INDOLES

IX.* METHOD OF SYNTHESIZING DINORDEOXYESEROLINE SYSTEMS SUBSTITUTED ON THE INDOLINE NITROGEN ATOM†

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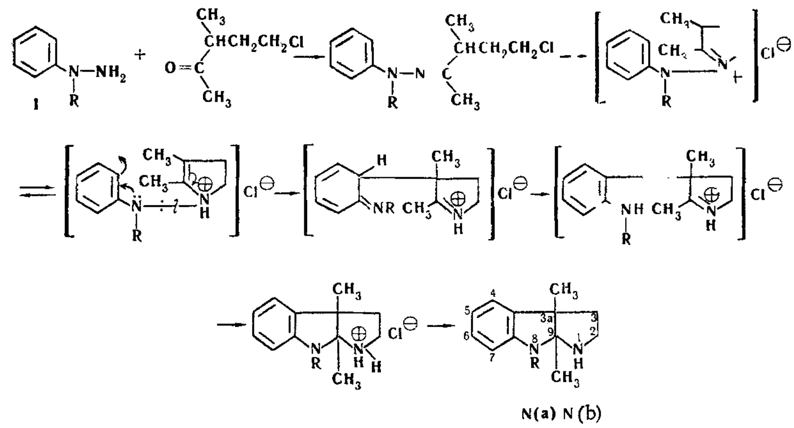
A new method is proposed for the synthesis of dinordeoxyeserolines and echibolines having alkyl substituents at the indoline nitrogen atoms. This method is based on the reaction of N_α-substituted arylhydrazines with γ-halogeno ketones having an α-methine group in neutral media.

In a previous paper [1], the synthesis of the tricyclic system of eserine by the condensation of arylhydrazines with γ-halogeno ketones having an α-methine group on boiling in a neutral alcoholic medium was described.

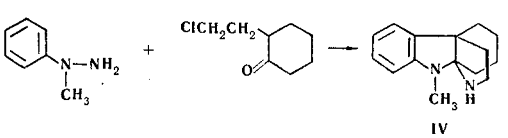
If an unsymmetrical N_α-substituted phenylhydrazine (I) is used in a similar reaction, the condensation product is a dinordeoxyeseroline system substituted at the indole nitrogen atom (II, III).



II $R=CH_3$; III $R=CH_2C_6H_5$

This reaction scheme is based on the partially proved mechanism of the synthesis of tryptamines [2] and on the Fischer synthesis of indoles [3].

The reaction of α-methylphenylhydrazine with 2-(β-chloroethyl)cyclohexanone yielded N(a)-methylechiboline (8-methyl-3a,9-tetramethylenedinordeoxyeseroline) (IV) [4].



IV

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*For Communication VIII, see [8].

† See USSR Patent No. 201,411 (1966).

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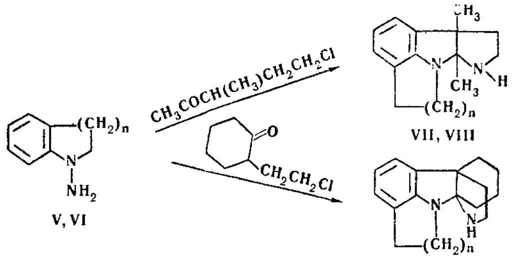
The condensation of 1-aminoindoline (V) and 1-amino-1,2,3,4-tetrahydroquinoline (VI) with 5-chloro-3-methylpentan-2-one gave good yields of the corresponding tetracyclic eseroline compounds VII and VIII. The analogous reaction of the arylhydrazines V and VI with 2-(β-chloroethyl)cyclohexanone leads to the formation of the pentacyclic echibolines IX and X.



V, VI

VII, VIII

IX, X

V, VII, IX $n=1$; VI, VIII, X $n=2$

The bases synthesized were purified by high-vacuum distillation, recrystallization from hexane, and high-vacuum sublimation. The purity of the substances obtained was checked by chromatography on paper and in a thin layer of alumina.

Compound II gives a normal monoacetyl derivative on boiling in the water bath with equimolar amounts of acetic anhydride and pyridine. The other bases synthesized undergo pronounced resinification under the action of acetic anhydride. With molar and bimolar amounts of picric acid, the N(a)-substituted bases give, respectively, red mono- and yellow dipicrates.

The UV spectra of the eseroline derivatives synthesized have two absorption maxima in 80% ethanol in the regions around 240 and 290 nm which are characteristic for the indoline absorption of the tricyclic structural basis of compounds of the eseroline and echiboline series [4,5].

The PMR spectra confirm the tricyclic eseroline structure for compounds II and VII.

EXPERIMENTAL

General Method for the Condensation of Halogeno Ketones with Arylhydrazines. A solution of 0.05 mole of an arylhydrazine and 0.05 mole of a halogeno ketone in 100 ml of methanol was boiled under reflux for 8 h. The methanol was distilled off from the reaction mixture in vacuum, the residue was dissolved in 100 ml of hot 0.1 N hydrochloric acid, and the neutral impurities were extracted with ether. The aqueous extract was boiled with 0.5 g of activated carbon for 5 min and was filtered. The filtrate was brought to pH 12 with caustic soda and the base that separated out was extracted with benzene. The benzene extract was distilled under reduced pressure in a current of inert gas. The picrates were obtained in absolute ether and were recrystallized from a small amount of methanol.

Compounds II-IV and VII-X were synthesized by this method.

9-Methylnordeoxyeseroline (II). Yield 57%, bp 124°C (3 mm); n_D^{20} 1.5690; d_4^{20} 1.0389; R_{f1} 0.60, R_{f2} 0.89, R_{f3} 0.69 *. UV spectrum†: λ_{max} 247, 299 nm, log ε 4.22, 3.63. PMR spectrum‡ (in CCl_4): 3a-CH_3 (1.15 s); 9-CH_3 (1.19 s); 8-CH_3 (2.67 s); 2-CH_2 (2.2-2.8 m); 3-CH_2 (1.4-1.9 m); NH (2.16 s); H_4 (6.77 d, $J_{4,5}$ = 8 Hz), H_5 (6.38 t, $J_{5,4,6}$ = 8 Hz); H_6 (6.81 t, $J_{6,5,7}$ = 8 Hz); H_7 (6.04 d, $j_{7,6}$ = 8 Hz). Found %: C 77.42, 77.47; H 9.00, 9.16. $C_{13}H_{18}N_2$. Calculated %: C 77.18; H 8.98. Monopicrate – red, mp 167-168°C. Found %: C 53.04, 53.08; H 4.88, 5.01. $C_{13}H_{18}N_2 \cdot C_6H_3N_3O_7$. Calculated %: C 52.90; H 4.91. Dipicrate – yellow, mp 190-191°C. Found %: C 45.20, 45.38; H 3.90, 3.95. $C_{13}H_{18}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 45.45; H 3.66. Monoacetyl derivative, mp 95-96°C (from hexane). R_{f_1} 0.69, UV spectrum: λ_{max} 255, 305, 355 nm, log ε

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*Here and below, R_{f1} is the chromatographic mobility in a thin layer of alumina (activity grade II) in the benzene–isopropanol (9 : 1) system, the spots being revealed with iodine vapor; R_{f2} and R_{f3} are the chromatographic mobilities on "slow" paper of the Volodarskii mill, the spots being revealed with ninhydrin; R_{f2} is the mobility in the n-butanol–pyridine–water (1 : 1 : 1) system; and R_{f3} is that in the n-butanol–acetic acid–water (4 : 1 : 5) system.

† The UV spectra here and below were recorded on an EPS-3T instrument (Hitachi) in 80% ethanol.

‡ The PMR spectra were taken on a JNM-4H-100 instrument with a working frequency of 100 MHz. The values of the chemical shifts in ppm on the δ scale relative to tetramethylsilane are given in parentheses; s–singlet, d – doublet, t–triplet, m–multiplet.

4.06, 3.48, 1.84. PMR spectrum (in $CDCl_3$): 3a-CH_3 (1.12 s), 9-CH_3 (1.72 s), CH_3CO (1.89 s), 8-CH_3 (3.01 s), 2-CH_3 (3.14-3.47 m), 3-CH_2 (1.92-2.42 m), H_4 (6.99 d, $J_{4,5}$ = 8 Hz), H_5 (6.62 t, $J_{5,4,6}$ = 8 Hz), H_6 (7.09 t, $J_{6,5,7}$ = 8 Hz), H_7 (6.34 d, $J_{7,6}$ = 8 Hz). Found %: C 73.61, 73.77; H 8.07, 8.16. $C_{15}H_{20}N_2O$. Calculated %: C 73.74; H 8.26.

8-Benzyl-9-methyldinordeoxyeseroline (III). Yield 54%, bp 165°C (1 mm); R_{f1} 0.69, R_{f2} 0.84, R_{f3} 0.86. UV spectrum: λ_{max} 247, 297 nm, log ε 4.09, 3.46. Found %: C 81.79, 81.91; H 7.61, 7.76. $C_{19}H_{22}N_2$. Calculated %: C 81.97; H 7.97. Dipicrate – yellow, mp 174°C. Found %: C 50.74, 50.84; H 3.77, 3.81. $C_{19}H_{22}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 50.54; H 3.69.

7,8-Dimethylene-9-methyldinordeoxyeseroline (VII). This was obtained from the hydrazine V [bp 109-110°C (11 mm); n_D^{20} 1.5917 [6]]. Yield 52%, bp 124-125°C (1 mm); mp 54-56°C; R_{f1} 0.68, R_{f2} 0.84, R_{f3} 0.82. UV spectrum: λ_{max} 244, 291 nm, log ε 3.83, 3.33. PMR spectrum ($CD_3OD:D_2O$, 4:1): 3a-CH_3 (1.52 s), 9-CH_3 (1.83 s), 3-CH_3 (1.95-2.50 m), 2-CH_2 (2.75-3.30 m), 8-CH_2 (3.33-3.67 m), 7-CH_2 (3.91, broad peak), H_5 (6.80 t, $J_{5,4,6}$ = 8 Hz), H_4 (6.87 d, $J_{4,5}$ = 8 Hz), H_6 (6.78 d, $J_{6,5}$ = 8 Hz), H exchanged (4.86 s). Found %: C 78.31, 78.43; H 8.33, 8.37. $C_{14}H_{18}N_2$. Calculated %: C 78.46; H 8.47. Dipicrate – yellow, mp 168-169°C. Found %: C 46.42, 46.53; H 3.53, 3.70. $C_{14}H_{18}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 46.43; H 3.59.

9-Methyl-7,8-trimethylenedinordeoxyeseroline (VIII). This was obtained from the hydrazine VI [bp 141-143°C (10 nm); mp 54-55°C [7]]. Yield 60%, bp 127-128°C (1 mm); R_{f1} 0.69, R_{f2} 0.86, R_{f3} 0.78. UV spectrum: λ_{max} 254, 317 nm, log ε 3.85, 3.36. Found %: C 78.78, 78.88; H 9.00, 9.09. $C_{15}H_{20}N_2$. Calculated %: C 78.89; H 8.84. Dipicrate – yellow, mp 211-212°C. Found %: C 47.18, 47.24; H 3.84, 3.88. $C_{15}H_{20}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 47.23; H 3.82.

7,8-Dimethylene-3a,9-tetramethylenedinordeoxyeseroline (7,8-dimethyleneechiboline) (IX). Yield 61%, bp 136-138°C (1 mm), mp 107-109°C; R_{f1} 0.69, R_{f2} 0.84, R_{f3} 0.82. UV spectrum: λ_{max} 246, 293 nm, log ε 3.83, 3.48. Found %: C 69.68, 79.82; H 8.36, 8.43. $C_{16}H_{20}N_2$. Calculated %: C 79.96; H 8.39. Dipicrate – yellow, mp 188°C. Found %: C 48.12, 48.26; H 3.70, 3.82. $C_{16}H_{20}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 48.15; H 3.75.

3a,9-Tetramethylene-7,8-trimethylenedinordeoxyeseroline (7,8-trimethyleneechiboline) (X). Yield 70%, bp 142-146°C (1 mm); mp 46-48°C; R_{f1} 0.63, R_{f2} 0.80, R_{f3} 0.82. UV spectrum: λ_{max} 249, 303 nm, log ε 3.77, 2.28. Found %: C 79.91, 80.11; H 8.42, 8.53. $C_{17}H_{22}N_2$. Calculated %: C 80.27; H 8.72. Dipicrate – yellow, mp 194-195°C. Found %: C 48.90, 49.02; H 4.03, 4.18. $C_{17}H_{22}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 48.88; H 3.97.

3a,9-Tetramethylenenordeoxyeseroline (8-methylechiboline) (IV) [4]. Yield 50%, bp 123-125°C (1 mm); R_{f1} 0.68. UV spectrum (in 50% ethanol): λ_{max} 246, 293 nm, log ε 3.32, 3.38. Found %: C 78.70, 78.83; H 8.90, 8.96. $C_{15}H_{20}N_2$. Calculated %: C 78.89; H 8.84. Dipicrate – yellow, mp 187-188°C. Found %: C 47.27, 47.36; H 4.05, 4.06. $C_{15}H_{20}N_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 47.23; H 3.83.

LITERATURE CITED

1. I. I. Grandberg and T. A. Ivanova, KhGS [Chemistry of Heterocyclic Compounds], 6, 480 (1970).
2. I. I. Grandberg, N. M. Przheval'skii, V. N. Vysotskii, and R. A. Khmel'nitskii, KhGS [Chemistry of Heterocyclic Compounds], 6, 477 (1970).
3. B. Robinson, Chem. Rev., 63, 373 (1963).
4. H. Fritz and P. Losacher, Ann., 709, 135 (1967).
5. A. Jackson and A. Smith, J. Chem. Soc., 1964, 5510.
6. A. N. Kost, L. G. Yudin, Yu. A. Berlin, and A. P. Terent'ev, ZhOKh, 29, 3820 (1959).
7. A. N. Kost, L. G. Yudin, and A. P. Terent'ev, ZhOKh, 29, 1949 (1959).
8. I. I. Grandberg, T. I. Zuyanova, N. M. Przheval'skii, and V. I. Minkin, KhGS [Chemistry of Heterocyclic Compounds], 6, 753 (1970).