N,N'-ACYLATED 2,4-DIAZABICYCLO[3.3.1]NONANES AND 2,4-DIAZABICYCLO [3.2.1]OCTANES FROM ALICYCLIC BISAZOMETHINES

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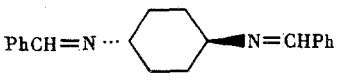
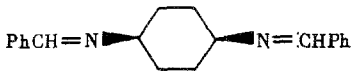
There is little information on the synthesis of bridged structures with two nitrogen atoms in the 1 and 3-positions [1, 2]. Saturated annelated diazaheterocycles have been obtained, like the monocyclic compounds, by reacting diamines $R^1NHCHR^2CHR^3NHR^1$ (I) with aldehydes, but this method is successful only for five- and six-membered heterocycles. When R^1 in (I) is alkyl, the reaction takes place with any RCHO [3], when R^1 is Ac, with CH_2O only [4], and when R^1 is H, no reaction takes place [2, 5].

We have recently shown that acylation of bisazomethines $RCH=(CH_2)_nN=CHR$ with aromatic acid chlorides in a polar medium affords N,N'-acylated 1,3-diazaalkanes with 5- to 8-membered rings [6]. We have now attempted to obtain by this method some acylated 2,4-diazabicyclo[3.3.1]nonanes and 2,4-diazabicyclo[3.2.1]-octanes by reacting azomethines (II)-(VI) with benzoyl chloride under the conditions described in [6].



(II)



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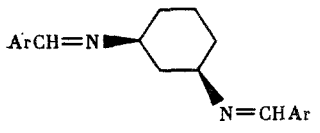
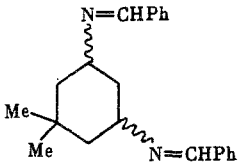
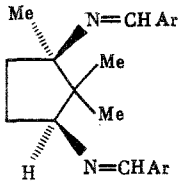


(IV)



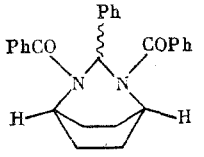
(V)



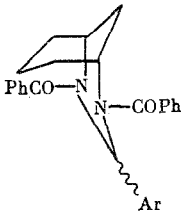
(VI)

Ar = Ph(a); p-$MeOC_6H_4$(b); p-$O_2NC_6H_4$(c); p-HOC_6H_4(d).

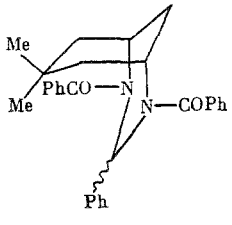
Examination of molecular models shows that 1,3-diazaalkanes can be formed from (IV)-(VI) only. Cyclization of (II) is impossible by virtue of the trans orientation of the azomethine groups, and cyclization of (III) is unlikely as a result of strains in the hypothetical diazabicyclo[3.2.2]nonane system (VII). The products (VIII) and (IX) expected on cyclization of (IV) and (V) are not strained. The system (X) is slightly strained as a result of the departure of the angles in the cyclopentane ring from the tetrahedral values, and of spatial interaction of the methyl groups at C^1 and C^8.



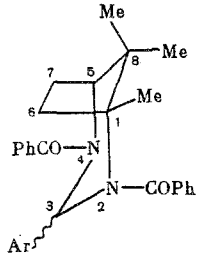
(VII)



(VIII)



(IX)



(X)

Ar = Ph(a); p-$MeOC_6H_4$(b); p-$O_2NC_6H_4$(c); p-HOC_6H_4(d).

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In fact, benzoylation of (II) gave only trans-1,4-dibenzoylaminocyclohexane (trans-(XI)) and trans-1-benzoylamino-4-benzaldiminocyclohexane (XII), which was unexpectedly stable to benzoyl chloride (2 hours' boiling in acetonitrile). The sole product of the benzoylation of (III) was the bis-amide, cis-(XI). Benzoylation of (IVa) gave two isomers with the composition $C_{27}H_{26}N_2O_2$, which were separated chromatographically on silica gel. X-ray structure determination and the ^{13}C and ^1H NMR spectra showed both isomers to be the 2,4-diazabicyclo[3.3.1]-nonane (VIIIa), with the cyclohexane ring in the chair form, and the heterocyclic ring in the boat form, but in one of these the proton at C^3 occupied the exo position, and in the other the endo position relative to the cyclohexane ring.

Similarly, (IVb) gave the pure exo- and endo-(VIII).

The isomers of (VIII) differed in their melting points, solubilities, and some chemical properties. For example, attempts to demethylate endo-(VIIIb) with BBr_3 resulted in cleavage to cis-1,3-dibenzoylaminocyclohexane (XIII), while exo-(VIIIb) gave satisfactory yields of exo-(VIIId). This was evidently due to differences in the geometry of the intermediate complexes with BBr_3.

In the benzoylation of the mixture of cis- and trans-isomers of (V), their proportions were not determined, and the yield of product was therefore calculated on the total (V). Column chromatography of the reaction products gave an inseparable mixture of exo- and endo-(IX). A similar reaction with (VIb) and (VIc) gave the corresponding (Xb) and (Xc) as mixtures of the exo- and endo-isomers, which were not separated as a result of the similarity of their R_f values. 1R,3S-(VI) was used in the reaction, and consequently the optically pure epimers of (X) were obtained. The yields of (Xb) and (Xc) were much lower than that of (VIII) as a result of the steric hindrance mentioned above. The spatial structure of heterocycles (IX) and (X) has not been established.

EXPERIMENTAL

Melting points were determined on a Boetius hot plate. Mass spectra were obtained on a Varian MAT CH-6, and ^{13}C and ^1H NMR spectra on a Bruker WM-25 spectrometer (250 MHz, δ from TMS). Column chromatography was carried out on silica gel L 100 × 160 μ. Chromatography was followed on Silufol. The elemental analyses of all the compounds obtained were in agreement with the calculed values. (II)-(V) were obtained as described in [6], and (VI) as in [7].

trans-1,4-Dibenzylideneaminocyclohexane (II). trans-1,4-Diaminocyclohexane* (1.00 g) and 1.86 g of benzaldehyde were boiled in 5 ml of ethanol for 5 min. Yield of (III) 88.5%, mp 175-176°C (from hexane). PMR spectrum ($CDCl_3$, δ, ppm): 1.75-1.90 m (8H, cyclohexane), 3.28 br (2H, =N—CH), 7.46 m (6H, Ph, m- and p-H), 7.73 m (4H, Ph, o-H), 8.36 s (2H, HC=N).

cis-1,4-Dibenzylideneaminocyclohexane (III) was obtained similarly. Yield 75.9%. Obtained in two modifications: 1.93 g of (III) in 7 ml of hot ethanol was cooled slowly to 40°C, and the solution decanted from the crystals (mp 138-140°C) and cooled to 0°C, whereupon the crystals which separated (mp 127-129°C) were filtered off. The modification with mp 127-129°C had PMR spectrum ($CDCl_3$, δ, ppm): 1.65-1.85 m (4H, cyclohexane), 2.00-2.15 m (4H, cyclohexane), 3.45 br (2H, HCN=), 7.40 m (6H, Ph), 7.75 m (4H, Ph), 8.35 s (2H, HC=N). The modification with mp 138-140°C had PMR spectrum ($CDCl_3$, δ, ppm): 1.45-2.50 m (8H, cyclohexane), 3.42 m (2H, HCN=), 7.38 m (6H, Ph), 7.77 m (4H, Ph), 8.28 s (2H, HC=N). A mixture of both forms (possibly syn- and anti-isomers) was used for benzoylation.

cis-1,3-Dibenzylideneaminocyclohexane (IVa) was obtained similarly, from 0.50 g of cis-1,3-diaminocyclohexane and 0.93 g of benzaldehyde. Yield 63%, mp 96-98°C (from hexane), PMR spectrum ($CDCl_3$, δ, ppm): 1.35-2.15 m (8H, cyclohexane), 3.15-3.55 m (2H, HCN=), 7.25-7.55 m (6H, Ph), 7.65-7.85 m (4H, Ph), 8.31 s (2H, HC=N).

cis-1,3-Di(p-methoxybenzylideneamino)cyclohexane (IVb). A mixture of 4.34 g of cis-1,3-diaminocyclohexane, 10.3 g of p-methoxybenzaldehyde, and 15 ml of methanol was boiled for 5 min, evaporated under reduced pressure, and the residue crystallized from a mixture of benzene and hexane (1:1) with the addition of 1 g of alumina to clarify the solution. Yield 62.5%, mp 143-144°C. PMR spectrum ($CDCl_3$, δ, ppm): 1.4-2.1 m (8H, cyclohexane), 3.25-3.40 m (2H, HCN), 3.83 s (6H, MeO) 6.92 d and 7.69 d (8H, Ph), 8.28 s (2H, HC=N).

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Mixture of cis- and trans-Isomers of 1,3-(Dibenzylideneamino)-5,5-dimethylcyclohexane (V). To 6.33 g of $LiAlH_4$ in 100 ml of dry THF was added over 20 min with stirring 9.43 g of dimedone dioxime [8] in 150 ml of THF. The mixture was boiled for 4 h, decomposed with a mixture of 7 ml of water and 20 ml of THF, the solid washed with ether (2 × 50 ml), and the filtrate evaporated to give 48% of a mixture of stereoisomeric 1,3-diamino-5,5-dimethylcyclohexanes (viscous oil, fumed in air). To 3.77 g of this mixture was added 10 ml of methanol and 5.73 g of benzaldehyde, and the mixture boiled for 5 min, evaporated, 50 ml of hexane and 5 g of alumina (Brockman grade II) added, boiled for 2 min, filtered hot, and kept and −20°C for 24 h. Yield of (V) 21%, mp 51-63°C, mass spectrum: m/z 318. The hexane filtrate was evaporated to give 2.94 g (35%) of (V) as an oil. Workup of the mother liquors gave a further 19% of (V) as an oil. The mixture of isomers was benzoxylated without separation or further purification.

cis(1R, 3S)-1,3-Di-(p-methoxybenzylideneamino)-1,2,2-trimethylcyclopentane (VIb). A mixture of 1.20 g of cis-(1R, 3S)-diamino-1,2,2-trimethylcyclopentane disulfate [9], 1.36 g of $MeCOONa \cdot 3H_2O$, and 1.36 g of p-methoxybenzaldehyde was boiled for 3 h in 50 ml of absolute ethanol. The mixture was then evaporated to dryness, diluted with water and chloroform, evaporated, the residue treated with dilute methanol (1:1) cooled to −20°C, and after 24 h filtered to give 10.6% of (VIb), mp 145.5-146.5°C (from hexane), m/z 378. PMR spectrum ($CDCl_3$, δ, ppm): 1.18 s (3H), 1.24 s (3H), 1.35 s (3H, Me), 1.60-2.40 m (4H, CH_2CH_2), 3.23 s and 3.25 s (6H, MeO), 3.52 m (1H, HCN=), 6.77 m and 7.80 m (8H, Ph), 8.12 s and 8.17 s (2H, HC=N).

cis-(1R,3S)-1,3-Di-(p-nitrobenzylideneamino)-1,2,2-trimethylcyclopentane (VIc). A mixture of 5.55 g of cis-(1R,3S)-diamino-1,2,2-trimethylcyclopentane disulfate, 5.38 g of anhydrous sodium acetate, and 4.95 g of p-nitrobenzaldehyde was boiled for 3 h in 100 ml of absolute ethanol, 5.38 g of anhydrous sodium acetate added and boiled for 3 h, evaporated to dryness, 50 ml of water added, and extracted with chloroform. The extracts were washed with water and evaporated, and a solution of the residue in 200 ml of hot hexane was slowly cooled to 20°C. After 24 h, the p-nitrobenzaldehyde was quickly filtered off, the filtrate cooled to 0°C, and the solid recrystallized from hexane to give 4.9% of (VIc), mp 136.5-138.0°C, m/z 408. PMR spectrum (C_6D_6, δ, ppm): 1.03 s (3H), 1.08 s (3H), 1.11 s (3H, Me), 1.50-2.20 m (4H, CH_2CH_2), 3.37 m (1H, HCN=), 7.42 m and 7.87 m (8H, Ph), 7.77 and 7.83 s (2H, HC=N).

Benzoylation of trans-1,4-Dibenzylideneaminocyclohexane (II). To 1.00 g of (II), 0.70 g of triethylamine, and 15 ml of dry acetonitrile was added over 10 min 0.97 g of benzoyl chloride in 5 ml of acetonitrile. The mixture was boiled for 0.5 h, evaporated, the residue treated with water and chloroform, filtered, the chloroform layer evaporated, the residue and filtered material boiled in 5 ml of chloroform, and the hot solution filtered to give 45% of trans-(XI), decomposed without melting at ∿320°C, m/z 322, very sparingly soluble in organic solvents. The chloroform filtrate gave 19% of (XII), mp 226-229°C (from methanol), m/z 306. PMR spectrum ($CDCl_3$, δ, ppm): 0.95-2.45 m (8H, cyclohexane), 2.95-3.45 m (1H, HCN=), 3.65-4.35 m (1H, HCN<), 5.97 d (1H, HN), 7.25-7.95 m (10H, Ph), 8.30 s (1H, HC=N).

Benzoylation of cis-1,4-Dibenzylideneaminocyclohexane (III). The reaction was carried out as for the benzoylation of (II). Yield of cis-(XI) 100%, mp 190-205°C (from ethyl acetate). PMR spectrum ($CDCl_3$, δ, ppm): 1.65-1.90 m (8H, cyclohexane), 4.10 br (2H, HCNCO), 6.47 d (2H, HN), 7.30-7.50 m (6H, Ph), 7.70-7.80 m (4H, Ph).

exo-and endo-2,4-Dibenzoyl-3-phenyl-2,4-diazabicyclo[3.3.1]nonanes (VIIIa). To a mixture of 3.26 g of (IVa), 2.26 g of triethylamine, and 30 ml of dry acetonitrile was added over 10 min 3.16 g of benzoyl chloride in 5 ml of acetonitrile. The mixture was boiled for 0.5 h, evaporated, water and chloroform added, and the chloroform layer washed with water and evaporated to give 4.1 g of an oil which was applied to a column (silica, l 15 cm, d 3 cm). Elution with benzene followed by a mixture of benzene, ether, and chloroform (6:1:2) gave 82.6% of a mixture of exo- and endo-(VIIIa) as an oil, R_f 0.25 (Silufol, benzene—ether (3:1)). In this system, the exo- and endo-isomers of (VIIIa) had R_f values of 0.24 and 0.26. The mixture of isomers of (VIIIa) (3.8 g) was applied to a column (silica, l 15 cm, d 3 cm), and eluted successively with mixtures of benzene and ether in ratios 20:1, 10:1, 5:1, and 3:1. The chromatographically homogeneous fractions were combined and evaporated, to give 12% of exo-(VIIIa), mp 235-236°C, (separated very slowly from methanol), and 2.4% of endo-(VIIIa), mp 276-278°C (from methanol, separated rapidly). There remained 3.05 g of a mixture of exo- and endo-(VIIIa). The isomers had identical mass spectra, m/z 410, together with ions ($M^+ - Ph$), ($M_3^+ - PhCO$), and (PhCO).

exo- and endo-2,4-Dibenzoyl-3-p-methoxyphenyl-2,4-diazabicyclo[3.3.1]nonanes (VIIIb). To a mixture of 7.00 g of (IVb), 2.32 g of propylene oxide, and 130 ml of acetonitrile was added over 15 min 5.62 g of benzoyl chloride, and the mixture boiled for 4 h and kept for four days. The precipitate was crystallized from methanol–chlorofrom (4:1), to give 0.50 g of exo-(VIIIb), mp 271.5-272.0°C. The filtrate was applied to a column (silica, l 7 cm, d 10 cm) and eluted with benzene followed by benzene–ether–chloroform (8:1:1). The chromatographically homogeneous fractions were combined and evaporated to give 17.0% of exo-(VIIIb) and 10.1% of endo-(VIIIb), mp 211.0-211.5°C (from methanol). The mass spectra of the isomers were identical, m/z 440, together with ions ($M^+ - p\text{-}MeOC_6H_4$), $M^+ - PhCO$), and (PhCO).

Reaction of Isomers of (VIIIb) with BBr_3. To 1.85 g of BBr_3 in 7 ml of chloroform was added over 4 min with stirring 0.55 g of exo-(VIIIb) in 15 ml of chloroform. The mixture was stirred for 3 h, basified with conc. ammonia, the chloroform layer washed with water and aqueous KOH, and the aqueous solution acidified with HCl and extracted with chloroform (4 × 25 ml). The extracts were washed with water, evaporated, and crystallized from 5 ml of methanol to give 37.6% of exo-(VIIId), mp 276-277°C, m/z 426. Reaction of endo-(VIIIb) with BBr_3 was carried out similarly to give 93.4% of insoluble (XIII), mp 292-293.5°C, m/z 322.

exo- and endo-2,4-Dibenzoyl-7,7-dimethyl-3-phenyl-2,4-diazabicyclo[3.3.1]nonanes (IX). The reaction was carried out as in the preparation of (VIII), using 6.28 g of the mixture of stereoisomers of (V), 4.32 g of triethylamine, and 5.54 g of benzoyl chloride. Following workup as described in the preparation of (VIII), the mixture was applied to a column (silica, l 15 cm, d 7 cm), and eluted with benzene followed by benzene–ether (8:1). The progress of the separation was followed as described above. TLC of the fractions with R_f 0.4 and 0.3 on Silufol (benzene–THF, 5:1) showed that the separation was only partial, both fractions being mixtures with R_f 0.4 and 0.3. The mass spectra of both fractions showed peaks with m/z 438, together with the fragment ions ($M^+ - Ph$), ($M^+ - PhCO$), and (PhCO). The overall yield of the mixture of exo- and endo-(IX) was 2.15 g (24.8%).

exo- and endo-(1R,5S)-2,4-Dibenzoyl-1,8,8-trimethyl-3-(p-methoxyphenyl)-2,4-diazabicyclo[3.2.1]octanes (Xb). The benzoylation of (VIb) and the chromatograhic separation of the mixture of exo- and endo-(Xb) were carried out as described above. From 0.18 g of (VIb), 0.10 g of triethylamine, and 0.134 g of benzoyl chloride there was obtained 0.09 g (40.4%) of a mixture of exo- and endo-(Xb) as a viscous oil, R_f 0.3 (Silufol, benzene–ether (3:1)). Mass spectrum, m/z 468; fragment ions ($M^+ - MeO_6H_4$), ($M^+ - PhCO$), (PhCO).

exo- and endo-(1R,5S)-2,4-Dibenzoyl-1,8,8-trimethyl-3-(p-nitrophenyl)-2,4-diazabicyclo[3.2.1]octanes (Xc). The benzoylation of (VIc) and the chromatographic separation of the mixture were carried out as described above. From 0.30 g of (VIc), 0.148 g of triethylamine, and 0.206 g of benzoyl chloride there was obtained 31.0% of a mixture of exo- and endo-(Xc) as a viscous oil, R_f 0.25 (Silufol, benzene–ether (3:1)). Mass spectrum, m/z 483; fragment ions ($M^+ - NO_2C_6H_4$), ($M^+ - PhCO$), (PhCO).

CONCLUSIONS

Benzoylation of bisazomethine derivatives of 1,3-diaminocyclohexane and 1,3-diaminocyclopentane has given 3-aryl-2,4-dibenzoyl-2,4-diazabicyclo,3.3.1]-nonanes and 3-aryl-2,4-dibenzoyl-2,4-diazabicyclo[3.2.1]octanes.

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