	95–96[f]	88	174–177[g]	31	65
p-*n*-Butyl	183–186[d]	41	66	153–154[e]	51	85–86[h]	92	195–197[i]	26	66
o-Ethyl	[v]			130–131[j]	70	74–75[j]	80	165–170[k,l]	30	49
o-*n*-Butyl	172–175	26	36	87–89[m]	3					
None				[v]		48–49[n]	81	135–140[o]	40	92

[a] Pandya and Vahida, ref. 6. [b] Matsuo, *J. Biol. Chem.*, **35**, 291–296 (1918). [c] Barger and Walpole, *J. Chem. Soc.*, 1724 (1909). [d] Sommelet and Marszak, *Compt. rend.*, **198**, 2256–2258 (1934). [e] Stoermer and Wodarz, *Ber.*, **61B**, 2323–2330 (1928). [f] Calcd.: neut. equiv., 208.1. Found: neut. equiv., 210.2, 211.4. [g] Calcd.: neut. equiv., 113.3. Found: neut. equiv., 111.7, 110.6, 111.5. [h] Calcd.: neut. equiv., 222.1. Found: neut. equiv., 221.8, 220.0, 221.9. [i] Calcd.: neut. equiv., 120.3. Found: neut. equiv., 117.6, 117.4. [j] Paal and Schiedewitz, *Ber.*, **63B**, 766–778 (1930). [k] Neutral equivalent; theory, 106.3. Found: 108.0, 108.9. [l] Most of the samples for the determinations of neutral equivalents were prepared by Doris Colley and analyses were made by Audrey Grubin. [m] Stoermer and Ladewig, *Ber.*, **47**, 1795–1803 (1914). [n] Vavon, *Compt. rend.*, **149**, 999; "Beilstein," **9**, 509. [o] Rupe, *Ann.*, **369**, 319 (1909); "Beilstein," **9**, 511. [v] Purchased.

Experimental

p-**Butoxybenzaldehyde.**—The alkoxybenzaldehydes were made by converting phenolic aldehydes into alkoxybenzaldehydes by the method Cohen and Dudley[5] used for the preparation of alkoxybenzoic acid esters. In a typical synthesis, one half mole each of *p*-hydroxybenzaldehyde and *n*-butyl bromide were added to 200 ml. of absolute alcohol in which 11.5 g. of sodium had been dissolved. After refluxing for six hours, the alcohol was distilled off and the residue was added to 500 ml. of water. Twenty-five grams of salt then was added and the mixture was extracted thrice with ether and the solution was washed with sodium hydroxide solution. The ether then was distilled off and the residue was vacuum distilled.

p-**Methoxycinnamic Acid.**—The alkoxycinnamic acids, when not obtainable from Eastman Kodak Co., were made by condensing alkoxybenzaldehyes with malonic acid, with pyridine as catalyst, as described by Pandya and Vahida.[6] *p*-Methoxycinnamic acid was prepared by heating 0.50 mole each of *p*-methoxybenzaldehyde and malonic acid and 0.20 mole of pyridine in an open tube at 130° for twelve hours. The acid was isolated by dissolving the mixture in dilute sodium hydroxide, filtering, acidifying and filtering with suction. It was purified by recrystallization from aqueous alcohol.

p-**Propoxyhydrocinnamic Acid.**—The alkoxyhydrocinnamic acids were prepared by reduction of the corresponding alkoxycinnamic acids with hydrogen, with Raney nickel as catalyst. *p*-Propoxycinnamic acid (52 g.) was hydrogenated in 200 ml. of alcohol with 3 g. of Raney nickel under 25 lb. pressure in two hours. The alcoholic solution was concentrated to half its volume and hot water was added. On cooling the *p*-propoxyhydrocinnamic acid was precipitated almost quantitatively.

p-**Amyloxycinnamoyl Chloride.**—In a typical preparation of an alkoxycinnamoyl chloride, *p*-amyloxycinnamic acid was refluxed for one hour with four equivalents of thionyl chloride. The excess reagent was removed by evaporation in vacuum with the addition of benzene. The crude *p*-amyloxycinnamoyl chloride was used for condensation with amino alcohol hydrochlorides without further purification.

o-**Ethoxyhydrocinnamoyl Chloride.**—The alkoxyhydrocinnamoyl chlorides were prepared by the action of phosphorus pentachloride on the acids. *o*-Ethoxyhydrocinnamoyl chloride was prepared by refluxing equimolar

(1) Acknowledgment for advice is made to Dr. E. Emmet Reid, Research Adviser to the Department of Chemistry of the University of Richmond.

(2) J. Stanton Pierce, J. M. Salsbury and J. M. Fredericksen. THIS JOURNAL, **64**, 1691–1694 (1942).

(3) J. Stanton Pierce, J. M. Salsbury, Walter W. Haden and L. H. Willis, *ibid.*, **64**, 2884–2885 (1942).

(4) David H. Miller, in this Laboratory, prepared β-monobutylaminoethyl cinnamate hydrochloride, m. p. 132–133° (cor.). Calcd. for $C_{15}H_{22}O_2NCl$: Cl, 12.53. Found: 12.77. A. F. Beale, Jr., also carried out some work on this series of esters.

(5) J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1732–1751 (1910).

(6) Pandya and Vahida, *Proc. Indian Acad. Soc.*, **4A**, 134–139 (1936).

TABLE II[a]

β-METHYL-β-MONOALKYLAMINOPROPYL CINNAMATE, HYDROCINNAMATE, ALKOXYCINNAMATE AND ALKOXYHYDROCINNAMATE HYDROCHLORIDES, $ArCOOCH_2C(CH_3)_2NHR \cdot HCl$

Acid (Ar)	R	M. p., °C. (cor.)	Molecular formula	Chlorine, % Calcd.	Chlorine, % Found[b]	Free base B. p., °C.	Free base B. p., Mm.	Nitrogen, % Calcd.	Nitrogen, % Found[c]
Cinnamic	*n*-Propyl	164–165	$C_{15}H_{24}O_2NCl$	11.91	12.07				
Cinnamic	*n*-Butyl	162–163	$C_{17}H_{26}O_2NCl$	11.37	11.19				
Cinnamic	*n*-Amyl	112–113	$C_{18}H_{28}O_2NCl$	10.88	11.20				
Hydrocinnamic	*n*-Propyl	178–179	$C_{15}H_{26}O_2NCl$	11.82	12.12	177–178	3.5	5.32	5.50
Hydrocinnamic	*n*-Butyl	116–117	$C_{17}H_{28}O_2NCl$	11.29	11.59				
Hydrocinnamic	*n*-Amyl	85–86	$C_{18}H_{30}O_2NCl$	10.81	10.60	181–188	2.8	4.80	4.42
Hydrocinnamic	*n*-Hexyl	90–91	$C_{19}H_{32}O_2NCl$	10.37	10.05				
p-Methoxycinnamic	Ethyl	189–190	$C_{15}H_{24}O_3NCl$	11.30	11.38				
p-*n*-Butoxycinnamic	*n*-Propyl	144–145	$C_{21}H_{32}O_3NCl$	9.59	10.14				
	n-Butyl	154–155	$C_{21}H_{34}O_3NCl$	9.24	9.18				
o-Ethoxyhydrocinnamic	*n*-Propyl	Oil				193–196	3.0	4.56	4.32
p-*n*-Propoxyhydrocinnamic	*n*-Butyl	95–96	$C_{20}H_{34}O_3NCl$	9.53	9.83				
p-*n*-Butoxyhydrocinnamic	*n*-Butyl	109–111	$C_{21}H_{36}O_3NCl$	9.19	9.57				

[a] In this table are listed only the amino alcohol esters which were satisfactorily purified by recrystallization of the hydrochloride or distillation of the free base. These products are being tested pharmacologically by Dr. H. B. Haag, of the Medical College of Virginia, and will be reported elsewhere. [b] Chloride was determined by the Volhard method as modified by J. R. Caldwell and H. V. Moyer, *Ind. Eng. Chem., Anal. Ed.*, 7, 38, 39 (1935). [c] Nitrogen was determined by titration of the free base with standard hydrochloric acid, with modified methyl red as indicator.

quantities (0.15 mole) of *o*-ethoxyhydrocinnamic acid and phosphorus pentachloride on a boiling water-bath for one hour. The phosphorus oxychloride was removed by vacuum distillation and the acid chloride was purified by vacuum distillation.

Hydrochlorides of β-Methyl-β-monoalkylaminopropyl Cinnamates, Alkoxycinnamates, Hydrocinnamates and Alkoxyhydrocinnamates.—The β-monoalkylamino-β-methylpropanols were prepared and condensed with aroyl halides by methods described in previous publications[1,2] from this Laboratory. Equimolar quantities of amino alcohol hydrochlorides and aroyl halides were heated on a water-bath from one to six hours, depending on the rate of reaction. In a few cases an oil-bath, heated gradually to 150°, was used. As in previous reports, the reaction mixture was dissolved in water, filtered and extracted with isopropyl ether to remove impurities, and treated with sodium hydroxide to set free the amino alcohol esters. These esters were taken up in isopropyl ether and the hydrochlorides precipitated by addition of dry hydrogen chloride. Various solvents were used for recrystallization but a mixture of anhydrous acetone and anhydrous ether proved satisfactory in most cases. In a few cases in which recrystallization of the hydrochloride of the amino alcohol ester did not take place readily, the free base was purified by vacuum distillation.

Summary

The hydrochlorides of a series of β-methyl-β-monoalkylaminopropyl cinnamates, hydrocinnamates, alkoxycinnamates and alkoxyhydrocinnamates have been prepared and described.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

The Occurrence of Rutin in a Wild Cherry, *Prunus melanocarpa* (A. Nels.) Rydb.

BY JAMES F. COUCH

In connection with the researches being conducted at this Laboratory[2] on the production of rutin for medicinal use a species of wild cherry was examined with the result that significant quantities of rutin were found in the leaves. This is the first species of the genus *Prunus* from which this glucoside has been isolated, although the presence of other flavonol glucosides in different species of the genus has been reported.

Rochleder[3] found a trace of a quercetin glucoside in *P. cerasus* L., and Finnemore[4] isolated quercimeritrin from a commercial bark probably of *P. emarginata* Walp. Power and Moore[5] obtained less than 0.1% of a quercetin glucoside which they named serotrin from the leaves of *P. serotina* Ehrh. This substance melted at the same temperature as quercimeritrin but on comparison with an authentic sample the authors concluded that it was a different substance.

Rutin has now been found in the leaves of "black chokecherry" (*P. melanocarpa* (A. Nels.) Rydb.) in substantial quantities. This species ranges from Alberta and British Columbia southward to California and New Mexico[6] in accessible

(1) One of the Laboratories of the Bureau of Agricultural & Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) J. F. Couch, C. F. Krewson, J. Naghski and M. J. Copley, *Bur. Agri. Ind. Chem.*, AIC-115, April, 1946. [Processed.]

(3) F. Rochleder, *S-Ber. Wien. Acad.*, Abt. II, **59**, 219–247 (1869).

(4) H. Finnemore, *Pharm. J.*, **85**, 604–607 (1910).

(5) F. B. Power and C. W. Moore, *J. Chem. Soc.*, **97**, 1099–1112 (1910).

(6) I. Tidestrom, *Flora of Utah and Nevada*, "U. S. Natl. Herbarium," Vol. 25, Gov't. Printing Office, Washington, D. C., 1925, p. 285.