SYNTHETIC RESEARCHES IN THE FIELD OF CURARE ALKALOIDS

XVIII. Synthesis of the Methiodide of 1,3,4-(1'Hydroxy-3'-Methyl-4'-Ethylidene-pentane-1', 3', b, 5'-Triyl)-3, 4, 5, 6-Tetrahydro-β-Carboline*

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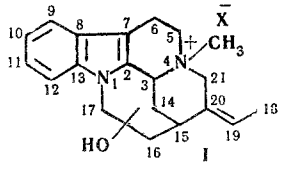
The methiodide of 1,3,4-(1'-hydroxy-3'-methyl-4'-ethylidenepentan-1', 3', b, 5'-triyl]-3,4, 5, 6-tetrahydro-δ-carboline is synthesized.

Mavacurine is a monoquaternary alkaloid of gourd curare. It was first isolated by T. Wieland from the plant Strichnos toxifera [2]. From the study of its transformation products, and from spectroscopic data, it was assigned structure I, where the position of the hydroxyl remains unknown. [3–6]. Though mavacurine itself has no appreciable curare activity, its synthesis is undoubtedly of interest, since it occurs in close natural conjunction with bisquaternary alkaloids of considerable activity.



We have synthesized compound XV by the route shown in Figure 1.

Glutaconic esters (II, R= CH_3, C_2H_5) were converted by condensation with acetoacetic ester III into esters of β-(α'-ethoxycarbonylacetonyl)glutaric acid (IV, R= CH_3, C_2H_5). Catalytic reduction of the latter (IV, R= CH_3) gave a mixture of isomeric carbinols, which distillation converted to methyl β-methoxycarbonylmethyl-γ-ethoxycarbonyl-$\Delta^{\gamma-\delta}$-caproate (V) and β-methoxycarbonyl-methyl-γ-ethoxycarbonyl-δ-valerolactone (VI). Hydroxymethyl derivatives (VII, R=Me, Et) obtained by the action of formaldehyde on the triester IV, in alkaline solution, were submitted to acid hydrolysis (10% hydrochloric acid), when they gave β-carboxymethyl-γ-acetyl-δ-valerolactone (VIII, R=H). Treatment of the lactone VIII (R=H) in ethanol solution with hydrogen bromide gave the bromoesters IX (R=Me, Et), which on distillation split off alkyl halide to give lactone VIII (R=Me). Chromatography on alumina led to the isolation of, in addition to lactone VIII (R=Et) the dehydrobromination product X. γ-Carbaloxymethyl-δ-acetyl-N-[β'-(3-indolylethyl)]-α-piperidone (XI, R= CH_3, C_2H_5) is obtained by condensing tryptamine with bromoester X (R= CH_3, C_2H_5), or with diethyl β-(α'-acetylvinyl)glutarate X. The corresponding acid XI (R=H) was synthesized from the triester IV (R=Me), by reacting it with tryptamine, followed by saponification of the resultant Schiff's base XII.

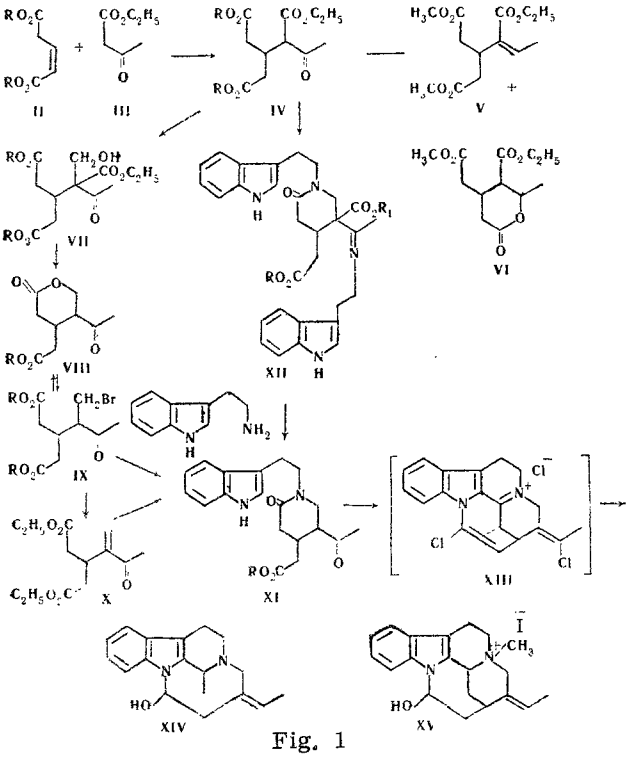


Fig. 1

Cyclization to the pentacyclic system XIII, with simultaneous replacement of the carbonyl by chlorine, was effected by treatment with phosphorus pentachloride in chloroform. The resultant compound XIII is very labile, and readily undergoes oxidation because of the presence of three additional double bonds in the polycyclic molecule. Here, after reduction it is possible to isolate only oxidized products. Reduction of the trichloride XII with zinc in acetic acid, followed by treatment of tertiary base XIV with methyl iodide gives the methiodide XV, whose composition corresponds to that of mavacurine iodide.

EXPERIMENTAL

Dimethyl β-(α'-ethoxycarbonylacetonyl)glutarate (IV, R= CH_3). A solution of NaOMe was prepared from 1.3 g Na in 50 ml MeOH, stirred and held at 20°, while 43.0 g acetoacetic ester was added, the mixture left for 15 min, and then 50.0 g dimethyl glutaconate added. The whole was stirred and refluxed for 6 hr. The alcohol was vacuum-distilled off, and after cooling the residue poured into 200 ml water, and the oily

*For part XVIII see [1].

material which separated was extracted with ether. (240 ml). The extract was dried over Na_2SO_4, the solvent evaporated off, and the residue vacuum-distilled. Yield 45.2 g (55.2%), bp 122–124° (0.28 mm), 136–138° (0.46 mm), d_4^{20} 1.1727, n_D^{20} 1.4598, MR_D 67.20. Calculated 67.21. Found: C 54.53; H 6.71%. Calculated for $C_{13}H_{20}O_7$: C 54.15; H 6.94%.

Diethyl β-(α'-ethoxycarbonylacetonyl)glutarate (IV, R=C_2H_5). Prepared similarly, yield 48.4%, bp 122–124° (0.26 mm), 126–128° (0.3 mm), d_4^{20} 1.1140, n_D^{20} 1.4521, MR_D 76.06, Calculated 76.44.

Methyl β-methoxycarbonylmethyl-γ-ethoxycarbonyl-$\Delta^{\gamma-\delta}$ carboxylate (V) and β-methoxycarbonylmethyl-γ-ethoxycarbonyl-δ-caprolactone (VI). 3 g Raney Ni was added to a solution of 13.2 g compound IV (R=Me) in 25 ml MeOH. Hydrogenation was run at 18–20°, at atmospheric pressure, and for 48 hr. The catalyst was separated off, the solvent vacuum-distilled off, and the residue distilled. Two cuts were taken: 1) methyl β-methoxycarbonylmethyl-γ-ethoxycarbonyl-$\Delta^{\gamma-\delta}$-caproate (V), yield 2.1 g (16.5%), 124–125° (0.15 mm), d_4^{20} 1.1763, n_D^{20} 1.4542, MR_D 64.38. Calculated 64.89; 2) β-methoxycarbonylmethyl-γ-ethoxycarbonyl-δ-caprolactone (VI), yield 4.3 g (34.4%), bp 132–133° (0.17 mm), d_4^{20} 1.1352, n_D^{20} 1.4569, MR_D 52.83. Calculated 53.28. Found: C 55.51; H 6.55%. Calculated for $C_{12}H_{18}O_6$ C 55.81; H 6.97%.

Dimethyl β-(α'-ethoxycarbonyl-α'-hydroxymethylacetonyl)glutarate (VIII, R=CH_3). 10 ml 40% aqueous formaldehyde, previously neutralized with 0.4 ml 0.1 N NaOH, was added over a period of 5 min, to 30.5 g dimethyl β-(α'-ethoxycarbonylacetonyl)glutarate in 52 ml MeOH. In addition 1 ml 0.1 N NaOH was added as catalyst, and stirring continued for 4 hr at 20°. The resultant solution was concentrated under vacuum to half volume, the residue poured into 100 ml glacial AcOH, and the oily material which separated out was extracted with ether (150 ml). After drying over Na_2SO_4 the solvent was removed, and the residue vacuum-distilled, to give 18.2 g (54.2%) product, bp 138–140° (0.4 mm), d_4^{20} 1.1788, n_D^{20} 1.4576, MR_D 73.53. Calculated 73.37. Found: C 52.68; 52.64; H 6.75; 6.60%. Calculated for $C_{14}H_{22}O_8$: C 52.83; H 6.92%.

Diethyl β-(α'-ethoxycarbonyl-α'-hydroxymethylacetonyl)glutarate (VIII, R=C_2H_5). Prepared similarly to the above. Yield 42.1%, bp 141–142° (0.3 mm), d_4^{20} 1.272, n_D^{20} 1.4560, MR_D 82.92. Calculated 82.63.

β-Carboxymethyl-γ-acetyl-δ-valerolactone (VIII, R=H). 18.2 g diethyl β-(α'-ethoxycarbonyl-α'-hydroxymethylacetonyl)glutarate was saponified with 165 ml 10% HCl (6 hr refluxing and stirring). The HCl was vacuum-distilled off, and the residue distilled, to give 7.1 g of the required product (62.2%). Bp 170–176° (0.26 mm), d_4^{20} 1.2200, n_D^{20} 1.4582, MR_D 44.21. Calculated 44.20. Found: C 54.26; H 6.44%. Calculated for $C_9H_{12}O_5$: C 54.10; H 6.00%.

2,4-Dinitrophenylhydrazone, mp 176.5–178° (ex water + iso-PrOH 1:1). Found: C 47.69; H 3.90; N 14.76; 14.77%. Calculated for $C_{15}H_{16}N_4O_8$: C 47.37; H 4.21; N 14.73%.

When a liquid specimen of VIII (R=H) was allowed to stand with MeOH, it crystallized, mp 88–90° (ex MeOH). Found: C 54.01; H 6.02%. Calculated for $C_9H_{12}O_5$: C 54.10 H 6.00%.

Dimethyl β-(α'-bromomethylacetonyl)glutarate (IX, R=CH_3). 2.7 g β-carboxymethyl-γ-acetyl-δ-valerolactone in 30 ml dry MeOH was cooled to 0° and saturated with dry HBr gas. Then the mixture was left for 12 hr at 20°. The MeOH was vacuum-distilled off, the residue poured into 40 ml water, and the material extracted with ether (100 ml). The extract was washed with 10% Na_2CO_3 (2 × 20 ml), and water (20 ml), then dried over Na_2SO_4, and the solvent vacuum-distilled off. Yield of bromoester 3.1 g (74.1%), d_4^{20} 1.3687, n_D^{20} 1.4746, MR_D 63.41. Calculated 63.98.

Vacuum-distillation caused a molecule of MeBr to split off, to give β-methoxycarbonyl-γ-acetyl-δ-valerolactone (VIII, R=Me). Yield 26.6%, bp 110.5–112.5° (0.15 mm), d_4^{20} 1.1750, n_D^{20} 1.4535; MR_D 49.2. Calculated 49.76. Found: C 56.21; 56.14; H 6.55; 6.79%. Calculated for $C_{10}H_{14}O_5$: C 56.07; H 6.54%.

Diethyl β-(α'-acetylvinyl)glutarate (X). Bromoester IX (R=Et) was prepared by saturating lactone VIII (R=H) in EtOH solution with HBr, and 23.6 g was chromatographed on an alumina of activity II. Elution with ether + petrol ether (1:5) gave diethyl β-(α'-acetylvinyl)glutarate, yield 7.4 g (30.2%), bp 105–106° (0.21 mm), d_4^{20} 1.1501, n_D^{20} 1.4799, MR_D 63.3. Calculated 63.35. Found: C 60.93; H 7.63%. Calculated for $C_{13}H_{20}O_5$: C 60.94; H 7.82%.

The ether eluate gave β-ethoxycarbonylmethyl-γ-acetyl-δ-valerolactone, yield 0.5 g (2.13%), bp 100–104° (0.08 mm), d_4^{20} 1.0821, n_D^{20} 1.4799, MR_D 54.5. Calculated 54.2. Found: C 58.01; H 7.40%. Calculated for $C_{11}H_{16}O_5$: C 57.9; H 7.02%.

γ-Methoxycarbonylmethyl-δ-acetyl-N-[β'-(3-indolylethyl)]-α-piperidone (XI, R=CH_3). 1.1 g tryptamine in 30 ml MeOH was boiled for 1 hr with 0.92 compound IX, and a few crystals of KI, then 0.21 g $NaHCO_3$ added, and the whole boiled for 5 hr. The products were cooled, the precipitate separated off, the filtrate concentrated under vacuum, the residue dissolved in 30 ml $CHCl_3$, and the extract washed with 15 ml N HCl, then with 20 ml water, and the solvent removed. The residue was triturated with 50 ml dry ether, and vacuum-dried. To purify the material (0.36 g), it was dissolved in $CHCl_3$ (30 ml), and chromatographed on an alumina column (10 × 40 mm). The eluant was $CHCl_3$. After removing the $CHCl_3$ under vacuum, the residue was dissolved in dry acetone, left to stand for 12 hr, filtered, the solvent distilled off, and the residue triturated with ether (40 ml). Yield 0.30 g (28.1%), mp 80–85° (decomp). Found: C 67.31; H 6.75; N 7.87; 7.99%. Calculated for $C_{20}H_{24}N_2O_4$: C 67.41; H 6.74; N 7.86%.

γ-Methoxycarbonylmethyl-δ-acetyl-N-[β'-(3-indolylethyl)]-α-piperidone (XI, R=CH_3). 2.45 g was mixed with 1.53 g tryptamine and 100 ml EtOH,

and the mixture refluxed for 5 hr in a stream of N. The EtOH was vacuum-distilled off, the residue dissolved in 60 ml $CHCl_3$, and washed with 30 ml 0.1 N HCl, then with 50 ml water. The solvent was removed, the residue triturated with ether (6 × 10 ml), then vacuum-dried. For purification, 0.1 g of the compound was dissolved in 15 ml $CHCl_3$ and chromatographed on a column of alumina of activity IV (10 × × 40 mm). $CHCl_3$ was the eluent. After removing the solvent the residue was treated with 10 ml dry acetone, filtered, and the solvent distilled off, after which the residue was triturated with ether (4 × 10 ml), and vacuum-dried, yield 0.07 g (1.99%), mp 49–51°. Found: C 68.02; H 6.73; N 7.49; 7.69%. Calculated for $C_{21}H_{26}N_2O_4$: C 68.1; H 7.03; N 7.56%.

γ-Methoxycarbonylmethyl-δ-ethoxycarbonyl-δ-[α'-(tryptimino)ethyl]-N-[β''-(3-indolylethyl)]-α-piperidone (XII, R = CH_3, R_1 = C_2H_5). 5.0 g tryptamine was dissolved in 70 ml MeOH, and the solution stirred, while 3 ml 33% aqueous formaldehyde solution was added, followed by 9.0 g compound IV (R=Me) in 50 ml 50% aqueous MeOH, after which stirring was continued for 4 hr longer, at 20°. Then the mixture was refluxed for 2 hr, the solvent distilled off, the residue triturated with 20 ml MeOH, and chromatographed on an activity IV alumina column (20 × × 60 mm). The eluate was concentrated, the residue triturated with ether (20 ml) and dried, yield 3.2 g (37.4%), mp 132–135°. Found: N 9.65%. Calculated for $C_{33}H_{38}N_4O_5$: N 9.80%.

The corresponding acid XII (R = R_1 = H) was prepared similarly from tryptamine, formaldehyde, and β-(α'-carboxyacetonyl)glutaric acid, yield 28.2%, mp 148–150°. Found: C 68.25; H 6.10; N 10.50%. Calculated for $C_{30}H_{32}N_4O_5$: C 68.16; H 6.06; N 10.67%.

γ-Carboxymethyl-δ-acetyl-N-[β'-(3-indolylethyl)]-α-piperidone (XI, R = H). 3.2 g compound XII (R = CH_3, R_1 = C_2H_5) was saponified with 25 ml MeOH and 25 ml 10% HCl (6 hr at 70°). The MeOH and HCl were vacuum-distilled off, the residue triturated with 10% HCl (50 ml), then dissolved in 3% NaOH, filtered, and precipitate was separated off and dried, yield 0.7 g (36.8%), did not melt up to 360° (ex EtOH). Found: C 66.45; H 6.12; N 8.11; 8.30%. Calculated for $C_{19}H_{22}N_2O_4$: C 66.67; H 6.43; N 8.18%.

Methiodide of 1,3,4-(1'-hydroxy-3'-methyl-4'-ethylidenepentane-1',3', b,5'-triyl)-3,4,5,6-tetrahydro-β-carboline (XV). 1.0 g compound XI (R=Me) was dissolved in 25 ml $CHCl_3$, cooled to -5°, and under N_2 2.5 g PCl_5 added, after which the mixture was allowed to stand for 24 hr at 18–20°, 20 ml ether added, the precipitate washed with ether (25 ml) by decantation, then dried in a vacuum-desiccator. Yield 0.64 g (55%), mp 146–156°. 635 mg compound XIII prepared was dissolved in 20 ml glacial AcOH, 10 ml water added, followed by 2 g Zn dust, and the whole refluxed for 2 hr in a current of N_2. The unreacted Zn was filtered off, the filtrate neutralized with ammonia (30 ml), and the compound extracted with $CHCl_3$ (350 ml). The extract was washed with water (50 ml), then concentrated under vacuum, yield 333 mg (85%), mp 196–199°. For purification, a $CHCl_3$ solution of 48 mg base was chromatographed on an alumina column (10 × 60 mm). 2 cuts were taken: 1) material eluted with $CHCl_3$, hydrochloride, yield 16 mg (33.3%), mp 185–190°. Found: N 8.82%. Calculated for $C_{19}H_{22}N_2O \cdot HCl$: N 8.78%; 2) material eluted with MeOH. Hydrochloride, yield 12.8 mg (24.2%), mp 212–215° (decomp). Found: N 7.44; Cl 10.16%. Calculated for $C_{19}H_{22}N_2O \cdot HCl \cdot 2H_2O$: N 7.63; Cl 9.84%.

A solution of 230 mg base XIV (ex hydrochloride mp 212–215°) in 30 ml MeOH, was heated for 4 hr, under reflux, with 1.5 ml MeI, the solvent taken off, the residue rubbed with ether (20 ml), and vacuum-dried. Yield 153 mg, material mp 136–148°. For purifications 60 mg was chromatographed on alumina (10 × 135 mm), and the cut collected which was eluted with acetone and MeOH (3:1). The solvent was distilled off, the residue rubbed with dry ether (20 ml), yield 28.2 mg (48.6%), mp 137–140°. Found: C 55.22; H 5.73; N 6.60%. Calculated for $C_{20}H_{25}IN_2O$: C 55.04; H 5.70; N 6.42%.

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