INDOLE DERIVATIVES

XXIII. Reduction of some Polyalkylated Tetrahydro-γ-Carbolines

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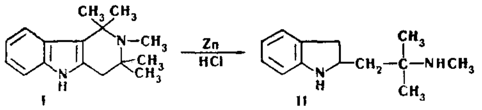
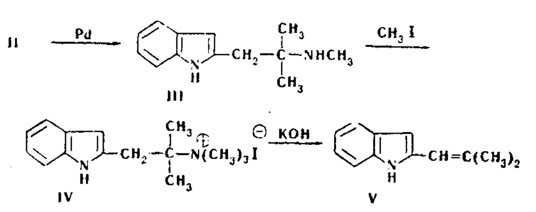
Reduction of 2, 2, 4-trimethyl-, 2, 2, 4, 4, 6-pentamethyl-, and 2, 2, 4, 4, 9-pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline gives 1, 2, 3, 4, 4*a*, 9*a*-hexahydro-γ-carbolines, along with products of destructive hydrogenation. The sole reduction product of 2, 2, 3, 4, 4-pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline is 2-(β-methylaminoisobutyl)indoline.

In a study of the reduction of 2, 2, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydro-γ-carboline the present authors previously showed [1] that the reaction mainly involves splitting of the piperidine ring to give an indoline belonging to the class of 2, 3-dihydro-α-tryptamines. Since this new reductive degradation of polyalkylated tetrahydro-α-carboline is interesting synthetically, it was decided to investigate the reduction of a series of other polyalkylated tetrahydro-γ-carbolines with substituents at the indole and piperidine nitrogen atoms, and having different degrees of branching at position 4, to ascertain the effects of structural factors on the direction of reduction.

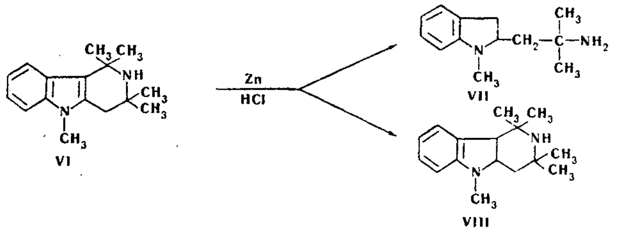
Alkylation of 2, 2, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydro-γ-carboline with methyl iodide in isopropanol gave 2, 2, 3, 4, 4-pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline (I). The latter was reduced with zinc dust in hydrochloric acid-ethanol containing mercuric chloride.



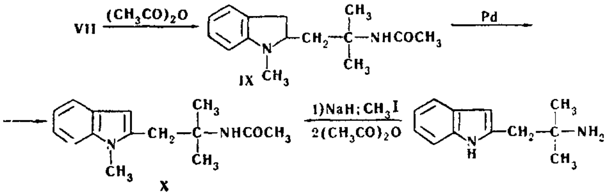
Vacuum distillation of the oily reaction product gave only one substance bp 110°–114° C (1 mm). That it was 2-(β-methylaminoisobutyl)indoline (II) (yield approximately 65%), was shown by dehydrogenation over palladium black converting it to 2-(β-methylaminoisobutyl)indole (III), which was converted by exhaustive methylation to 2-(β-dimethylaminoisobutyl)indole methiodide (IV). Hofmann degradation of IV gave 2-isobutenylindole (V),



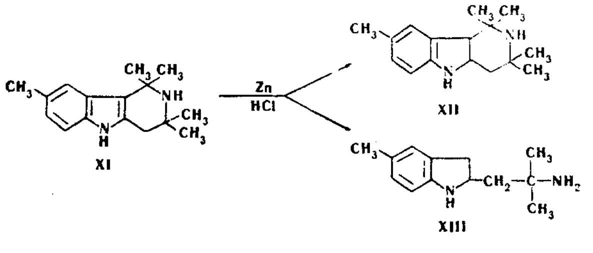
whose melting point and R_f for TLC on alumina were identical with those of a known specimen previously prepared [1]. Another starting compound, 2, 2, 4, 4, 9-pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline (VI), was obtained by Fischer cyclization of 2, 2, 6, 6-tetramethylpiperid-4-one with N-methylphenylhydrazine [2], and also by methylating the sodio derivative of 2, 2, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydro-γ-carboline, prepared using sodium hydride in dimethylformamide. Reaction of VI under the same conditions gave an oily product consisting of 1-methyl-2-(β-aminoisobutyl)indoline (VII), and 2, 2, 4, 4, 9-pentamethyl-1, 2, 3, 4, 4*a*, 9*a*-hexahydro-γ-carboline (VIII). After treatment of this mixture with acetic anhydride the resultant 1-methyl-2-(β-acetylaminoisobutyl)-indoline (IX) (22%) was separated from VIII (45%).



The structure of compound VIII was proven by dehydrogenating it over palladium black to the starting compound VI. The structure of IX, and hence that of indole VII, was proved by dehydrogenating IX to 1-methyl-2-(β-acetylaminoisobutyl)indole (X), identical with a specimen obtained by methylating the known compound 2-(β-aminoisobutyl)indole [1], then acetylating in the way previously described [1].

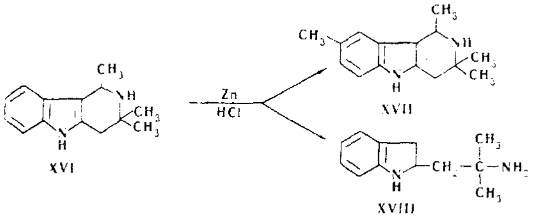


Reduction of 2, 2, 4, 4, 6-pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline (XI) gave an oil, which on chromatographing on alumina gave 2, 2, 4, 4, 6-pentamethyl-1, 2, 3, 4, 4*a*, 9*a*-hexahydro-γ-carboline (XII) in 17% yield, readily dehydrogenated to XI and to a 64% yield of 2-(β-aminoisobutyl)-5-methylindoline (XIII).



Acylation of XIII under ordinary conditions gave 1-acetyl-2-(β-acetylaminoisobutyl)-5-methylindoline (XIV). XIII is smoothly dehydrogenated over palladium black to give 2-(β-aminoisobutyl)-5-methylindole (XV).

Study of the reduction of 2,2,4-trimethyl-1,2,3,4-tetrahydro-γ-carboline (XVI) [1], less branched at position 4, revealed formation of 34% of the corresponding hexahydro derivative (XVII) and 45% of 2-(β-aminoisobutyl)indoline (XVIII), characterized as its diacetyl derivative (XIX). The latter was identical with the product previously obtained [1] by reductive degradation of 2, 2, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydro-γ-carboline.



EXPERIMENTAL

2, 2, 3, 4, 4-Pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline (I). 3 g (0.013 mole) 2, 2, 4, 4-Tetramethyl-1, 2, 3, 4-tetrahydro-γ-carboline [1], 10 ml MeI, and 10 ml PrOH were mixed and held at ~20° C for 48 hr. The precipitate was filtered off, dissolved in hot water, and made alkaline with K_2CO_3. The solid was filtered off, washed with water, and recrystallized from EtOH. Yield 8.9 g (84%) compound I, mp 174°–176° C. Found: C 79.21; 79.43; H 9.23; 9.22; N 11.62; 11.69%, calculated for $C_{16}H_{22}N_2$: C 79.28; H 9.15; N 11.56%.

2-(β-Methylaminoisobutyl)indoline (II) hydrochloride. 25.4 g (0.1 mole) I was reduced with 172 g Zn dust (added in portions) and 550 ml conc HCl plus 33 ml EtOH, in the presence of 0.2 g $HgCl_2$, with stirring and refluxing for 10 hr. Then the products were made alkaline with 40% NaOH solution until the zinc hydroxide dissolved. The oil was extracted with ether, dried over $MgSO_4$, the ether distilled off, and the residue vacuum distilled to give 14 g II bp 110°–114° C (1 mm). 19 g (65%) hydrochloride of compound II was obtained by dissolving the cut in ether, and adding ethereal hydrogen chloride, mp 256°–258° C. Found: N 10.30; 10.17; Cl 25.53; 25.48%, calculated for $C_{13}H_{22}N_2 \cdot 2HCl$: N 10.15; Cl 25.57%.

2-(β-Methylaminoisobutyl)indole (III). 3 g (0.016 mole) Indoline base II in 10 ml xylene was refluxed for 5 hr with 0.3 g Pd black. Yield 2.7 g (90%), mp 109°–110° C (ex heptane). Found: C 77.25; 77.47; H 8.97; 9.10; N 13.95; 14.11%, calculated from $C_{13}H_{18}N_2$; C 77.07; H 8.97; N 13.85%.

Hydrochloride. Mp 181°–182° C. Found: N 11.58; 11.69; Cl 14.54; 14.44%, calculated for $C_{13}H_{18}N_2 \cdot HCl$: N 11.54; Cl 14.60%.

2-(β-Dimethylaminoisobutyl)indole methiodide (IV). 0.25 g (1.3 mM) III, 0.5 g K_2CO_3, 0.75 g MeI, and 10 ml acetone were refluxed together for 2 hr. The acetone was distilled off, and the residue recrystallized from water. Yield 0.35 g IV, mp 191°–192° C, agreeing with the value given in the literature [1].

2-Isobutenylindole (V). 0.35 g (1 mM) Methiodide IV in 17 ml MeOH containing 1.2 g KOH, was heated for 3 hr at 60° C under N. The MeOH was distilled off, the residue poured into water, the precipitate filtered off, and washed with water, to give 0.13 g (76%) of V, mp 102°–103° C, [1] (ex petrol ether). Found: C 84.27; H 7.86; N 8.25%, calculated for $C_{12}H_{13}N$: C 84.17; H 7.65; N 8.18%.

2, 2, 4, 4, 9-Pentamethyl-1, 2, 3, 4-tetrahydro-α-carboline (VI). a) A mixture of 60 g (0.38 mole) 2, 2, 6, 6-tetramethylpiperid-4-one and 68 g N-methylphenylhydrazine in 300 ml 15% ethanolic HCl was refluxed for 1 hr, and the products left overnight. The precipitate was filtered off, dissolved in hot water, and made alkaline with K_2CO_3, when 0.9 g (43%) compound VI was obtained, mp 92°–93° C (ex n-heptane). The literature [2] gives 92°–93° C.

b) 45 g 2, 2, 4, 4-tetramethyl-1, 2, 3, 4-tetrahydro-γ-carboline dissolved in 100 ml dimethylformamide was added dropwise to a suspension of 7 g Na hydride in 50 ml dimethylformamide, the whole then stirred at room temperature for 1 hr, and 30 g MeI added dropwise. The products were kept for about 16 hr, then poured into water. The precipitate was filtered off, washed with hot water, dissolved in ether, and the solution dried over $MgSO_4$. The ether was distilled off, and the residue recrystallized from n-heptane. Yield 25 g (52%) VI, mp 92°–93° C.

1-Methyl-2-(β-acetylaminoisobutyl)indoline (IX) and 2, 2, 4, 4, 9-pentamethyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (VIII). 24 g (0.1 mole) VI was reduced with 180 g Zn dust in 640 ml conc HCl plus 100 ml water containing 0.2 g $HgCl_2$, as described above, and the products worked up in the usual way to give 17.7 g oil. 3 g of this and 4 ml Ac_2O were heated together on a steam bath for 30 min, the products poured into water, and extracted with ether. The ether was distilled off, and the residue crystallized, yield of IX 0.75 g (22%), mp 113°–114° C (ex n-heptane). Found: C 73.16; 73.38; H 8.88; 8.95; N 11.09; 11.26%, calculated for $C_{15}H_{22}N_2O$: C 73.13; H 9.00; N 11.36%. The aqueous solution was made alkaline with K_2CO_3 and extracted with ether, the ether solution dried over $MgSO_4$, removal of the ether gave 1.8 g (45%) compound VIII, as an oil which gradually crystallized, mp 44°–46° C (ex petrol ether). Found: C 78.79; 78.80; H 9.94; 9.70; N 11.45; 11.58%, calculated for $C_{16}H_{24}N_2$: C 78.63; H 9.89; N 11.46%.

Hydrochloride, mp 277°–278° C. Found: C 68.25; 68.22; H 8.80; 8.96; Cl 12.72; 12.51%, calculated for $C_{16}H_{24}N_2 \cdot HCl$: C 68.43; H 8.97; Cl 12.63%.

1-Methyl-2-(β-acetylaminoisobutyl)indole (X). a) Refluxing 0.7 g (2.8 mM) compound IX with Pd black in xylene for 2-1/2 hr, as described above, gave 0.6 g (85.7%) indole X, mp 122°–123° C (ex heptane). Found: C 73.86; 73.94; H 8.30; 8.34; N 11.32; 11.52%, calculated for $C_{15}H_{20}N_2O$: C 73.73; H 8.25; N 11.46%.

b) A solution of 2.5 g (0.013 mole) 2-(β-aminoisobutyl)indole I in 8 ml dimethylformamide was added to a stirred suspension of 0.45 g Na hydride in 4 ml dimethylformamide, the whole then stirred for 1 hr, after which 1.9 g MeI was added dropwise, and the mixture left overnight. The reaction products were poured into water, the oil extracted with ether and dried over $MgSO_4$. After distilling off the ether n-heptane was added to the residue, the precipitate (0.6 g) of starting material filtered off, the heptane distilled off, 4 ml Ac_2O was added to the residue, and the whole refluxed for 2 hr. The products were poured into water, and the precipitate filtered off. After 3 recrystallizations from n-heptane compound X had mp 122°–123° C, mass 1 g (31%).

2, 2, 4, 4, 6-Pentamethyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XII) and 2-(β-aminoisobutyl)-5-methylindoline (XIII). 28 g (0.11 mole) 2, 2, 4, 4, 6-Pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline [3] (XI) was reduced with 223 g Zn dust and 800 ml HCl in the presence of 0.3 g $HgCl_2$ in 100 ml water, as described above. 20 g oil was obtained, which was column chromatographed on alumina activity grade IV. 0.8 *l* petrol ether (bp 40°–60° C) was used for elution. Removal of the solvent by distillation gave 3.5 g (17%) compound XII, bp 134°–135° C (1.5 mm), n_D^{20} 1.5465. Found: C 78.48; 78.71; H 9.80; 10.00%, calculated for $C_{16}H_{24}N_2$: C 78.63; H 9.89%.

The residue in the column was eluted with 1 *l* ether, and removal of the ether left 16 g (64%) compound XIII as an oil, which crystallized on cooling, mp 32°–34° C (ex petrol ether). Found: C 76.10; H 9.73; N 13.71; 13.51%, calculated for $C_{13}H_{20}N_2$, C 76.42; H 9.86; N 13.71%.

Dihydrochloride, mp 206°–207° C. Found: C 56.39; 56.24; H 7.80; 7.86; Cl 25.00; 25.06%, calculated for $C_{13}H_{20}N_2 \cdot 2HCl$: C 56.31; H 7.99; Cl 25.57%.

2, 2, 4, 4, 6-Pentamethyl-1, 2, 3, 4-tetrahydro-γ-carboline (XI). Refluxing 0.75 g (3 mM) compound XII in xylene with Pd black, as above, gave 0.6 g (80%) XI, mp 174°–176° C.

1-Acetyl-2-(β-acetylaminoisobutyl)-5-methylindoline (XIV). 4.6 g (0.02 mole) indoline XIII and 9 ml Ac_2O were heated together on a steam bath for 1 hr. The products were poured into water, the solid filtered off, yield 4.2 g (64%) compound XIV, mp 108°–109° C (ex benzene–petrol ether). Found: C 70.65; 70.70; H 8.55; 8.39; N 9.80; 9.77%, calculated for $C_{17}H_{24}N_2O_2$: C 70.65; H 8.39; N 9.72%.

2-(β-Aminoisobutyl)-5-methylindole (XV). Refluxing 2 g (0.01 mole) indoline **XIII** in xylene with Pd black, as above, gave 1.5 g (75%) indole **XV**, mp 110°–111.5° C (ex cyclohexane). Found: C 77.07; 77.28; H 9.10; 8.98; N 14.00; 14.21%, calculated for $C_{13}H_{18}N_2$: C 77.18; H 8.96; N 13.84%.

2, 2, 4-Trimethyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XVII) and 1-acetyl-2-(β-acetylaminoisobutyl)indoline (XVIII). 9.4 g (0.044 mole) 2, 2, 4-Trimethyl-1, 2, 3, 4-tetrahydro-γ-carboline [1] was reduced as described above, giving 6.9 g product which was column chromatographed on alumina activity grade IV. Elution with petrol ether (bp 60°–80° C) gave 3.16 g (34%), compound **XVII**, mp 164°–166° C (ex benzene–petrol ether). Found: C 78.01; 77.94; H 9.22; 9.27; N 12.85; 12.98%, calculated for $C_{14}H_{20}N_2$: C 77.72; H 9.32; N 12.95%.

The residue in the column was eluted with $CHCl_3$, when 3.74 g (45%) oil was obtained, giving one spot in TLC on alumina. 0.4 g this compound and 0.92 g Ac_2O were refluxed together for 1 hr, and the products poured into water. The solution was made alkaline with K_2CO_3, extracted with ether, and the extracts dried over $MgSO_4$. The ether was distilled off, when there remained 0.35 g (60%) 1-acetyl-2-(β-acetylaminoisobutyl)indoline **XIX**, mp 142°–143° C [1] (ex benzene–petrol ether). Found: C 70.22; 70.40; H 8.16; 8.23; N 10.08; 10.23%, calculated for $C_{16}H_{22}N_2O_2$: C 70.40; H 8.08; N 10.21%.

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