New Compounds: Certain Alkanolamine Esters Likely to Possess Anesthetic Activity

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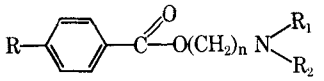
The synthesis of a new series of alkanolamine esters is described. Esterification of 1,1′-iminodi-2-propanol with benzoyl chloride applying the Schotten-Baumann conditions afforded either the mono or diester according to the molecular ratio of the reactants but never the amide. With the more powerful acylating agent *p*-nitrobenzoyl chloride the diester-amide was always obtained even when equimolecular amounts of the reactants were used. Esterification of the *N*-methyl derivative of the amino alcohol with benzoyl chloride yielded in all cases the diester while esterification *via* the interaction of the dichloro analog of the amino alcohol and the appropriate silver salt invariably yielded the monoester even when excess of the silver salt was used.

THE VAST MAJORITY of the existing local anesthetics have been synthesized with the following fundamental structural requirements: an aromatic acid with or without a nuclear substituent in which the acid grouping has been esterified with an amino alcohol of simple or complex consititution.



Scheme I

In the present investigation, the mono- and diesters of 1,1′-iminodi-2-propanol (Table I) were prepared in the hope that the new products would show superior anesthetic activity[1] with less side effects.

The esterification of 1,1′-iminodi-2-propanol was successfully achieved *via* three different procedures: (*a*) the Schotten-Baumann conditions, (*b*) blocking the =NH prior to acylation to prevent amide formation, and (*c*) replacing the hydroxyl groups in the amino alcohol with halogen and reacting the halogeno derivative thus obtained with the appropriate silver salt.

Cope and Hancock (1), applying the Schotten-Baumann conditions to a number of alkyl amino alcohols, reported that the main product was the amide while Abou-Zeid and Gabali (2) disclosed that with diethanolamine only the diester was formed. With 1,1′-iminodi-2-propanol the authors have observed that the rate of the esterification depends solely on the molecular ratio of the reactants. When 1 mole of the amino alcohol interacted with 1 mole of benzoyl chloride, the monoester was produced, and if the amount of the acid chloride was doubled, the diester was obtained. The failure of amide formation with diethanolamine and 1,1′-iminodi-2-propanol may be attributed to the steric hindrance displayed by the bulky diethanol and di-isopropanol radicals flanking the =NH group. The fact that diethanolamine always affords the diester while 1,1′-iminodi-2-propanol affords either the mono- or diester according to conditions, may be easily accounted for by a consideration of the reactivity of the alcoholic groups in the two amino alcohols. It has long been known that in reactions in which the hydrogen atom of the alcoholic —OH is involved, a primary alcohol is far more reactive than a secondary (3). It follows, therefore, that the —OH in diethanolamine is more reactive than that in 1,1′-iminodi-2-propanol.

Using *p*-nitrobenzoyl chloride, which is a powerful acylating agent, resulted in attack of all available centers in the amino alcohol with the production of the diester amide, a result which is in accord with what has been reported earlier by other investigators (1, 2). As a consequence we resorted to Cope's method of blocking the =NH group by salt formation prior to acylation in order to prepare the diester amine which, however, was obtained but in poor yields. To improve the yield of the diester amine, its synthesis *via* the interaction of the dichloro analog of the amino alcohol and the appropriate silver salt was attempted. Application of this latter procedure, however, instead of affording the diester amine yielded a monoester with the second chlorine unreacted upon in spite of the use of excess of the silver salt. In the authors' opinion one of the contributing factors to the failure of the second chlorine atom to interact is steric hindrance.

EXPERIMENTAL

Schotten-Baumann Conditions—The dialkanolamine (the parent 1,1′-iminodi-2-propanol or its *N*-methyl derivative) (0.01 mole) mixed with 10% sodium hydroxide was treated with the acid chloride (0.01 or 0.02 mole) and cooling. In the case of benzoyl chloride, the insoluble viscous matter formed was washed and extracted with ether and the extract dried over anhydrous sodium sulfate. Then the ethereal extract was either concentrated until the separation of a crystalline solid mass (monoester) or completely evaporated and the oily material (diester) left converted to the corresponding picrate. The white solid forming with *p*-nitrobenzoyl chloride was washed with benzene and then crystallized again from benzene.

Cope's Conditions—1,1′-Iminodi-2-propanol (0.01 mole) dissolved in chloroform (25 ml.) was saturated with dry HCl gas till the separation of an oily top layer. Then finely powdered *p*-nitrobenzoyl chloride (0.01 mole) suspended in chloroform (25 ml.) was added and the whole was heated under reflux for 36 hr. The platelets separating were filtered, washed several times with ether, and crystallized from isopropyl alcohol.

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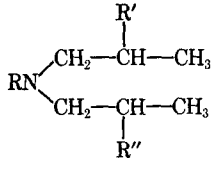
[1] The products at present are under preliminary screening for possible anesthetic action or any useful pharmacological activity.

TABLE I—ESTERS OF 1,1′-IMINODI-2-PROPANOL AND OF THE *N*-METHYL DERIVATIVE



Name	R	R′	R″	Method of Prep.	Yield, %	Solvent of Crystallization[a]	M.p.°C.[c]	Formula	Anal., %[b] Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
β-Benzoyloxy-β′-hydroxy-di(*n*-propyl)amine picrate	H +	OH	$OCOC_6H_5$	1	90	A	186–187	$C_{19}H_{22}N_4O_{10}$[d]	48.92	4.72	12.01	49.14	4.89	12.11
β-Benzoyloxy-β′-hydroxy-di(*n*-propyl)amine	H	OH	$OCOC_6H_5$	1	31	B	87–88	$C_{13}H_{19}NO_3$	...	...	5.90	...	...	5.93
β,β′-Dibenzoyloxy-di-(*n*-propyl)amine picrate	H +	$OCOC_6H_5$	$OCOC_6H_5$	1	70	A	160–162	$C_{26}H_{26}N_4O_{11}$[d]	54.73	4.56	9.82	54.83	4.71	10.00
β,β′-Di-*p*-nitrobenzoyloxy-di(*n*-propyl)amine hydrochloride	H +	$OCOC_6H_4NO_2$-*p*	$OCOC_6H_4NO_2$-*p*	2	12	C	190–192 dec.	$C_{20}H_{22}ClN_3O_8$[e]	...	...	8.98	...	...	8.68
β-Chloro-β′-*p*-nitrobenzoyloxy-di(*n*-propyl)amine	H	Cl	$OCOC_6H_4NO_2$-*p*	3	60	B	158–159	$C_{13}H_{17}ClN_2O_4$	...	...	9.31	...	...	8.94
N-Methyl-β,β′-dibenzoyloxy-di(*n*-propyl)amine picrate	CH_3 +	$OCOC_6H_5$	$OCOC_6H_5$	1	21	A	142	$C_{27}H_{28}N_4O_{11}$	55.47	4.79	9.58	55.38	4.89	9.55
N-Methyl-β,β′-di-*p*-nitrobenzoyloxy-di(*n*-propyl) amine	CH_3	$OCOC_6H_4NO_2$-*p*	$OCOC_6H_4NO_2$-*p*	1	82	B	114–115	$C_{21}H_{23}N_3O_8$[d]	56.62	5.16	9.44	55.17	5.49	9.20

[a] A, ethanol; B, benzene; C, isopropyl alcohol. [b] Analyses performed by Alfred Bernhardt, Germany and El Nasr Laboratories, U.A.R. [c] Melting points were performed by the capillary tube method and are uncorrected. [d] Isolated as the picrate. [e] Isolated as the hydrochloride.

Halide–Silver Salt Method—*β,β'-Dichloro-di(n-propyl)amine Hydrochloride*—Thionyl chloride (12 ml.) was slowly added to 1,1'-iminodi-2-propanol (2 Gm.) with stirring and cooling until a homogeneous liquid was obtained. Then the excess thionyl chloride was distilled *in vacuo* and the residue was washed several times with chloroform and acetone. The salt that was obtained in 86% yield as white microcrystals melted at 197–198°.

Anal.—Calcd. for $C_6H_{14}Cl_3N$: C, 35.12; H, 6.83; Cl, 51.22; N, 6.83. Found: C, 34.77; H, 6.73; Cl, 51.52; N, 6.73.

The aqueous solution of the salt was rendered alkaline with cold saturated sodium hydrogen carbonate solution and the freed base rapidly extracted with ether. Then the extract was dried over anhydrous sodium sulfate for 24 hr. before the ether was evaporated *in vacuo*. The base thus obtained was immediately used in the condensation reaction.

Condensation with the Appropriate Silver Salt—The silver salt (3 Gm.) was intimately mixed with the halogeno base (0.9 Gm.) in a 100-ml. round-bottom flask. A condenser was fitted to the flask and the whole setup was dipped into a preheated oil bath at 130–140° for a few minutes. The mixture was then allowed to cool, then benzene (40 ml.) was added and the whole was refluxed for 48 hr. after which it was filtered while hot. Light feathery crystals cropped out on cooling and concentrating the benzene solution.

REFERENCES

(1) Cope, A. C., and Hancock, E. M., *J. Am. Chem. Soc.*, **66**, 1448(1944).

(2) Gabali, E., Doctoral dissertation, Cairo University, 1960.

(3) Norris, J. F., "The Principles of Organic Chemistry," 3rd ed., McGraw-Hill Book Company, Inc. New York, N. Y., 1931, pp. 99–100.

Keyphrases

Alkanolamine esters
Monoester, 1,1'-iminodi-2-propanol—synthesis
Diester, 1,1-iminodi-2-propanol—synthesis
p-Nitrobenzoyl Cl—acylating agent

Communications

Enzyme Inhibitors XXII. Identity of Inhibitor Binding Site on Adenosine Deaminase

Sir:

Investigators concerned with active sites or receptor sites in macromolecules have interest in the number and types of binding sites that exist in the biological sample. In enzyme systems, whenever competitive inhibitors are studied, it is possible that the inhbitor is complexed at the active site of the enzyme. However, it is also possible that the inhibitor is complexed to an entirely different site. When two or more inhibitors of an enzyme have been prepared and evaluated as enzyme inhibitors, it is possible that they complex to the same site on the enzyme or to different sites. It occurred to us that it might be possible to obtain information concerning the identity or nonidentity of inhibitor binding sites by combining in one inhibitor the moieties which make a contribution to binding in two different inhibitors. For example, in a variety of 9-substituted adenines, it has been found that the adenine moiety of these inhibitors makes a contribution to binding to the enzyme, adenosine deaminase (1). Furthermore, it has been observed (2) that adenosine deaminase possesses a hydrophobic area which is important in the formation of a complex with the 9-substituent of some 9-*n*-alkyladenines (I). In addition, adenosine deaminase has a specific hydroxyl binding site (2, 3) which makes a contribution to complex formation of the hydroxyl group in a compound such as 9-(2-hydroxyethyl)adenine. Therefore, if the adenine moiety of the 9-*n*-alkyladenines and the 9-(2-hydroxyethyl)adenine (II) is complexed to the same site on the enzyme, it should be possible to prepare very potent inhibitors by combining in one molecule the alkyl chain and the 2-hydroxyethyl group at the 9 position of the adenine nucleus. Such a class of compounds would be the 9-(1-hydroxy-2-alkyl)adenines (III). These compounds were prepared by a modification of a general procedure (4) which involves the condensation of the appropriate amino alcohol with 5-amino-4,6-dichloropyrimidine. The resulting 5-amino-6-chloro-4-(1-hydroxy-2-alkylamino)pyrimidine was cyclized with triethyl