SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF CYCLIC DIACETALS OF SEBACALDEHYDE

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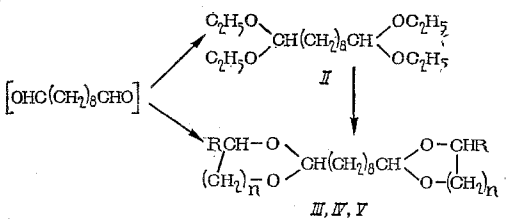
UDC 615.216.5:547.461.8].012.1+615.216.5: 547.461.8]015.4

We showed earlier that cyclic diacetals of saturated and unsaturated C_2-dialdehydes, for example, succinaldehyde, fumaraldehyde, and butyne-2-dial, possess a Myanesin-like property, while the quaternary salts of their bis-aminomethyl derivatives are highly active blocking agents of n-cholinoreactive systems of skeletal muscles [1-5]. One of the representatives of the investigated series of compounds is produced by the chemicopharmaceutical industry of the USSR under the name "dioxonium" as a muscle relaxant of average duration of effect.

This research is a continuation of the study of derivatives of sebacaldehyde. There is interest in these compounds because a series of examples exists of appearance of a curare-like activity in materials (Imbretil, Prestonal, etc.) in which the distance between the bisquaternary ammonium groups amount to approximately 20 Å [6-8], as in the corresponding sebacaldehyde derivatives.

Of the methods described in the literature [9-12] for the synthesis of the starting sebacaldehyde (I), the most convenient was found to be Rosenmund method of catalytic reduction of the diacid chloride of sebacic acid with hydrogen in the presence of a palladium catalyst in xylene. For the purpose of preventing polymerization of the dialdehyde, the formed solution was used directly for obtaining sebacic diacetals, which are easily formed both upon reaction of the solution with orthoformic ester (II) and upon its treatment with glycols in the presence of p-toluenesulfonic acid with azeotropic distillation of water (III,IV). Diacetal (V) was obtained conveniently by transacetalation of (II) with the α-monochlorohydrin of glycerin in toluene.



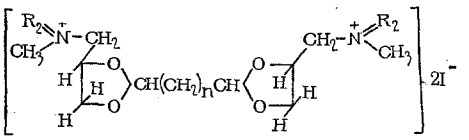
III: R=H, n=1
IV: R=CH$_3$, n=2
V: R=CH$_2$Cl, n=1

Synthesis of quaternary salts of bis-aminomethyl derivatives was accomplished by heating (V) with dimethylamine or pyrrolidine with subsequent transformation of the obtained bases into dimethyl iodides (VI) and (VII).

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 6, No. 2, pp. 10-14, February, 1972. Original article submitted October 27, 1970.

TABLE 1. Peak Toxicity and Effect on Motion Coordination of Cyclic Diacetals (I) in Experiments on White Mice upon Intraperitoneal Introduction

Compound	LD_{50} (mg/kg)	ED_{50} (mg/kg)	
		experiments on a rotating rod	tube test (after 60 min)
III	2 400 (1 690–3 408)	980 (676–1421)	—
IV	290 (170–478)	430 (318–580)	275 (216–346)
V	1 500 (1 071–2 100)	180 (120–270)	—



VI: $R_2N=(CH_3)_2N$, n = 8

VII: $R_2N=$  n = 8

VIII: $R_2N=(CH_3)_2N$, n = 2

IX: $R_2N=$  n = 2

Compounds (IV-VII) are polysteroisomeric mixtures, containing a various number of diastereoisomers, depending on the thermodynamic and kinetic conditions of their formation. The maximum number is determined by the formula $2^{n-1}(2^{n+1})$, where n is the number of pairs of asymmetric carbon atoms in the acetal rings (in this case, n = 2).

Diacetals (III), (IV), and (V) are reminiscent of Myanesin-like materials (Table 1) in their general effect in experiments on mice upon intraperitoneal introduction of solutions in olive oil. Compound (V) possessed the greatest activity and was 2.5 times more active and 3 times less toxic than the corresponding derivative of succinaldehyde [3]. Compound (III) differs little from the succinaldehyde analog in activity and toxicity. Compound (IV) is more toxic and its toxic effect is developed more slowly. Compound (IV) has an effect on motion coordination and muscle tone only in toxic doses.

The bis-quaternary ammonium salts (VI) and (VII) displayed a high curare-like activity (Table 2) in experiments oncats with electrical stimulation of the sciatic nerve and registration of contraction of the gastrocnemius muscle, in experiments on rabbits (test of lowering the head), and on isolated nerve–muscle preparation of the rat diaphragm. Results obtained earlier [13, 14] in the investigation of the curare-like effect of the corresponding derivatives of succinaldehyde (VIII) and (IX), and also the activity of d-tubocurarine are presented for comparison.

Compounds (VI) and (VII) can be assigned to compounds of mixed type in mechanism of curare-like effect. In experiments on cats, in certain cases before onset of nerve–muscle blockage, these compounds caused a small increase in amplitude of muscle contraction, but intravenous introduction of proserine (50 μg/kg) either did not affect their effect or caused a weak antagonistic effect. In experiments on the direct muscle of a frog stomach, compounds (VI) and (VII) cause a predominately cholinolytic effect, in contrast to (VIII) and (IX). Dilutions preventing the effect of acetylcholine by 50% for (VI) and (VII) amount to $2.13 \cdot 10^{-5}$ ($1.09\text{-}3.17 \cdot 10^{-5}$) and $2.15 \cdot 10^{-6}$ ($1.08\text{-}3.22 \cdot 10^{-6}$), respectively.

However, compounds (VI) and (VII) cause spasmodic muscle contraction in doves. Thus, (VI) and (VII) do not differ from one another in mechanism of effect, but the effect of these compounds depends on the species characteristics of the cholinoreceptor structures of the skeletel muscles to an even greater degree than this was noted [14] for derivatives of succinaldehyde. The average duration of effect in experiments on cats for (VI) amounts to 23.6 min (20.4-26.8) and to 22.0 min (19.5-24.5) for (VII). Consequently, these materials differ little in length of curarizing effect from analogs of the series of diacetals of succinaldehyde.

EXPERIMENTAL

Sebacaldehyde (I). Through a mixture of 200 ml of xylene, 4 g of catalyst (5% palladium on barium sulfate), 0.4 ml of regulator (0.1 g of sulfur quinoline in 1 ml of xylene), and 20 g of the diacid chloride of sebacic acid with stirring and boiling was passed a stream of hydrogen for 10-12 h. Then the catalyst was filtered and the obtained aldehyde was used for obtaining the acetals without separation from solution.

1, 1, 10, 10-Tetraethoxydecane (II). To the obtained solution of (I) was added 200 ml of absolute ethanol, 25 g of the ethyl ester of orthoformic acid, and 0.2 ml of concentrated hydrochloric acid; the mixture was heated to boiling and left overnight. Then the solution was neutralized with piperidine, the solvent was evaporated in vacuum, the precipitated piperidine hydrochloride was filtered, and the residue was fractionated in vacuum. The fraction with bp 150-155° (2 mm) was used for further transacetalation. Yield was 14.6 g

TABLE 2. Curarizing Activity of Quaternary Ammonium Salts in Experiments on Cats (ED_{50}), Rabbits (TLH*), and Isolated Nerve–Muscle Preparation of Rats (EK_{50}†) and Peak Toxicity for White Mice (LD_{50}) upon Intraperitoneal Introduction (with confidential limits, P = 0.05)

Compound	ED_{50} (mg/kg)	TLH (mg/kg)	EK_{50}	LD_{50} (mg/kg)
VI	0,025 (0,018÷0,032)	0,45 (0,43÷0,47)	$2,03 \cdot 10^{-6}$ ($0,64 \cdot 10^{-6}$–3,42 $\times 10^{-6}$)	1,6 (1,3÷1,9)
VII	0,1 (0,02÷0,018)	0,174 (0,156÷0,192)	$2,2 \cdot 10^{-7}$ ($1,96 \cdot 10^{-7}$–2,44 $\times 10^{-7}$)	1,0 (0,92÷1,09)
VIII	0,012 (0,010÷0,014)	0,154 (0,134÷0,174)	$5,34 \cdot 10^{-6}$ ($3,20 \cdot 10^{-6}$÷7,48 $\times 10^{-6}$)	7,15 (6,00–8,50)
IX	0,005 (0,003÷0,007)	0,096 (0,082–0,110)	$2,72 \cdot 10^{-6}$ ($1,61 \cdot 10^{-6}$÷3,83 $\times 10^{-6}$)	1,0 (0,7÷1,47)
d-Tubocurarine	0,113 (0,077÷0,149)	0,232 (0,221–0,243)	$1,34 \cdot 10^{-6}$ ($1,15 \cdot 10^{-6}$–1,53 $\times 10^{-6}$)	0,45 (0,37÷0,54)

*TLH is the dose causing lowering of the head in rabbits.
† EK_{50} is the dilution decreasing contraction of the rat diaphragm by 50%.

(55%). This fraction contained about 85% of the acetal, judging from the obtained amount of p-nitrophenylhydrazone of (I) [9]. The pure material can be isolated by repeated distillation, bp 150-153° (2 mm), n_D^{20} 1.434. Found, % C 67.23; H 11.95. $C_{18}H_{38}O_4$. Calculated, %: C 67.56; H 12.02.

1,8-Bis-(1'-dioxolanyl-2')-octane (III). To a solution of (I) was added 10.4 g of ethylene glycol and 0.1 g of p-toluenesulfonic acid and the mixture was heated in a flask fitted with a Dean–Stark attachment until separation of water ceased. The cooled solution was washed with an aqueous solution of sodium carbonate and dried; the solvent was distilled in low vacuum and the residue was fractionated. The fraction with bp 130-150° (2 mm) crystallized. Yield was 10.4 g (48%) of colorless crystals, mp 43-44° (from hexane). Found, %: C 65.33; H 10.21. $C_{14}H_{26}O_4$. Calculated, %: C 65.08; H 10.15.

1,8-Bis-(4'-methyl-1',3'-dioxolanyl-2')-octane (IV). The material was obtained analogously to the preceding, using 15 g of butane-1,3-diol. After distillation of solvent the residue was recrystallized from ethanol. We obtained 12.8 g (48%) of colorless crystals, mp 55-60°. Found, %: C 68.44; H 10.69. $C_{18}H_{34}O_4$. Calculated, %: C 68.75; H 10.90.

1,8-Bis-(4'-chloromethyl-1',3'-dioxolanyl-2')-octane (V). A mixture of 15 g of (II), 10.4 g of the α-monochlorohydrin of glycerin, 150 ml of toluene, and 0.1 g of p-toluenesulfonic acid was heated with stirring to 120° and the ethanol and toluene mixture was distilled. The reaction solution after cooling was washed with an aqueous solution of potassium carbonate and dried, the toluene was distilled in low vacuum, and the residue was fractionated. The fraction having bp 190-200° (1 mm) was collected, after which it crystallized. We obtained 10.5 g (62.5%) of colorless crystals, mp 30-40° (from ethanol). Found, %: C 53.77; H 7.92; Cl 19.73. $C_{16}H_{28}Cl_2O_4$. Calculated, %: C 54.08; H 7.94; Cl 19.95.

1,8-Bis-(4'-dimethylaminomethyl-1',3'-dioxolanyl-2')-octane (VIa). A mixture of 17.7 g of (V) and 13.5 g of dimethylamine was heated for 5 h in an autoclave (volume 250 ml), gradually raising the temperature from 100 to 150°. After cooling 100 ml of ether was added, the dimethylamine hydrochloride was filtered, and the solution was washed with water, dried with anhydrous sodium sulfate, and distilled. The fraction was collected having bp 195-205° (1 mm), n_D^{20} 1.464. Yield 15 g (80%).

Dimethyl Iodide of (VI). To a solution of 2 g of (VIa) in 10 ml of acetone was added 2 ml of methyl iodide. The precipitated colorless oil crystallized upon rubbing. After recrystallization from absolute ethanol 1.3 g (74%) of colorless crystals were obtained, mp 170-175°. Found, %: C 40.27; H 7.35; N 4.02; I 38.98. $C_{22}H_{46}I_2N_2O_4$. Calculated, %: C 40.25; H 7.01; N 4.27; I 38.67.

1,8-Bis-(4'-pyrrolydinomethyl-1',3'-dioxolanyl-2')-octane (VIIa). The compound was obtained analogously to (VIa) from 17.7 g of (V) and 17.5 g of pyrrolidine. Yield was 18 g (84%), bp 220-230° (2 mm), n_D^{20} 1.484.

Dimethyl Iodide of (VII). To a solution of 2 g of (VIIa) in 20 ml of acetone was added 2 ml of methyl iodide. An oil precipitated which did not crystallize upon standing or heating the mixture. It was separated from solvent, 30 ml of absolute ethanol and activated carbon were added, and the mixture was filtered. Absolute ether was added to the filtrate and the precipitate was separated repeatedly from the solvent. After being maintained in vacuum, 2 g (60%) of yellow caramel-like mass remained. Found, %: C 43.05; H 6.60; N 4.57; I 35.09. $C_{26}H_{50}I_2N_2O_4$. Calculated, %: C 44.07; H 7.11; N 3.95; I 35.82.

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