INDOLES

VII. A New Method for the Synthesis of Dinoreserine Systems*

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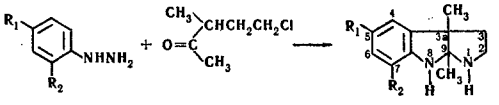
A new method for the synthesis of the tricyclic system of eserine on the basis of the reaction of arylhydrazines with γ-halogenocarbonyl compounds possessing an α-methyl group in neutral media [2] has been proposed.

As is well known, the natural alkaloid physostigmine (eserine) and a number of compounds having the basic tricyclic structure of eserine are important physiologically active substances. These compounds are generally synthesized from an indole system substituted in position 3 [4]. On investigating the field of application of the method of synthesizing tryptamine and its derivatives that we have described previously [5], we have found that, on being boiled in neutral aqueous ethanolic solutions with γ-chloro ketones having an alkyl substituent in the α-position with respect to the carbonyl group, arylhydrazines form 9-alkyl derivatives of dinordeoxyeseroline in good yields:



I

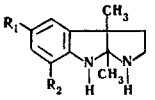
$R_1, R_2 = H, CH_3, OCH_3$

II-VI

The mechanism of this reaction may be suggested on the basis of the mechanism of the synthesis of the tryptamines [1] and that of the Fischer indole synthesis [6]. Special investigations on the mechanism of the process will be published subsequently.

The diacetyl derivatives and dipicrates of compounds II-VI have been prepared, and their UV spectra have been recorded (see Tables 1 and 2). The dipicrates were formed when the bases were treated with molar and bimolar amounts of picric acid in absolute ether under the usual conditions. The diacetyl derivatives were readily obtained by heating the basis with an excess of acetic anhydride. It was impossible to obtain crystalline diacetyl derivatives of compounds IV and VI under these conditions. It must be mentioned that, in contrast to the synthesis of the tryptamines, the best yields of compounds of the eserine system are obtained when the reaction is carried out in 99%, and not 90%, methanol.

Table 1. 9-Methyldinordeoxyeserolines (II-VI)

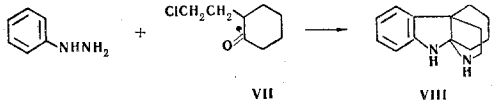


Compound	R_1	R_2	Bp, °C (pressure, mm)	Mp, °C	R_f	UV spectrum λ_{max}, nm	UV spectrum log ε	Empirical formula	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Yield, %
II	H	H	115—117 (1)	71—72	0.68	223 240 282	3.80 3.85 3.35	$C_{12}H_{16}N_2$	76.4	8.7	76.5	8.6	91.2
III	CH_3	H	120—121 (1)	48—50	0.75	245 297	3.79 3.06	$C_{13}H_{18}N_2$	76.7	8.9	77.2	9.0	59.0
IV	H	CH_3	114—115 (1)	78—80	0.76	242 290	3.80 3.38	$C_{13}H_{18}N_2$	76.7	8.6	77.2	9.0	54.6
V	OCH_3	H	156—157 (1)	—	0.63	275	3.66	$C_{13}H_{18}N_2O$	71.3	8.5	71.5	8.3	65.9
VI	H	OCH_3	150—152 (2)	—	0.72	245 290	3.90 3.42	$C_{13}H_{18}N_2O$	71.0	8.3	71.5	8.3	64.2

*For Part VI, see [1].

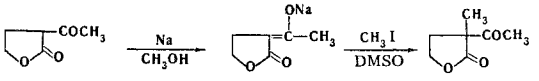
Table 2. Diacetyl Derivatives and Dipicrates of 9-Methyldinordeoxyeserolines (II-VI)

Compound	Diacetyl derivatives: mp, °C	UV spectrum: λ_{max}, nm	UV spectrum: log ε	empirical formula	found, %: C	found, %: H	calculated, %: C	calculated, %: H	Dipicrates: mp, °C	empirical formula	found, %: C	found, %: H	calculated, %: C	calculated, %: H
II	143—144	245 275	4.27 3.37	$C_{16}H_{26}N_2O_2$	70.2	7.3	70.6	7.4	184,5—185,5	$C_{12}H_{16}N_2 \cdot 2C_6H_3N_3O_7$	44.7	3.6	44.6	3.4
III	153—154	251	4.13	$C_{17}H_{22}N_2O_2$	71.5	7.7	71.3	7.7	178,5—179	$C_{13}H_{18}N_2 \cdot 2C_6H_3N_3O_7$	45.5	3.8	45.4	3.7
IV	—	—	—	—	—	—	—	—	142—143	$C_{13}H_{18}N_2 \cdot 2C_6H_3N_3O_7$	45.5	3.7	45.4	3.7
V	184—185	250 284	4.09 2.49	$C_{17}H_{22}N_2O_3$	67.3	7.1	67.5	7.3	132—133	$C_{13}H_{18}N_2O \cdot 2C_6H_3N_3O_7$	44.3	3.7	44.4	3.6
VI	—	—	—	—	—	—	—	—	112—113	$C_{13}H_{18}N_2O \cdot 2C_6H_3N_3O_7$	45.5	3.7	44.4	3.6



We have successfully used the reaction found for the synthesis of 3a,9-tetramethylenedinordeoxyeseroline (VIII), Compound VIII which forms the basis of the alkaloid echitamine, has been obtained previously by the Schmidt reaction from 4a-(2-carboxyethyl)-1,2,3,4-tetrahydro-4aH-carbazole and was named 1,2,3,4-tetrahydro-4a,9a-iminoethanocarbazole (echiboline) [7].

We synthesized the initial 2-(β-chloroethyl)cyclohexanone (VII) by a known method from the ethylene ketal of ethyl 2-oxocyclohexylacetate [8]. The other initial ketone – 5-chloro-3-methylpentan-2-one (I) – was obtained by the hydrochloric acid treatment of α-acetyl-α-methyl-γ-butyrolactone, which is formed in 82% yield by the action of methyl iodide on a solution of the sodium derivative of α-acetylbutyrolactone in dimethyl sulfoxide. This method of methylation raises the yield of acetylmethylbutyrolactone and shortens the time of the reaction in comparison with the previously-known methods of methylating acetylbutyrolactone [9, 10].



The opening of the acetylmethylbutyrolactone ring by boiling hydrochloric acid (1 : 1) gave the γ-chloroketone (I) containing the γ-keto alcohol, which could not be separated by distillation but was successfully removed by treatment with hot concentrated hydrochloric acid and subsequent distillation of the γ-chloro ketone with steam. The pure chloro ketone can be obtained in higher yield by adding acetylmethylbutyrolactone dropwise to boiling concentrated hydrochloric acid with simultaneous steam distillation.

EXPERIMENTAL

α-Acetyl-α-methyl-γ-butyrolactone. Some 2.3 g (0.1 mole) of metallic sodium was dissolved in 25 ml of absolute methanol, and 12.8 g (0.1 mole) of α-acetyl-γ-butyrolactone was added. After 30 min, the methanol was distilled off in vacuum at 60°C, the residue was dissolved in 20 ml of absolute dimethyl sulfoxide, and, with stirring, 21 g (0.15 mole) of methyl iodide was added to the solution in a flask fitted with a reflux condenser (the reaction is highly exothermic). The mixture was heated at 50°C for 1 hr, 100 ml of absolute benzene was added, and the sodium bromide was filtered off and carefully washed with benzene. The precipitate was dissolved in 30 ml of water and the lactone was extracted with benzene. The combined benzene solutions were distilled in vacuum. This gave 11.6 g (81.7%) of α-acetyl-α-methyl-γ-butyrolactone with bp 125-128°C (20 mm), n_D^{20} 1.4560. UV spectrum (the UV spectra here and below were taken on an EPS-3T instrument in ethanol.) λ_{max} 219 nm, log ε 2.33. IR spectrum (the IR spectra here and below were taken on a JASCO IR-S instrument in a thin layer with a NaCl prism.): $\nu_{C=O}$ 1710, 1768 cm^{-1}.

5-Chloro-3-methylpentan-2-one (I). a) Some 35.5 g (0.25 mole) of α-acetyl-α-methyl-γ-butyrolactone was added to a six-fold volume of boiling conc. HCl and the I formed was simultaneously steam-distilled off from the reaction flask. The distillate was neutralized with potassium carbonate and the oily layer was extracted with ether. The ethereal extract was dried with sodium sulfate, the ether was driven off, and the residue was distilled in vacuum. This gave 26.3 g (79%) of I, bp 87-88°C (38 mm), n_D^{20} 1.4384 [9], R_f 0.84 [on Al_2O_3 of activity grade II in the benzene-methanol (9 : 1) system]. IR spectrum: $\nu_{C=O}$ 1718 cm^{-1}.

b) Some 38 g of α-acetyl-α-methyl-γ-butyrolactone was slowly added to 130 ml of boiling HCl (1 : 1). The reaction mixture was cooled with ice and neutralized with potassium carbonate, and the I was extracted with ether. The ethereal extract was dried with magnesium sulfate, the ether was evaporated off, and the residue was distilled in vacuum. This gave 30 g (70.4%) of I with bp 78-80°C (37 mm), n_D^{20} 1.4390, containing 5-hydroxy-3-methylpentan-2-one (the IR spectrum showed ν_{OH} at 3450-3500 cm^{-1}). The substance obtained was treated with a fivefold volume of conc. HCl, the reaction mixture was heated to the boil, and the pure I was distilled off with steam. This gave 26 g of I, identical with that obtained by method (a).

3a,9a-Tetramethyldinordeoxyeseroline (VIII). Some 5.4 g (0.05 mole) of phenylhydrazine and 8 g (0.05 mole) of 2-(β-chloroethyl)cyclohexanone (VII) were dissolved in 100 ml of methanol, the solution was boiled for 8 hr, the methanol was distilled off in vacuum, the residue was dissolved in 100 ml of hot 0.1 N HCl, the neutral impurities were removed by extraction with ether, and the aqueous solution was saturated with solid caustic soda. The base that separated out was recrystallized from a mixture of benzene and petroleum ether (1 : 1). This gave 8.8 g (82.5%) of VIII with mp 124-125°C [7], R_f 0.77 [on "slow" paper of the Volodarskii mill in the n-BuOH-AcOH-H_2O (4 : 1 : 5) system, the spots being revealed with Ehrlich's reagent and with ninhydrin]. UV spectrum: λ_{max} 225, 240, 290 nm; log ε 3.77, 3.85, 3.36. Found %: C 78.1; H 8.4. $C_{14}H_{18}N_2$. Calculated %: C 78.4; H 8.5. Dipicrate of VIII, mp 190-191°C (decomp., from methanol). Found %: C 46.4; H 3.6. $C_{14}H_{18}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 46.4; H 3.6.

The other 9-methyldinordeoxyeserolines (II-VI, Tables 1 and 2) were obtained similarly. If, after alkalizing, the base separated in the form of an oil, it was extracted with benzene and the benzene extract was distilled in vacuum in a current of inert gas.

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