REACTION OF TETRASUBSTITUTED BISPIDONES AND 1,3-DIAZAADAMANTANONES*

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The preparation of the following compounds is described: 2,4,6,8-tetraphenyl-3,7-diazabicyclo-[3,3,1]nonan-9-one (*I*), 2,4,6,8-tetra(4-methoxyphenyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (*II*), 2,4,6,8-tetra(3-pyridyl)-3,7-diazabicyclo[3,3,1]-nonan-9-one (*III*), 4,8,9,10-tetraphenyl-1,3-diazaadamantan-6-one (*VI*), 4,8,9,10-tetra(4-methoxyphenyl)-1,3-diazaadamantan-6-one (*VII*) and 4,8,9,10-tetra(3-pyridyl)-1,3-diazaadamantan-6-one (*VIII*). After hydrogenation of these compounds on Raney-Ni as catalyst at 150—200°C and 100 kp hydrogen pressure 2,4,6,8-tetracyclohexyl-3,7-diazabicyclo[3,3,1]nonan-9-ol (*IV*), 4,8,9,10-dicyclohexyldiphenyl-1,3-diazaadamantan-6-ol (*IX*), 4,8,9,10-tetracyclohexyl-1,3-diazaadamantan-6-ol (*XI*), 4,8,9,10[di(4-methoxycyclohexyl)-di(4-methoxyphenyl)]-1,3-diazaadamantan-6-ol (*X*), 2,4,6,8-tetra(3-pyridyl)-3,7-diazabicyclo[3,3,1]nonan-9-ol (*V*), and 2,6-di(3-pyridyl)piperidin-4-ol (*XIV*) have been isolated. On reduction with lithium aluminum hydride 4,8,9,10-tetra(4-methoxyphenyl)-1,3-diazaadamantan-6-ol (*XII*) and 4,8,9,10-tetra(3-pyridyl)-1,3-diazaadamantan-6-ol (*XIII*) have been obtained.

The synthesis of 1,3-diazaadamantan was studied by a number of authors[1]. The preparation of substituted piperidones as starting substances for the synthesis of substituted bispidones is the topic of the papers by Petrenko-Kritschenko and coworkers[2-5]. Especially well described is the preparation of derivatives of 1,5-diphenyl-3,7-diazaadamantan-9-one[6-13]. Chiavarelli and coworkers[14] study in their paper the synthesis and some reactions of tetrasubstituted bispidones and 1,3-diazaadamantanones.

Our work was directed to tetrasubstituted compounds and to the preparation of some derivatives with possible physiological activity. In contrast to preceding studies which use substituted acetone as starting material, we used for synthesis acetone, ammonium acetate and aromatic aldehyde. On reaction of benzaldehyde, acetone and ammonium acetate 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (*I*) was prepared which on boiling with paraformaldehyde in tetrachloromethane afforded 4,8,9,10-tetraphenyl-1,3-diazaadamantan-6-one (*VI*). Among substituted aromatic aldehydes 4-methoxybenzaldehyde was used for the reaction with acetone and am-

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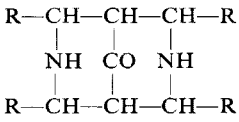
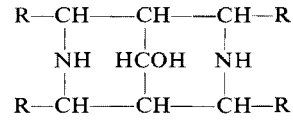
monium acetate, affording 2,4,6,8-tetra(4-methoxyphenyl)-3,7-diazabicyclo[3,3,1]-nonan-9-one (*II*). When compound *II* was refluxed with paraformaldehyde in an ethanol–dioxane mixture 4,8,9,10-tetra(4-methoxyphenyl)-1,3-diazaadamantan-6-one (*VII*) was obtained. Of the heterocyclic aldehydes studied only 3-formylpyridine reacted successfully with acetone and ammonium acetate giving 2,4,6,8-tetra(3-pyridyl)-3,7-diazabicyclo[3,3,1]nonan-9-one (*III*) which on boiling in dimethylformamide gave 4,8,9,10-tetra(3-pyridyl)-1,3-diazaadamantan-6-one (*VIII*).

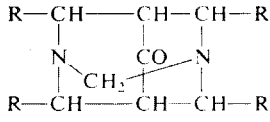
The tetrasubstituted derivatives prepared were hydrogenated under high pressure on Raney nickel, at 150-200°C. In the case of tetraphenyl derivatives hydrogenation takes place relatively easily. A temperature of 150°C or 170°C suffices for the hydrogenation of aromatic rings, either all four or only two. Hydrogenation of the keto to hydroxy group also takes place. Thus, from the reaction mixture after hydrogenation of 2,4,6,8-tetraphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (*I*) 2,4,6,8-tetracyclohexyl-3,7-diazabicyclo[3,3,1]nonan-9-ol (*IV*) was isolated and from the hydrogenation mixture of 4,8,9,10-tetraphenyl-1,3-diazaadamantan-6-one (*VI*) both 4,8,9,10-tetracyclohexyl-1,3-diazaadamantan-6-ol (*XI*) and 4,8,9,10-dicyclohexyl-diphenyl-1,3-diazaadamantan-6-ol (*IX*) (the positions are not determined) have been obtained. In tetraphenyl derivatives with the substituents in para position hydrogena-



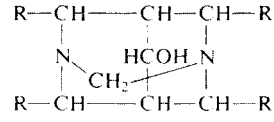
I, R = phenyl
II, R = 4-methoxyphenyl
III, R = 3-pyridyl



IV, R = cyclohexyl
V, R = 3-pyridyl



VI, R = phenyl
VII, R = 4-methoxyphenyl
VIII, R = 3-pyridyl



IX, R = cyclohexyl or phenyl*
X, R = 4-methoxycyclohexyl or 4-methoxyphenyl*
XI, R = cyclohexyl
XII, R = 4-methoxyphenyl
XIII, R = 3-pyridyl

* The molecule contains two residues of each kind, their true position has not been determined.

tion of the keto group and of the two aromatic cycles takes place only in the case of substances of diazaadamantanes type. From the mixture after hydrogenation of 4,8,9,10-tetra(4-methoxyphenyl)-1,3-diazaadamantan-6-one (*II*) 4,8,9,10-[di(4-methoxycyclohexyl)-di(4-methoxyphenyl)]-1,3-diazaadamantan-6-ol (*X*) (the positions were not determined) was isolated. On hydrogenation of 2,4,6,8-tetra(4-methoxyphenyl)-3,7-diazabicyclo[3,3,1]-nonan-9-one (*II*) a mixture of substances was formed from which the corresponding hydrogenated derivative could not be isolated. In the case of tetrapyridyl derivatives hydrogenation of the oxo group takes place, giving a hydroxy group, and at elevated temperatures the adamantane skeleton is cleaved under formation of a piperidine derivative. Thus, from the hydrogenate of 4,8,9,10-tetra(3-pyridyl)-1,3-diazaadamantan-6-one (*III*) 2,6-di(3-pyridyl)piperidin-4-ol(*XIV*) was isolated.

The reduction of the oxo group to the hydroxy group under preservation of the aromatic system is possible with lithium aluminum hydride. Thus 4,8,9,10-tetra(4-methoxyphenyl)-1,3-diazaadamantan-6-ol (*XII*) and 4,8,9,10-tetra(3-pyridyl)-1,3-diazaadamantan-6-ol (*XIII*) have been isolated in high yield.

EXPERIMENTAL

The melting points are uncorrected. The IR spectra were measured on a Perkin - Elmer 325 and UR-10*(Zeiss, Jena) spectrophotometer, the mass spectra were recorded on a LKB 9000 instrument. The NMR spectra were measured in deuteriochloroform with a Varian XL 100-15 apparatus, using tetramethylsilane as internal reference.

2,4,6,8-*Tetraphenyl*-3,7-*diazabicyclo*[3,3,1]*nonan*-9-*one* (*I*) was prepared by condensation of benzaldehyde with acetone in ammonium acetate in ethanol. M.p. 249—250°C; yield 41%. Lit.[14] gives m.p. 253—254°C.

4,8,9,10-*Tetraphenyl*-1,3-*diazaadamantan*-6-*one* (*VI*) was prepared from compound *I* and paraformaldehyde by boiling in tetrachloromethane. B.p. 224—225°C; yield 64%. Lit.[14] gives m.p. 229—230°C.

2,4,6,8-*Tetra*(4-*methoxyphenyl*)-3,7-*diazabicyclo*[3,3,1]*nonan*-9-*one* (*II*). To a solution of 61·7 g of ammonium acetate in 500 ml of ethanol 23·2 g of acetone and 217·8 g of 4-methoxybenzaldehyde were added and the mixture stirred and allowed to stand at room temperature overnight. The separated precipitate was filtered off under suction and washed several times with ethanol. After crystallization from a mixture of ethanol and dioxan (1 : 1) a compound was obtained of m.p. 221—222°C; yield 111.5 g (79%). It was dried in a vacuum at 80°C for 6 hours. For $C_{35}H_{36}N_2O_5$ (564·7) calculated: 74·44% C, 6·43% H, 4·96% N; found: 74·12% C, 6·39% H, 4·92% N.

4,8,9,10-*Tetra*(4-*methoxyphenyl*)-1,3-*diazaadamantan*-6-*one* (*VII*). A mixture of 16·8 g of compound *II*, 300 ml of ethanol–dioxan (1 : 1) and 3 g of paraformaldehyde was refluxed for 4 hours. The compound obtained had m.p. 191—192°C; yield 13·6 g (79%). It was dried *in vacuo* at 80°C for 6 hours. For $C_{36}H_{36}N_2O_5$ (576·7) calculated: 74·97% C, 6·29% H, 4·86% N; found: 74·54% C, 6·45% H, 4·96% N.

2,4,6,8-*Tetra*(3-*pyridyl*)-3,7-*diazabicyclo*[3,3,1]*nonan*-9-*one* (*III*). Acetone (29·4 g) and 3-formylpyridine (214·2 g) was added to 77 g of ammonium acetate in 500 ml of ethanol and the mixture

allowed to stand at room temperature for 30 days. The precipitate formed was filtered off under suction and the product crystallized from dioxan, m.p. 252–253°C. Yield 51·6 g (27%). For $C_{27}H_{24}N_6O$ (448·5) calculated: 72·30% C, 5·39% H, 18·74% N; found: 71·94% C, 5·28% H, 18·48% N.

4,8,9,10-*Tetra*(3-*pyridyl*)-1,3-*diazaadamantan*-6-*one* (*VIII*). A mixture of 13·5 g of compound *III*, 3 g of paraformaldehyde, and 250 ml of N,N-dimethylformamide was heated at 100°C for 4 hours. The solution was filtered and a substance crystallized out from the filtrate which after drying at 50°C and 15 Torr had m.p. 290–291°C. Yield 10·2 g (73%). For $C_{28}H_{24}N_6O$ (460·5) calculated: 73·02% C, 5·25% H, 18·25% N; found: 72·74% C, 5·46% H, 18·26% N.

Hydrogenation of compound I: 3 g of compound *I* were hydrogenated in 100 ml of ethanol on Raney nickel in a rotatory autoclave at 170°C and 100 kp pressure of hydrogen for 1 hour. The mixture was filtered and the material on the filter, together with the catalyst, was dissolved in benzene and the catalyst used was filtered off. The filtrate was concentrated in a vacuum and the residue recrystallized from dioxan. Yield 0·8 g (27%) of a product melting at 236–237°C, that was identified as 2,4,6,8-tetracyclohexyl-3,7-diazabicyclo[3,3,1]nonan-9-ol (*IV*). For $C_{31}H_{54}N_2O$ (470·8) calculated: 79·09% C, 11·56% H, 5·95% N; found: 79·15% C, 11·50% H, 5·78% N. $M^+ =$ = 470; IR spectrum (in $CHCl_3$); 1450, 2850, 2930, 3300 cm^{-1}; NMR (δ in deuteriochloroform): multiplet 0·6–2·4, maxima 1·2 and 1·8 (does not contain phenyls).

Hydrogenation of compound VI: Ten grams of compound *VI* were hydrogenated on Raney nickel in 200 ml of ethanol in a rotatory autoclave at 150°C and 100 kp hydrogen pressure for one hour. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was triturated with ethanol. After one day's standing the precipitated material was filtered off under suction and recrystallized from dioxan. The yield of 4,8,9,10 tetracyclohexyl-1,3-diazaadamantan-6-ol (*XI*) was 4 g (40%), m.p. 227–228°C. For $C_{32}H_{54}N_2O$ (482·8) calculated: 79·61% C, 11·24% H, 5·80% N; found: 79·62% C, 10·86% H, 5·79% N. $M^+ = 482$; IR spectrum (in chloroform): 1450, 2850, 2930, 3300 cm^{-1}; NMR (δ in deuteriochloroform): multiplet 0·6–2·4 with maxima at 1·2 and 1·8 (absence of phenyls). The solid residue from hydrogenation was dissolved in benzene. The catalyst used was filtered off and the filtrate concentrated in a vacuum. The residue was crystallized from dioxan, yield 4·1 g (41%), m.p. 266–267°C. The product was identified as 4,8,9,10-dicyclohexyldiphenyl-1,3-diazaadamantan-6-ol (*IX*). For $C_{32}H_{42}N_2O$ (470·6) calculated: 81·67% C, 8·98% H, 5·95% N; found: 81·50% C, 9·20% H, 5·84% N. $M^+ = 470$; IR spectrum (in chloroform): 1450, 1600, 2930, 3020, 3300 cm^{-1}; NMR (δ in deuteriochloroform): multiplet 0·6–4·0; singlet (phenyls) 7·28; the ratio of the signals, 3·2 : 1, corresponds to the theory.

Hydrogenation of compound VII: 3 g of compound *VII* were hydrogenated in 100 ml of ethanol on Raney nickel in a rotatory autoclave at 150°C and 100 kp hydrogen pressure for one hour. The mixture was heated and the catalyst used filtered off. The filtrate was concentrated and allowed to crystallize. After recrystallization from ethanol the yield of the product was 0·9 g (30%), m.p. 225–226°C. It was identified as 4,8,9,10-[di(4-methoxycyclohexyl)-di(4-methoxyphenyl)]-1,3-diazaadamantan-6-ol (*X*). For $C_{36}H_{50}N_2O_5$ (590·8) calculated: 73·18% C, 8·53% H, 4·74% N; found: 73·21% C, 8·69% H, 4·88% N. IR spectrum (in CCl_4): 1250, 1510, 1610, 2930, 3300 cm^{-1}; NMR (δ in deuteriochloroform); multiplet (phenyl) 6·86; singlet (methoxycyclohexyl) 3·26; singlet (methoxyphenyl) 3·76; the ratio of the signals, 5·2 : 1, corresponds to the theory.

Hydrogenation of compound III: Three grams of compound *III* were hydrogenated in 100 ml of ethanol on Raney nickel in a rotatory autoclave at 170°C and 100 kp hydrogen pressure for one hour. The mixture was heated and filtered, the filtrate concentrated to half of its volume and allowed to crystallize. After further crystallization from ethanol the yield was 0·7 g (23%), m.p, 313–314°C. The product was identified as 2,4,6,8-tetra(3-pyridyl)-3,7-diazabicyclo[3,3,1]nonan-

-9-ol (*V*). For $C_{27}H_{26}N_6O$ (450·6) calculated: 71·97% C, 5·82% H, 18·65% N; found: 72·08% C, 6·08% H, 18·18% N. $M^+ = 450$; IR spectrum (in chloroform): 1440, 1590, 3030, 3240 cm^{-1}.

Hydrogenation of compound VIII: Three grams of compound *VIII* were hydrogenated in 100 ml of ethanol on Raney nickel in a rotatory autoclave at 200°C and 100 kp hydrogen pressure for one hour. At 150°C hydrogenation did not take place. After filtration of the catalyst the filtrate was concentrated *in vacuo* to half its volume. The starting compound (0·6 g) crystallized out first. The mother liquors were evaporated *in vacuo* and the residue dissolved in ethanol, the solution was purified by filtration through a column of alumina, evaporated, and the residue crystallized from an ethanol–heptane (1 : 1) mixture. Yield 0·7 g (23%), m.p. 204—205°C. The product was identified as 2,6-di(3-pyridyl)piperidin-4-ol (*XIV*). For $C_{15}H_{17}N_3O$ (255·3) calculated: 70·56% C, 6·71% H, 16·46% N; found: 70·83% C, 6·63% H, 16·18% N. $M^+ = 255$; IR spectrum (in chloroform): 1440, 1590, 2970, 3300 cm^{-1}.

4,8,9,10-*Tetra*(4-*methoxyphenyl*)-1,3-*diazaadamantan*-6-*ol* (*XII*): Lithium aluminum hydride (0·1 g) was added to a stirred solution of 1·5 g of compound *VII* in 50 ml of tetrahydrofuran and the mixture was refluxed on a water bath for 24 hours. It was then decomposed with 2 ml of water, boiled shortly and filtered. The residue on the filter was mixed with dioxan, the mixture heated and filtered again. The filtrates were combined and evaporated *in vacuo*. The residue was crystallized from ethanol. Yield 1·3 g (87%), m.p. 247—248°C. For $C_{36}H_{38}N_2O_5$ (578·7) calculated: 74·71% C, 6·62% H, 4·84% N; found: 74·85% C, 6·66% H, 4·63% N. IR spectrum (in chloroform): 1250, 1510, 1610, 3010 cm^{-1}; oxo group is absent.

4,8,9,10-*Tetra*(3-*pyridyl*)-1,3-*diazaadamantan*-6-*ol* (XIII): It was obtained in a manner similar to that used for the preceding compound, on reduction of compound *VIII* with lithium aluminum hydride, yield 80%, m.p. 302—303°C. For $C_{28}H_{26}N_6O$ (462·6) calculated: 72·70% C, 5·66% H, 18·17% N; found: 72·31% C, 5·71% H, 17·93% N; IR spectrum (in KBr): 1430, 1580, 3220; oxo group is absent.

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