Ossian Aschan, *Chem. Abstracts*, **14**, 3654 (1916); *Ofversigi Finska Vetenskaps Soc.*, **58**, 122 (1915). Ossian Aschan, *Ann.*, **324**, 1 (1902). Wallace H. Carothers, *Chem. Rev.*, **8**, 353 (1931) (includes bibliography of 254 references). Gustav Egloff, *et al.*, *J. Phys. Chem.*, **35**, 1825 (1931) (includes bibliography of 159 references). Engler and Routala, *Ber.*, **43**, 388–397 (1910); **42**, 4613–4620 (1909); **42**, 4620 (1909). Gangloff and Henderson, THIS JOURNAL, **39**, 1420 (1917).

Summary

1. Isoprene and pentene-2 react in the presence of anhydrous aluminum chloride to form two polymers, one insoluble, the other soluble in hydrocarbon solvents.

2. The amount of the soluble polymer formed is a function of the pentene-2 present. The hardness is an inverse function of the amount of pentene-2 present.

3. The amount of the insoluble polymer is an inverse function of the pentene-2 present.

DAYTON, OHIO

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF MIAMI UNIVERSITY]

ALKAMINE ESTERS OF AROMATIC ACIDS: NOVOCAINE ANALOGS. II[1]

BY HARVEY C. BRILL

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A search of the chemical literature relating to the novocaine type of anesthetic reveals very few compounds of the type $-O(CH_2)_nN\overset{x}{\underset{y}{}}$. A small number[2] have been made by comparison with the number of the type with identical substituents.

The difficulty of preparing secondary amines with dissimilar alkyl groups appears to have inhibited the investigative curiosity of workers in this field.

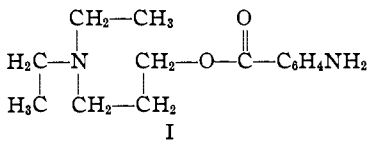
A study of the effects on the properties of the novocaine class of compounds of groups of this sort seemed worth while when the influence of such arrangements in the properties of the barbituric acid type of hypnotics, *e. g.*, Ipral, Amytal, Luminal, etc., is considered. In the absence of any considerable number of trustworthy generalizations that relate chemical

[1] Brill, THIS JOURNAL, **47**, 1134 (1925).

[2] (a) Volwiler and Adams, U. S. Patent 1,476,934 (Dec. 11, 1923), have made γ-butylallyl, γ-*n*-propylallyl, γ-isopropylallyl and γ-isoamylallylaminopropyl esters of benzoic acid; (b) v. Braun and Kirschbaum, *Ber.*, **52**, 2011 (1919), described a phenyl analog of novocaine, namely, the β-*p*-aminophenylmethylaminoethyl ester of *p*-aminobenzoic acid; (c) v. Braun and Braunsdorf, *ibid.*, **54**, 208 (1921), listed β-ethylallyl, β-ethylstyryl and β-ethylfuromethylaminoethyl esters of *p*-aminobenzoic acid; (d) Thorp has patented the hydrochloride of the benzoic ester of 1-methylethylamino-3-methylethylamino-2-hydroxypropane, U. S. Patent 1,193,649 (Aug., 1916). These compounds are reported to possess anesthetic properties.

structure and physiological activity, the only means of learning of the effects of such relationships is to prepare compounds of slight structural differences and study the effects of such changes.

Kamm[3] has made the γ-diethylaminopropyl ester of *p*-aminobenzoic acid (I) and pointed out its structural similarity to cocaine (II). The structural resemblance between cocaine and γ-isopropylethylaminopropyl benzoate (III) appears more striking than between the pair pointed out by Kamm. This resemblance is really still more pronounced between (III) and tropacocaine (IV).



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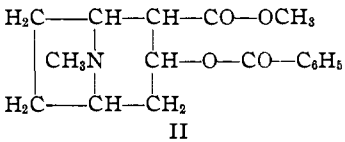

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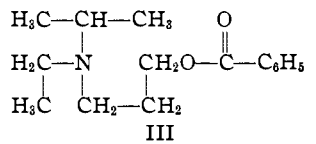

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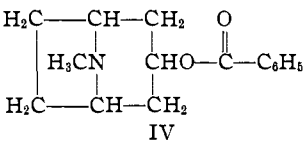

IV

If close similarity of structures between anesthetics of the novocaine type and cocaine or tropacocaine is conducive to high anesthetic activity, it should be worth while to study γ-isopropylethylaminopropyl benzoate. The hydrochloride of this ester in water solution is acid to litmus, and would be somewhat irritating to the tissues on this account. Such compounds are improved in their effects by lowering their acidity by the introduction of an amino group in the aromatic radical or by forming salts with acids that are weaker than hydrochloric or sulfuric.[4] Even when an aromatic group is substituted for one of the substituent alkyls in the amino, v. Braun and Kirschbaum[2b] found that these compounds possessed marked anesthetic properties, provided they were made basic by the introduction of amino groups. When the acidity is allowed to rise, however, the compound becomes irritating, as is evidenced by the properties of β-phenylethylaminoethyl benzoate, which has a numbing effect but is pepper-like in its irritation on the tongue.

Experimental Part

The hydrochlorides of these anesthetic compounds can be made readily by condensing a benzene solution of the acid chloride taken in about 10% excess of the theoretical amount with a benzene solution of the theoretical quantity of the amino alcohol. The reaction is completed by occasionally shaking and warming on a steam-bath under a reflux for several hours. White crystalline precipitates form during the heating or immediately on cooling.

[3] Kamm, THIS JOURNAL, **42**, 1030 (1920).

[4] Pope, British Patent 260,346 (July, 1925), preparation of borocaines; Watson Williams, *Lancet*, **1**, 16 (1926); Copeland and Notton, *Brit. Med. J.*, **11**, 547 (1925).

The mixed secondary amines are most readily prepared in the pure state by alkylating the mono-alkyl aniline by means of the alkyl halide under a reflux, warming for one to five hours on a steam-bath to complete the reaction. The salt of this tertiary amine that results precipitates as a solid mesh of crystals or as a thick gelatinous paste in the case of the higher alkyls. It is dissolved in 12% hydrochloric acid solution, nitrosated at low temperature in the presence of ice with energetic stirring and the secondary amine released by the use of sodium hydroxide and steam distillation in the regular manner as described by Vanino and other laboratory manuals. No attempts were made to separate the nitroso derivative. Yields of these secondary amines ranged from 35 to 73% of the theoretical. The low yields are obtained with the low molecular weight alkyl halides and the higher molecular weight members, hexyl halide and above. To obtain high yields the former should be condensed in a closed vessel to prevent loss through volatilization of the halide, while the high molecular weight members react too slowly to give high yields before appreciable decomposition takes its toll.

The Tertiary Amines.—The dialkyl amino alcohols were made by condensation on the steam-bath of the secondary amine with 20% excess over the equivalent amount of the chlorohydrin. The tertiary base is set free, removed from the water solution by ether extraction, dried by means of anhydrous sodium sulfate and recovered by careful fractional distillation. The use of reduced pressure lessens the decomposition and increases the yields.

TABLE I

BOILING POINTS OF SOME SECONDARY AND TERTIARY AMINES

	B. p., °C.		B. p., °C.
Ethylmethylamine	36–37	γ-Ethylmethylaminopropanol	170
Ethylisopropylamine	76	β-Phenylethylaminoethanol	268
Ethyl-*n*-butylamine	108–9	β-Ethylisopropylaminoethanol	175
Ethylmethylaniline	202	γ-Ethylisopropylaminopropanol	188
Ethylisopropylaniline	211	β-Ethyl-*n*-butylaminoethanol	195
Ethyl-*n*-butylaniline	247		

TABLE II

SOME PROPERTIES OF CERTAIN ALKAMINE ESTERS

	Hydrochlorides	Formula	M. p., °C.	Nitrogen, % Calcd.	Found
A	γ-Ethylmethylaminopropyl benzoate[a]	$C_{13}H_{19}NO_2 \cdot HCl$	123	5.46	5.32
B	β-Phenylethylaminoethyl propionate[b]	$C_{13}H_{19}NO_2 \cdot HCl$	171	5.46	5.56
C	β-Ethylisopropylaminoethyl benzoate	$C_{14}H_{21}NO_2 \cdot HCl$	96	5.15	5.13
D	γ-Ethylisopropylaminopropyl benzoate	$C_{15}H_{23}NO_2 \cdot HCl$	105	4.90	4.87
E	β-Ethyl-*n*-butylaminoethyl cinnamate[5]	$C_{17}H_{25}NO_2 \cdot HCl$	151	4.49	4.42
F	γ-Diethylaminopropyl *p*-methoxycinnamate[c,6]	$C_{17}H_{25}NO_3 \cdot HCl$	142	4.27	4.30
G	γ-Piperidylpropyl *p*-nitrobenzoate[d]	$C_{15}H_{20}N_2O_4 \cdot HCl$	205		
H	γ-Piperidylpropyl *p*-aminobenzoate[e,7]	$C_{15}H_{22}N_2O_2 \cdot HCl$	213	9.38	9.40

[a] Slightly deliquescent. [b] Quite irritating to tongue; acid to litmus. [c] Compound slightly more toxic than apothesin.[7] [d] Free from the hydrochloride, m. p. 78°. [e] Free from the hydrochloride, m. p. 49°.

The compounds A, B, C, D, E, F and H possess anesthetic properties. The irritating effects of (B) are so pronounced that its anesthetic properties

[5] Brill, U. S. Patent, 1,817,670 (1931).

[6] Wildman and Throp, U. S. Patent, 1,193,649 (1916).

[7] Barnes and Adams, THIS JOURNAL, **49**, 1313 (1927).

are not so apparent. The results of careful tests for the physiological properties which are being made on these substances will be reported in a subsequent communication.

Summary

1. Several alkamine alcohols of the type $HO-(CH_2)_nN^x_y$ and secondary and tertiary amines are described.
2. Esters of these alcohols are recorded and described.
3. These esters are reported to possess anesthetic properties.

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

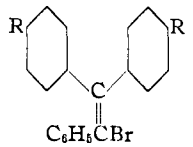
SYNTHESES WITH TRIARYLVINYLMAGNESIUM BROMIDES. TRIARYLACRYLIC ACIDS AND THE INDONES DERIVED FROM THEM

BY C. FREDERICK KOELSCH[1]

RECEIVED FEBRUARY 6, 1932 PUBLISHED JUNE 6, 1932

It has been shown recently[2] that triphenylvinyl bromide reacts with magnesium to form a Grignard reagent which can be carbonated to give triphenylacrylic acid. The present paper describes the results obtained in similar reactions where certain substituted triphenylvinyl bromides were used

Two disubstituted triphenylvinyl bromides were studied: α-phenyl-β,β-di-*p*-tolylvinyl bromide (I, R = CH_3) and α-phenyl-β,β-di-*p*-anisylvinyl bromide (I, R = OCH_3). Both of these compounds reacted with magnesium to form Grignard reagents which on carbonation yielded the correspondingly substituted acrylic acids (II). The elimination of water from these acids led to the formation of 6-methyl-2-phenyl-3-*p*-tolylindone (III, R = CH_3) and of 3-*p*-anisyl-6-methoxy-2-phenylindone (III, R = OCH_3)



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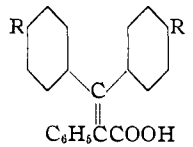

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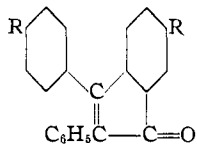

III

While all monosubstituted triphenylvinyl bromides having the substituent in one of the β-phenyl groups should exist in two stereoisomeric forms, the isolation of both of these forms was accomplished in only one of three cases studied. α,β-Diphenyl-β-*p*-chlorophenylvinyl bromide was obtained in the *cis* form (IV, R = Cl) and in the *trans* form (V, R = Cl); only the *cis* form of α,β-diphenyl-β-*p*-tolylvinyl bromide (IV, R = CH_3),

[1] National Research Fellow in Chemistry.

[2] Koelsch, THIS JOURNAL, **54**, 2045 (1932).