AZABICYCLO COMPOUNDS. X.*

THE PREPARATION OF 1-AZABICYCLO(2,2,2)OCTANES DEUTERATED AT THE POSITIONS 2, 3 AND 4

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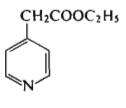
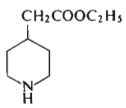
In order to study the formation and the structure of some ionic species in mass spectra of 1-azabicyclo(2,2,2)octane and its methyl homologues (*cf.*[1]) we needed derivatives deuterated at the positions 2,3 and 4. In this paper we describe the preparation of 2,2-dideutero- (*V*), 3-deutero- (*XI*), 3,3-dideutero- (*XII*), and 4-deutero-1-azabicyclo(2,2,2)octane (*XIV*).
For the synthesis of 2,2-dideuteroderivative *V* we made use of an analogous procedure, employed by Pracejus[2] for the preparation of 2,2-dimethyl-6,6-dideutero-1-azabicyclo(2,2,2)-octane.



I



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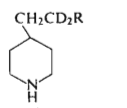
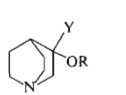


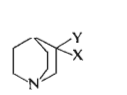
III, R = OH
IV, R = Br

V

VI



VII, Y = R = H,
VIII, Y = D, R = H,
IX, Y = H, R = Ts,
X, Y = D, R = Ts



XI, X = H, Y = D,
XII, X = Y = D

XIII, R = Br
XIV, R = D

On hydrogenation of ethyl pyridylacetate hydrochloride (*I*) in the presence of Adams catalyst ethyl piperidylacetate (*II*) was obtained which was then transformed by lithium aluminum deuteride to the corresponding 1,1-dideutero-2(4-piperidyl)ethanol (*III*). On reaction of the amino alcohol *III* with 70% hydrobromic acid at elevated temperature the hydrobromide of the bromo derivative *IV* was obtained, from which the free base was set free on treatment with 0·01M-NaOH. The base underwent intramolecular cyclisation to the required dideutero derivative *V*. Amino ketone *VI* served as the starting material for the synthesis of 3-deuterated derivatives. Its re-

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duction with lithium aluminum hydride or lithium aluminum deuteride gave corresponding amino alcohols *VII* or *VIII*, respectively. From these compounds tosylates *IX* and *X* were prepared on treatment with *p*-toluenesulfonyl chloride in pyridine, which were then reduced[3] with lithium aluminum deuteride to the corresponding 3-deutero- (*XI*) or 3,3-dideutero-1-azabicyclo(2,2,2)octane (*XII*), respectively. The 4-deuteroderivative *XIV* was obtained in good yield on reduction of the formerly described[4] 4-bromo-1-azabicyclo(2,2,2)octane (*XIII*) with zinc powder in O-deuteroacetic acid.

EXPERIMENTAL

The melting points and the boiling points are not corrected. Samples for analysis were dried at 2—4 Torr for 12 hours. For chromatography alumina of activity II (according to Brockmann) was used and the thin-layer chromatograms were detected with iodine vapours. The mass spectra were measured on a LKB 9000 apparatus, ionisation energy being 70 eV.

Ethyl 4-Piperidylacetate (*II*)

An ethanolic solution of hydrogen chloride (pH of the solution 2—3) was added to 3·3 g (0·02 mol) of ethyl 4-pyridylacetate (*I*) (prepared from ethyl isonicotinate according to the literature[5,6]) and the mixture was allowed to stand for 20 minutes. Ethanol was then evaporated *in vacuo* and the remaining hydrochloride (m.p. 133—135°C) was dissolved in 80 ml of ethanol. To this solution 60 mg of platinum oxide were added and the mixture was hydrogenated at atmospheric pressure and room temperature. After 50 hours hydrogenation (consumption of hydrogen 1421 ml; theoretical value 1360 ml of hydrogen) the catalyst was filtered off, washed with 3 ml of ethanol and the ethanolic solution was evaporated to dryness on a rotatory evaporator (bath temperature 40°C, 20 Torr). The crystalline hydrochloride was suspended in 20 ml of ether and then decomposed under external cooling with 10 ml of a 20% sodium hydroxide solution. The organic layer was separated, the aqueous phase extracted four times with 20 ml of ether, and the combined ethereal extracts were washed with 5 ml of water, dried over potassium carbonate and evaporated. Distillation of the residue gave 3·07 g (90%) of the product, b.p. 110—113°C at 13 Torr (Hickman flask). Literature[7] gives 67°C/03 Torr, and lit.[7] 123—127°C/15 Torr.

1,1-Dideutero-2-(4-piperidyl)ethanol (*III*)

To a suspension of 0·77 g of lithium aluminum deuteride in 20 ml of ether (dried over lithium aluminum hydride and freshly distilled) stirred for 10 minutes 1·71 g (0·01 mol) of amino ester *II* in 15 ml of ether was added under stirring at room temperature. After 10 hours heating to boiling temperature the reaction mixture was decomposed under external cooling with ice and water with 0·77 ml of water, 0·77 ml of 15% sodium hydroxide, and 2·3 ml of water. Finally, the mixture was shortly boiled. Inorganic material was filtered off under suction and then digested with three 20 ml portions of an ether–benzene mixture (1 : 1) and three times with 20 ml portions of ethanol–benzene (1 : 1). The combined extracts were dried shortly over potassium carbonate and the solvent was evaporated under reduced pressure. The oily residue was distilled from a Hickman flask to afford 620 mg (47·2%) of a product, b.p. 94—96°C/0·8 Torr (bath temperature 130 to 135°C). For $C_7H_{13}D_2NO$ (131·2) calculated: 64·07% C, 13·06% H + D, 10·68% N; found: 64·05% C, 12·96% H + D, 10·96% N.

1,1-Dideutero-2-(4 piperidyl)bromoethane Hydrobromide (*IV*)

A mixture of 1050 mg (8 mmol) of compound *III* and 20 ml of 70% hydrobromic acid was heated in a pressure tube at 100—110°C for 7 hours. After evaporating the reaction mixture to dryness (rotational evaporator, 40°C/20 Torr) the residue (3·02 g) was recrystallised twice (char-

coal) from a mixture of ethyl acetate and ethanol (10 : 1) to give 1·81 g (92%) of hydrobromide *IV*, m.p. 181–182°C. For $C_7H_{13}D_2Br_2N$ (275·1) calculated: 30·57% C, 6·23 H + D, 5·09% N, 58·11% Br; found: 30·78% C, 6·35% H + D, 5·14% N, 57·66% Br.

2,2-Dideutero-1-azabicyclo(2,2,2)octane (*V*)

To 375 ml of an approx. 0·1M-NaOH solution 1·70 g of hydrobromide *IV* in 260 ml of water was added under stirring at 55–65°C over two hours. After one hour stirring at this temperature the reaction mixture was additioned with 5 ml of 40% sodium hydroxide and steam distilled. The distillate (approx. 200 ml) containing the bases was neutralised with 0·5M-HCl (consumption 11·2 ml, 90·5%), evaporated to dryness under reduced pressure and the residue was dissolved in 5 ml of water. After addition of an equal amount of ether the bases were set free by addition of 1 g solid potassium hydroxide. The organic layer was separated and the aqueous one was extracted with five 5 ml portions of ether. The ethereal solution was dried over potassium carbonate and potassium hydroxide and ether was distilled off using a distillation column. The residue (0·7 g) gave after sublimation (bath temperature 100–110°C) 0·6 g (83·1%) of a product, m.p. 166–167°C (sealed capillary). For $C_7H_{11}D_2N$ (113·2) calculated: 74·27% C, 13·35% H + D, 12·37% N; found: 74·14% C, 13·05% H + D, 12·09% N.

Picrate: Yellow crystals, m.p. 284–285°C (ethanol). For $C_{13}H_{14}D_2N_4O_7$ (342·3) calculated: 45·61% C, 5·30% H + D, 16·37% N; found: 45·69% C, 5·25% H + D, 16·28% N.

3-Deutero-3-hydroxy-1-azabicyclo(2,2,2)octane (*VIII*)

To a suspension of 0·4 g (95 mmol) of lithium aluminum deuteride in 20 ml of ether 3·8 g (30 mmol) of aminoketone *VI* (prepared according to lit.[8]) in 20 ml of ether were added under stirring over 10 minutes. After 5 hours refluxing the reaction mixture was decomposed with 0·4 ml of water, 0·5 ml of 15% sodium hydroxide, 1·2 ml of water and, then shortly boiled. The separated inorganic salts were filtered off and digested three times with 20 ml of an ether–ethanol mixture (10 : 1). The combined filtrates were dried over potassium carbonate, the solvents were evaporated and the residue was recrystallised twice from acetone (charcoal). The analytically pure preparation (2·35 g; 60·3%) had m.p. 231–232°C. For $C_7H_{12}DNO$ (128·2) calculated: 65·58% C, 11·01% H + D, 10·94% N; found: 65·52% C, 11·05% H + D, 11·02% N.

3-Hydroxy-1-azabicyclo(2,2,2)octane (*VII*)

This was prepared on reduction of 3·0 g of amino ketone *VI* with 1 g of lithium aluminum hydride in an analogous manner as the deuterated derivative *VIII*. The yield was 1·95 g, *i.e.* 64%, m.p.224 to 226°C. Lit.[9] gives 225–227°C.

3,3-Dideutero-1-azabicyclo(2,2,2)octane (*XII*)

To a solution of 1·9 g (14·8 mmol) of compound *VIII* in 26 ml of pyridine 3·09 g (16·2 mmol) of *p*-toluenesulfonyl chloride in 13 ml of pyridine were added under stirring and external cooling with ice and water (bath temperature –3 to 0°C) over 10 minutes. The mixture was stirred at this temperature for 4 hours and then allowed to stand at room temperature for 36 hours, under occasional shaking. The excess *p*-toluenesulfonyl chloride was decomposed with 1·2 ml of water and the mixture evaporated on a rotatory evaporator to dryness (bath temp. 40°C/18 Torr). The viscous residue was dissolved in 10 ml of water, additioned with 30 ml of chloroform and alkalised with solid potassium hydroxide to pH 12–13. The chloroform layer was separated and the aqueous one extracted with three 30 ml portions of the same solvent. The chloroform

solution was dried over potassium carbonate, filtered and evaporated under reduced pressure. The oily residue (3·38 g) contained five substances according to thin-layer chromatography. After chromatography on an alumina column (130 g, column length 25 cm, ether–methanol 99 : 1 as eluent) 1 040 mg (24·3%) of an oily tosylate (*X*) were obtained. To a suspension of 0·4 g of lithium aluminum deuteride in 20 ml of ether the crude tosyl derivative *X* (1 040 mg) dissolved in 20 ml of ether was added under stirring and the mixture was refluxed for 8 hours. It was then decomposed with 10 ml of 10% sulfuric acid and the ethereal layer was separated. The aqueous phase was alkalised with 40% sodium hydroxide (5 ml) to separate the bases which were then steam distilled. The distillate was neutralised with hydrochloric acid and after evaporation to dryness the crude hydrochloride (291 mg) dissolved in 2 ml of water, and the bases were set free on addition of solid potassium hydroxide and extracted with ether (5 times 2 ml). After drying the ethereal extract over potassium carbonate and potassium hydroxide the solvents were evaporated and the residue (105 mg; 32·4%), after cooling, gave a crystalline solid, m.p. 162 to 165°C (after sublimation, bath temperature 100—105°C). The molecular weight found by means of mass spectrum was 113; for $C_7H_{11}D_2N$ m.w. is 113·2.

Picrate: Yellow crystals, m.p. 284—285°C (ethanol). For $C_{15}H_{14}D_2N_4O_7$ (342·2) calculated: 45·61% C, 5·30% H + D, 16·37% N; found: 45·87% C, 5·42% H + D, 16·67% N.

3-Deutero-1-azabicyclo(2,2,2)octane (*XI*)

Using 950 mg of hydroxy derivative *VII* and 1·55 g of *p*-toluenesulfonyl chloride in 12·5 ml of pyridine and working up the reaction mixture as above 600 mg (25·8%) of an oily *p*-toluenesulfonyl derivative *IX* were obtained. After reduction of this compound with lithium aluminum deuteride in 20 ml of ether–tetrahydrofuran (3 : 1) mixture and working up in the usual manner 75 mg (31·4%) of a crude product were obtained, m.p. 159—162°C (sealed capillary). Mass spectrometrically determined mol. weight was 112, in full agreement with the theoretical value for $C_7H_{12}DN$ (112·2).

Picrate: Yellow needles, m.p. 282—284°C after two crystallisations from ethanol. For $C_{13}H_{15}DN_4O_7$ (341·3) calculated: 45·75% C, 5·02% H + D, 16·42% N; found: 46·06% C, 5·10% H + D, 16·37% N.

4-Deutero-1-azabicyclo(2,2,2)octane (*XIV*)

A solution of 780 mg of 4-bromo derivative *XIII* (m.p. 105—107°C, lit.[4] gives 89—89·5°C) in 13 g of O-deuteroacetic acid was mixed with 1·9 g of zinc dust (dried over phosphorus pentoxide at 2—4 Torr) and refluxed under stirring for 2 hours. Additional zinc dust (1 g) was then added and refluxing was continued for another 3 hours. The reaction mixture was cooled, alkalised with 40% sodium hydroxide, and the bases were steam distilled. After the usual work-up 450 mg of crude base were obtained which after sublimation at 100—110°C bath temperature gave a pure product, m.p. 166—168°C (sealed capillary). For $C_7H_{12}DN$ (112·2) calculated: 74·94% C, 12·58% H + D, 12·49% N; found: 75·15% C, 12·28% H + D, 12·65% N.

Picrate: Yellow needles, m.p. 284—286°C (ethanol). For $C_{13}H_{15}DN_4O_7$ (341·3) calculated: 45·75% C, 5·02% H + D, 16·42% N; found: 45·93% C, 4·92% H + D, 16·42% N.

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ANTHRACHINONFARBSTOFFE XI.*

BEITRAG ZUR CHEMIE DER 1,5-DISUBSTITUIERTEN ANTHRACHINONDERIVATE

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Im Zuge unserer Versuche über den partiellen Austausch der Substituenten in 1,5-disubstituierten Anthrachinonderivaten gegen die Alkylaminogruppe wurden neue Verbindungen dieser Reihe bereitet, deren Eigenschaften und Reaktionen wir in dieser Mitteilung zusammenfassen. Es wurde ein präparativ anwendbares Verfahren zur Darstellung von 1-Cyclohexylamin-5-chloranthrachinon (*V*) aus 1,5-Dichloranthrachinon ausgearbeitet. Durch Reaktion von 1,5-Anthrachinondisulfonsäure mit wäßrigen Aminlösungen unter Druck wurden 1-Cyclohexylaminoanthrachinon-5-sulfonsäure[1] (*Ia*) und 1-(2-Propylamino)anthrachinon-5-sulfonsäure (*Ib*) bereitet. Als Nebenprodukt entstand im ersten Fall 1,5-Dicyclohexylaminoanthrachinon (*IIa*) in einer Menge von 1—5%, und im zweiten Fall wurde 1,5-Di-(2-propylamino)anthrachinon (*IIb*) in Mengen bis zu 20% isoliert. Vom Hauptprodukt lassen sich die Dialkylaminoanthrachinone auf Grund ihrer größeren Löslichkeit in Lösungsmitteln (z. B. in Benzol) trennen.

Aus 1-Alkylaminoanthrachinon-5-sulfonsäure *Ia* wurden durch Entalkylierung und Benzoylierung 1-Amino- und 1-Benzoylaminoanthrachinon-5-sulfonsäure (*Ic*, *Id*) bereitet. Der Austausch der Sulfogruppe in den Aminoanthrachinonsulfonsäuren *Ia—Id* gegen eine primäre oder sekundäre Aminogruppe wurde in wäßrigem Milieu durch Behandlung mit Ammoniak, Cyclohexylamin und 2-Propylamin in einem geschlossenen Gefäß unter Druck untersucht. Die ausgeführten Reaktionen veranschaulicht Schema 1. Der durchgestrichene Pfeil bedeutet, daß die Reaktion nicht in der angedeuteten Richtung verläuft.

* X. Mitteilung: diese Zeitschrift *36*, 2005 (1971).