associated with neoquassin in the original substance, for it may represent a decomposition product resulting from the operation involved, or it is possible the unknown component was not eluted from the adsorbent. Both considerations seem doubtful, for a methanolic solution of the original material was rapidly and quantitatively passed through a column of aluminum oxide without separation or apparent change. However, a solution of neoquassin added to a solution of the uncrystallizable material failed to effect a synthesis of the original substance.

Summary

A hitherto unrecorded constituent of Jamaica quassia wood is described. It has the physical properties of an individual compound, but in reality consists of a complex of neoquassin and one or more unknown materials, which apparently separate as mixed crystals.

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

Local Anesthetics. II. Alkoxybenzoates of 2-Monoalkylamino-2-methyl-1-propanols and 2-Monoalkylamino-1-butanols[1,2]

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In a recent paper from this Laboratory,[3] the preparation of β-monoalkylaminoethanol esters of alkoxybenzoic acids was described. Goldberg, Ringk and Spoerri[4] reported aminobenzoates of β-monoalkylaminoethanols in which branching occurs on the alpha carbon of the amino alcohol.

We have mono-alkylated 2-amino-2-methyl-1-propanol and 2-amino-1-butanol, which are now on the market, and have been engaged in the preparation of esters of these amino alcohols with alkoxybenzoic, alkoxycinnamic, alkoxynaphthoic, diphenylacetic, acetyltropic, acetylmandelic and *p*- and *m*-nitrobenzoic acids, with the expectation of reducing the latter to the aminobenzoate esters. The recent report of Kremer and Waldman[5] on *p*-nitrobenzoic and *p*-aminobenzoic esters of 2-monoalkylamino-2-methyl-1-propanols makes it desirable to report the results thus far obtained. This paper takes up the preparation of 2-monoalkylamino-2-methyl-1-propanols, 2-monoalkylamino-1-butanols and the alkoxybenzoates of these amino alcohols.

Alkylation of 2-amino-2-methyl-1-propanol and 2-amino-1-butanol with the lower alkyl halides usually was carried out by heating equimolar quantities of the amino alcohol and alkyl bromide in a sealed tube or under reflux at 100° for two hours. For the introduction of the amyl, hexyl, heptyl, allyl and benzyl radicals, usually the molar quantity of amino alcohol was doubled and in the introduction of the latter two groups, chlorides were used instead of bromides. The reaction product was dissolved in dilute hydrochloric acid, separated from unchanged alkyl halide, in case the reaction was not complete, and treated with excess concentrated sodium hydroxide. The alkylation product rose to the surface of the hot solution as an oil. The oil was vacuum distilled and the distillate redistilled at atmospheric pressure. The 2-monoalkylamino-2-methyl-1-propanols except the allyl, solidified on cooling. Several of the 2-monoalkylamino-1-butanols showed a tendency to crystallize, reaching a maximum in the case of 2-monobenzylamino-1-butanol. The crystals of this compound, on separation, reverted to a mixture of liquid and crystals.

In a previous paper from this Laboratory,[3] the preparation and isolation of β-monoalkylaminoethyl alkoxybenzoate hydrochlorides was described. The same general procedure, with some modifications, was used to obtain hydrochlorides of alkoxybenzoates of 2-monoalkylamino-2-methyl-1-propanols and 2-monoalkylamino-1-butanols.

Experimental

Examples are given of the preparation of 2-*n*-amylamino-2-methyl-1-propanol and of the condensation of this amino alcohol with *p*-ethoxybenzoyl chloride.

2-*n*-Amylamino-2-methyl-1-propanol.—A mixture of 113 g. (0.75 mole) of *n*-amyl bromide and 134 g. (1.5 moles) of 2-amino-2-methyl-1-propanol was heated in two sealed tubes for two hours at 100°. The contents of the tubes were combined and dissolved in 500 ml. of water and 80 ml. of concentrated hydrochloric acid. No oil remained undissolved. To the acid solution was added a solution of 100 g. of sodium hydroxide in 100 ml. of water. The oil which rose to the surface was vacuum distilled, yielding

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

(4) Goldberg, Ringk and Spoerri, *ibid.*, **61**, 3562–3564 (1939).

(5) Kremer and Waldman, *ibid.*, **64**, 1089–1090 (1942).

108 g. of product, boiling 103–135° (30 mm.). On redistillation, there was obtained 70 g. (58%) of 2-*n*-amylamino-2-methyl-1-propanol; b. p. 212–222°.

TABLE I

β-MONOALKYLAMINOALKANOLS

R	Empirical formula	B. p., °C. (cor.)	M. p.,[a] °C. (uncor.)	Nitrogen, % Calcd.	Found
(a) 2-Monoalkylamino-2-methyl-1-propanols: $RNHC(CH_3)_2CH_2OH$					
Ethyl[b]	$C_6H_{15}ON$	167–170	72–73	11.95	11.91, 11.87
n-Propyl[b]	$C_7H_{17}ON$	185–188	56–57.5	10.68	10.41, 10.43
n-Butyl[b]	$C_8H_{19}ON$	202–204	68–69	9.64	9.59, 9.61
n-Amyl[b]	$C_9H_{21}ON$	218–221	56–59	8.80	8.50, 8.55
n-Hexyl	$C_{10}H_{23}ON$	235–238	62–62.5	8.08	7.82, 7.81
n-Heptyl	$C_{11}H_{25}ON$	253–256	50–52	7.48	7.13, 7.14
Iso-butyl[b]	$C_8H_{19}ON$	184–187	48–49	9.64	9.52
Iso-amyl[b]	$C_9H_{21}ON$	214–217	73–74	8.80	8.48, 8.52
Allyl	$C_7H_{15}ON$	183–187		10.84	11.20
Benzyl	$C_{11}H_{17}ON$	277–280	53–57	7.81	7.55, 7.55
(b) 2-Monoalkylamino-1-butanols: $RNHCH(C_2H_5)CH_2OH$					
Ethyl	$C_6H_{15}ON$	177–179		11.95	11.95, 11.96
n-Propyl	$C_7H_{17}ON$	192–193		10.68	10.44, 10.43
n-Butyl	$C_8H_{19}ON$	210–213		9.64	9.40, 9.47
n-Amyl	$C_9H_{21}ON$	227–230		8.80	8.52, 8.53
n-Hexyl	$C_{10}H_{23}ON$	247–252		8.08	7.68
n-Heptyl	$C_{11}H_{25}ON$	263–266		7.48	7.13, 7.15
Iso-butyl	$C_8H_{19}ON$	195–198		9.64	10.01, 10.04
Iso-amyl	$C_9H_{21}ON$	221–224			
Allyl	$C_7H_{15}ON$	194–197		10.84	10.91, 10.87
Benzyl	$C_{11}H_{17}ON$	283–285		7.81	7.51, 7.50

[a] The melting points of the distilled amino alcohols were taken without recrystallization of the products, since it was found that recrystallization raised the melting point only slightly. [b] Also prepared by Kremer and Waldman.[5]

Hydrochloride of *p*-Ethoxybenzoate of 2-Mono-*n*-amylamino-2-methyl-1-propanol.—To 15.9 g. (0.1 mole) of 2-mono-*n*-amylamino-2-methyl-1-propanol was added 12.5 ml. (0.15 mole) of concentrated hydrochloric acid. The excess hydrochloric acid was removed by vacuum evaporation. To the solid hydrochloride of 2-mono-*n*-amylamino-1-propanol was added 18.4 g. (0.1 mole) of *p*-ethoxybenzoyl chloride. The reaction mixture was heated, with occasional shaking, in an oil-bath at 100° for thirty minutes, at 130° for thirty minutes, and at 150° for fifteen minutes. The reaction mixture was dissolved in 60 ml. of 95% ethanol, poured into 800 ml. of *N* sodium hydroxide solution, and extracted with 125 ml. of isopropyl ether. The ether solution was extracted with 1500 ml. of 0.4 *N* hydrochloric acid. The acid solution was made basic with sodium hydroxide and the free base of the amino alcohol ester was extracted with 150 ml. of isopropyl ether. The isopropyl ether solution was saturated with dry hydrogen chloride, yielding 23 g. (67%) of an oily precipitate of the hydrochloride of β-mono-*n*-amylamino-β,β-(dimethyl)-ethyl *p*-ethoxybenzoate, which solidified within a few minutes. On two crystallizations from acetone, this product melted at 127–129°.

In this study, approximately sixty alkoxybenzoates of 2-monoalkylamino-2-methyl-1-propanols and 2-monoalkylamino-1-butanols were prepared, that their anesthetic activity might be tested. In some runs in which very insoluble ester hydrochlorides were formed, the products were isolated by precipitation with a large excess of hydrochloric acid and by filtration. Table II gives the melting points and chloride analyses of the hydrochlorides of the above alkoxybenzoates which were most readily crystallized.

TABLE II

β-MONOALKYLAMINOALKYL ALKOXYBENZOATE HYDROCHLORIDES

R	R'	M. p., °C. (uncor.)	Empirical formula	Chlorine, % Calcd.	Found
(a) β-Monoalkylamino-β,β-(dimethyl)-ethyl alkoxybenzoate hydrochlorides: $ROC_6H_4COOCH_2C(CH_3)_2NHR'\cdot HCl$					
p-Methyl	*n*-Butyl	154–155	$C_{16}H_{26}O_3NCl$	11.23	11.11
p-Ethyl	*n*-Amyl	128–129	$C_{18}H_{30}O_3NCl$	10.31	10.15
p-Ethyl	*n*-Hexyl	135–136	$C_{19}H_{32}O_3NCl$	9.91	9.82
o-Ethyl	*n*-Butyl	118–120	$C_{17}H_{28}O_3NCl$	10.75	10.86
m-Ethyl	*n*-Butyl	106–108	$C_{17}H_{28}O_3NCl$	10.75	10.67
m-Ethyl	*n*-Amyl	73–76	$C_{18}H_{30}O_3NCl$	10.31	9.82
p-*n*-Propyl	*n*-Butyl	98–100	$C_{18}H_{30}O_3NCl$	10.31	10.38
p-*n*-Propyl	*n*-Amyl	103–106	$C_{19}H_{32}O_3NCl$	9.91	10.06
p-*n*-Propyl	*n*-Hexyl	118–120	$C_{20}H_{34}O_3NCl$	9.53	9.34
p-*n*-Butyl	Ethyl	136–138	$C_{17}H_{28}O_3NCl$	10.75	10.47
p-*n*-Butyl	*n*-Propyl	105–107	$C_{18}H_{30}O_3NCl$	10.31	10.24
p-*n*-Butyl	*n*-Butyl	125–127	$C_{19}H_{32}O_3NCl$	9.91	9.66
p-*n*-Butyl	*n*-Hexyl	122–123	$C_{21}H_{36}O_3NCl$	9.19	9.21
p-*n*-Butyl	Benzyl	161–162	$C_{22}H_{30}O_3NCl$	9.05	9.02
o-*n*-Butyl	*n*-Butyl	91–94	$C_{19}H_{32}O_3NCl$	9.91	9.96
p-*n*-Amyl	*n*-Propyl	112–113	$C_{19}H_{32}O_3NCl$	9.91	10.00
p-*n*-Amyl	*n*-Butyl	125–126	$C_{20}H_{34}O_3NCl$	9.53	9.64
p-*n*-Amyl	*n*-Amyl	103–104	$C_{21}H_{36}O_3NCl$	9.19	9.01
p-*n*-Amyl	Benzyl	139–140	$C_{23}H_{32}O_3NCl$	8.74	8.79
p-*n*-Hexyl	*n*-Butyl	125.5–127	$C_{21}H_{36}O_3NCl$	9.19	9.11
p-*n*-Heptyl	*n*-Propyl	108–110	$C_{21}H_{36}O_3NCl$	9.19	9.11
p-*n*-Heptyl	*n*-Butyl	117–118	$C_{22}H_{38}O_3NCl$	8.86	8.80
p-*n*-Heptyl	*n*-Amyl	105–106	$C_{23}H_{40}O_3NCl$	8.57	8.56
p-*n*-Heptyl	*n*-Hexyl	105–107	$C_{24}H_{42}O_3NCl$	8.28	8.25
(b) β-Monoalkylamino-β-ethyl-ethyl alkoxybenzoate hydrochlorides: $ROC_6H_4COOCH_2CH(C_2H_5)NHR'\cdot HCl$					
p-Ethyl	Ethyl	184–185	$C_{16}H_{24}O_3NCl$	11.75	11.42
p-Ethyl	*n*-Butyl	134–135	$C_{17}H_{28}O_3NCl$	10.75	10.82
p-Ethyl	*n*-Hexyl	135–136	$C_{19}H_{32}O_3NCl$	9.91	9.88
p-Ethyl	Benzyl	181–184	$C_{20}H_{26}O_3NCl$	9.74	9.64
p-*n*-Propyl	*n*-Butyl	129–131	$C_{18}H_{30}O_3NCl$	10.31	10.25
p-*n*-Propyl	*n*-Hexyl	112–114	$C_{20}H_{34}O_3NCl$	9.53	9.33
p-Iso-propyl	*n*-Butyl	119–121	$C_{18}H_{30}O_3NCl$	10.31	10.29
p-*n*-Butyl	*n*-Butyl	114–116	$C_{19}H_{32}O_3NCl$	9.91	9.85
p-*n*-Heptyl	*n*-Propyl	108–109	$C_{21}H_{36}O_3NCl$	9.19	8.76

The β-monoalkylaminoalkyl alkoxybenzoate hydrochlorides reported in this paper are being tested pharmacologically by Dr. C. C. Haskell. The results will be reported elsewhere.

Summary

A series of hydrochlorides of alkoxybenzoates of 2-monoalkylamino-2-methyl-1-propanols and of 2-monoalkylamino-1-butanols is described.

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