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THERMAL AND CHEMICAL INTRAMOLECULAR N → N ACYL-MIGRATION IN 8-ACYL-3, 8-DIAZABICYCLO[3.2.1]OCTANES

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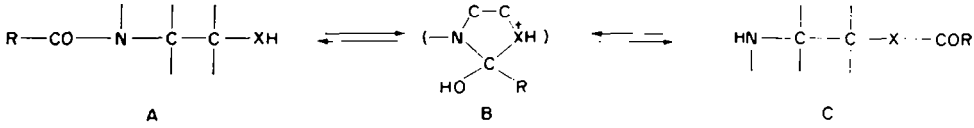
Abstract—The 8-acyl-3,8-diazabicyclo[3.2.1]octanes rearrange by thermal action to 3-acyl-3,8-diazabicyclo[3.2.1]octanes. The N (8) → N (3) acyl-migration is also induced by dilute alkali and by concomitant thermal and acid factors. Attempts to obtain the reverse acyl-migration were unsuccessful.

THE intramolecular acyl-migration of the type in which X can be oxygen, sulphur or nitrogen, and the atoms involved lie on adjacent carbon atoms, has received considerable attention in the field of organic reaction mechanism.[1] The formation of a cyclic



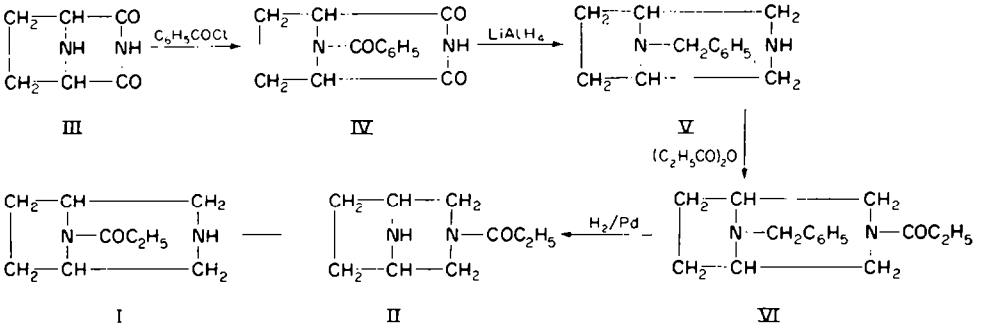
A B C

transition state (B), the stereochemistry of which determines the acyl-migration rate, is accepted as an explanation of the reaction.[2–4] The examples most studied are the N → O and O → N acyl-migrations, which are generally catalysed by acids or bases.[5–7] Only two examples of N → N′ acyl migration are described: viz. $PhCO(R)–N–CH_2–CH_2–NH_2 \rightarrow RNH–CH_2–CH_2–NH–COPh$.[8] When R = Ph, the rearrangement occurs spontaneously on liberation of the base from its hydrobromide; when R = cyclohexyl, migration occurs only by thermal action.

A new example of N → N′ acyl migration, in which the atoms involved are not on adjacent atoms, but are transannularly oriented is now presented. This rearrangement is induced by both thermal and chemical factors and it is irreversible. During a systematic investigation of the 3,8-diazabicyclo[3.2.1] octane derivatives, an attempt was made to condense 8-propionyl-3,8-diazabicyclo[3.2.1]octane (I) with an unreactive aralkyl halogenide in boiling toluene. After refluxing the reaction mixture for 24 hours the halogenide was recovered, together with a product (II; b.p. 0·2 mm 125–136°, m.p. 39–40°) which analysed for $C_{19}H_{18}N_2O$. The IR spectrum in CCl_4, although similar to that of I in the functional zone, differed in the finger print region due to the presence

[1] I. Mathieu and A Allais, *Cahiers de synthèse organique* Vol. VI; p. 384. Masson & C., Paris (1960).
[2] A. P. Phillips and R. Baltzly, *J. Amer. Chem. Soc.* **69**, 200 (1947).
[3] L. H. Welsh, *J. Amer. Chem. Soc.* **71**, 3500 (1949).
[4] G. Fodor, V. Bruckner, J. Kiss and G. Ohegyi, *J. Org. Chem.* **14**, 337 (1949).
[5] G. Fodor and K. Nàdor, *Nature, Lond.* **169**, 462 (1952).
[6] G. Fodor and K. Nàdor, *J. Chem. Soc.* 721 (1953).
[7] A. Nickon and L. F. Fieser, *J. Amer. Chem. Soc.* **74**, 5566 (1952).
[8] C. J. M. Stirling, *J. Chem. Soc.* 4351 (1958).

of a strong band near 1235 cm^{-1}. These data presented evidence for isomerisation and the structure of 3-propionyl-3,8-diazabicyclo[3.2.1]octane seemed the most probable for II. This was confirmed by an unambiguous synthesis. Thus 3,8-diazabicyclo[3.2.1]-octane-2,4-dione[9] (III) was benzoylated to 8-benzoyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (IV) which, on reduction, was transformed to the 8-benzyl-3,8-diazabicyclo[3.2.1]-octane (V). The latter gave with propionic anhydride the 3-propionyl-8-benzyl-3,8-diazabicyclo[3.2.1]octane (VI) which was eventually debenzylated to 3-propionyl-3,8-diazabicyclo[3.2.1]octane. The compound obtained by synthesis is identical (IR spectrum and m.p.) with the product obtained by rearrangement. As additional proof, the rearranged compound was transformed by methylation with formaldehyde and formic acid to a product which showed identity (IR spectrum) with an authentic sample of 3-propionyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (VII).[10]



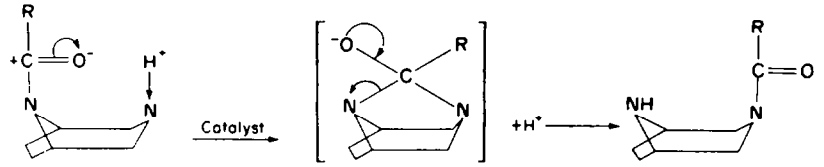
The hypothesis that acyl migration could be induced by thermal factors was found consistent: in fact, by refluxing I(a) in benzene, (b) in toluene or (c) by heating at 120° without solvent, rearrangement to II occurred. Periodical IR analyses of samples from (a), (b) and (c), showed that complete rearrangement was achieved after 32, 24 and 5 hours respectively.

Treatment of compound I with 10% sodium hydroxide for 4 hours yielded the rearranged product II (examined by IR analysis). The identification of II before distillation precluded any possibility that thermal rearrangement had taken place during purification. Attempts to obtain the reverse rearrangement in acid medium (aqueous or ethanolic hydrochloric acid) at room temperature were unsuccessful as II was recovered unchanged. Under more drastic conditions (refluxing in aqueous or ethanolic hydrochloric acid) hydrolysis of II occurred, yielding 3,8-diazabicyclo[3.2.1]-octane dihydrochloride (VIII).[9]

Surprisingly, I, on refluxing an ethanolic solution in the presence of a stream of dry hydrogen chloride, yielded, besides a small amount of VIII, an oily hydrochloride which on treatment with an ethereal solution of ammonia, gave II. Since ammonia does not induce rearrangement of I, the heating in an acid ethanolic solution must be responsible for the acyl migration. This result was confirmed by experiment, I being stable both in boiling ethanol and on standing at room temperature in an ethanolic solution of hydrogen chloride; moreover, I may be distilled with the Ronco technique[11] without appreciable modification.

[9] C. Cignarella, G. G. Nathansohn and E. Occelli, *J. Org. Chem.* **26**, 2747 (1961).
[10] G. Cignarella, E. Occelli and E. Testa, *J. Med. Pharm. Chem.* in press.
[11] K. Ronco, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta* **39**, 2088 (1956).

A general mechanism of this rearrangement, involving a cyclic intermediate[1] analogous with the transition state B may be postulated. The polarization of the amido-carbonyl group provides the center for nucleophilic attack at the carbonyl carbon atom:



I II

Whatever the action of the catalyst, it appears that the I → II acyl migration is essentially due to favorable steric factors, the orientation of the acyl group toward the hexatomic ring[12] being responsible for the formation of the cyclic intermediate.

The rearrangement may also be connected with the greater nucleophilicity of the 8-nitrogen atom of II as compared with that of the 3-nitrogen in I which should facilitate the 3 → 8 proton transfer. This hypothesis was confirmed experimentally,[13] the nucleophilic reaction between 3,8-diazabicyclo[3.2.1]octane and ethylene oxide (equimolar amount) yielded exclusively the 8-hydroxyethyl derivative.[14] It was also found that the 8-nitrogen of II is more basic (pk_a 7·75)[15] than the 3-nitrogen of I (pk_a 6·85)[15] thus suggesting a parallelism between nucleophilicity and basicity in the 3,8-diazabicyclo[3.2.1]octane series.

Finally, the experiments were repeated with the 8-benzoyl-derivative (IX). This compound was prepared by benzoylation of 3-benzyl-3,8-diazabicyclo[3.2.1]octane (X)[9] followed by catalytical hydrogenation of the 3-benzyl-8-benzoyl-3,8-diazabicyclo-[3.2.1]-octane (XI). Compound IX rearranged to the isomer 3-benzoyl-3,8-diazabicyclo[3.2.1]octane (XII) under similar conditions employed for the conversion of I to II. The analytical and IR data confirm the structure assigned to XII. It is noteworthy that the isolation of XII was carried out by crystallization from ether thus avoiding any doubt concerning a thermal rearrangement during purification of the product.

The IR spectrum of XII in CCl_4 shows, besides the tertiary-amide band at 1645 cm^{-1}, a strong band near 1260 cm^{-1} (already observed in the spectrum of II) which is lacking in the IR spectrum of IX. Furthermore, the IR spectra of various 3-acyl-8-alkyl-3,8-diazabicyclo[3.2.1]octanes show a similar strong band near 1260 cm^{-1}, which must therefore, be characteristic for the 3-acyl-diazabicyclo[3.2.1]octanes.

A similar rearrangement to be reported later has also been observed in the diazabicyclo[3.3.1]nonane series.[18]

[12] Similar orientation of substituents in position 8, due to the crowding effect of the endoethylenic bridge, is accepted in the tropane series.

[13] G. Cignarella, E. Occelli and E. Testa, unpublished work.

[14] This result disagrees with the known lowering of nucleophilic activity of amines due to branching on the α-carbon atom.[16,17] One might, however, object that this rule was proved by studies on primary amines and that piperidine was the only secondary amine investigated.[16] Therefore, no definite conclusions may be drawn concerning the reactivity of secundary amines.

[15] By potentiometric titration in aqueous methanol with 0·1 N H_2SO_4.

[16] M. E. Smith and H. Adkins, *J. Amer. Chem. Soc.* **60**, 657 (1938).

[17] E. Mc C. Arnett, J. G. Miller and A. R. Day, *J. Amer. Chem. Soc.* **72**, 5636 (1950).

[18] G. Cignarella and E. Testa, *Gazz. Chim. Ital.* in press.

EXPERIMENTAL

Preparation of 8-*propionyl*-3,8-*diazabicyclo*[3.2.1]*octane* (I)

3-*Benzyl*-8-*propionyl*-3,8-*diazabicyclo*[3.2.1]*octane*. Propionic anhydride (12·8 ml) was cautiously added at 0° to 6·7 g 3-benzyl-3,8-diazabicyclo[3.2.1]octane[9] (X) and the mixture heated 1·5 hr at 100°. After cooling, 10 ml 6N HCl was added and the unreacted anhydride extracted with ether. The aqueous layer was cooled to −5° and treated with excess 50% NaOH. The oil, which separated, was extracted with ether, the extracts dried (Na_2SO_4) and the solvent evaporated. The oily residue was distilled to give 7·4 g (86·5%) of the expected compound, b.p. 170–174° (1 mm). (Found: C, 74·13; H, 8·66; N, 10·91. $C_{16}H_{22}N_2O$ requires: C, 74·37; H, 8·58; N, 10·84%).

Debenzylation of 3-*benzyl*-8-*propionyl*-3,8-*diazabicyclo*[3.2.1]*octane*. A solution of 7·3 g of the compound in 60 ml absolute ethanol was hydrogenated in the presence of 3 g 10% palladium on charcoal at 60° and with 50 atm of hydrogen pressure. The hydrogenation proceeded smoothly. The catalyst was filtered off, the solvent evaporated and the residue on distillation yielded 4·3 g (89%) of I, b.p. 120–121° (0·1 mm). (Found: C, 64·11; H, 9·82; N, 16·62. $C_9H_{16}N_2O$ requires: C, 64·24; H, 9·58; N, 16·65%).

Preparation of 8-*benzoyl*-3,8-*diazabicyclo*[3.2.1]*octane* (IX)

3-*Benzyl*-8-*benzoyl*-3,8-*diazabicyclo*[3.2.1]*octane* (XI). To a stirred solution of 2.3 g X in 10 ml 2 N NaOH cooled to −5°, 1·92 g of benzoyl chloride was added dropwise, and the mixture stirred for 3 hr at room temp, then diluted with 10 ml water and extracted with ether. The extract was dried (Na_2SO_4) and the solvent evaporated to give 2·9 g of a viscous undistillable oil which was transformed by ethanolic hydrochloric acid to the hydrochloride (3 g), m.p. 219–221° (ethanol). (Found: C, 69·98; H, 6·48; N, 7·96; Cl, 10·57. $C_{20}H_{23}N_2ClO$ requires: C, 70·05; H, 6·76; N, 8·17; Cl. 10·34%).

Debenzylation of XI. The crude free base (XI), obtained from 2·8 g of the hydrochloride, was dissolved in 50 ml absolute ethanol and hydrogenated for 6 hr in the presence of 0·9 g 10% palladium on charcoal, at 60° and 60 atm of hydrogen pressure. The catalyst was filtered off, the solvent evaporated and the residue distilled to give 1·5 g (80%) of 8-benzoyl-3,8-diazabicyclo[3.2.1]octane (IX), b.p. 140–142° (0·5 mm). On standing the product solidified and was crystallized from ether, m.p. 82–83°. Found: C, 72·01; H, 7·55; N, 12·82. $C_{13}H_{16}N_2O$ requires: C, 72·19; H, 7·45; N, 12·95%).

Preparation of 3-*propionyl*-3,8-*diazabicyclo*[3.2.1]*octane* (II)

8-*Benzoyl*-3,8-*diazabicyclo*[3.2.1]*octane*-2,4-*dione* (IV). To a stirred solution of 3·6 g 3,8-diazabicyclo[3.2.1]octane-2,4-dione[9] (III) in 50 ml benzene and 2·5 g pyridine, 4·4 g benzoyl chloride was added. The mixture was heated 3 hr at 60° then allowed to stay 1 hr at room temp; on cooling a white compound precipitated which was washed with water and crystallized from ethanol to give 4·3 g (70%) of IV m.p. 157–158°. (Found: C, 64·02; H, 5·15; N, 11·30. $C_{13}H_{12}N_2O_3$ requires: C, 63·92; H, 4·95; N, 11·47%).

8-*Benzyl*-3,8-*diazabicyclo*[3.2.1]*octane* (V). To a stirred suspension of 5 g lithium aluminium hydride in 40 ml tetrahydrofurane, a solution of 4 g of IV in 100 ml tetrahydrofurane was added dropwise, then the mixture was refluxed under stirring for 7 hr. After cooling to −5°, 15 ml water was cautiously added and the reaction mixture stirred 1 hr at room temp. The inorganic matter was filtered off and washed with ether. The filtrate was dried (Na_2SO_4) and evaporated and the residue dissolved in 20 ml benzene and dried again (KOH). The solvent was evaporated and the residue distilled to give 2·5 g (76%) of V, b.p. 118–120° (0·6 mm). (Found: C, 77·11; H, 9·15; N, 13·76. $C_{13}H_{18}N_2$ requires: C, 77·18; H, 8·97; N, 13·84%). The dihydrochloride had m.p. 247–250° (ethanol). (Found: N, 10·40; Cl, 25·62; $C_{13}H_{20}Cl_2N_2$ requires: N, 10·17; Cl, 25·76%).

3-*Propionyl*-8-*benzyl*-3,8-*diazabicyclo*[3.2.1]*octane* (VI). To 2·4 g of V, cooled to 0°, 4·2 ml propionic anhydride was cautiously added. The reaction mixture was heated at 100° for 1·5 hr then cooled and poured into 10 ml 6 N HCl. The unreacted propionic anhydride was extracted with ether and the aqueous layer made alkaline with an excess 50% NaOH. An oil separated which was extracted with ether, the extract dried (Na_2SO_4) and evaporated. The residue was distilled to yield 2·45 g (80%) of VI, b.p. 150–151° (0·2 mm). (Found: C, 74·66; H, 8·66; N, 11·01. $C_{16}H_{22}N_2O$ requires: C, 74·37; H, 8·58; N, 10·84%).

Debenzylation of VI. A solution of 2·4 g of VI in 50 ml absolute ethanol was hydrogenated in the presence of 1 g 10% palladium on charcoal at 60° and 20 atm hydrogen pressure. After 6 hr the mixture was cooled, the catalyst removed by filtration and the solvent evaporated *in vacuo*. The

residue was distilled to give 1·1 g (71%) of 3-propionyl-3,8-diazabicyclo[3.2.1]octane (II), b.p. 125–126° (0·2 mm). On standing the product solidified and sublimed at 80° (0·1 mm), m.p. 39–40°. (Found: C, 64·35; H, 9·82; N, 16·62. $C_9H_{16}N_2O$ requires: C, 64·24; H, 9·58; N, 16·65.

Acyl migration $N_{(8)} \rightarrow N_{(3)}$

(a) *By thermal rearrangement.* I → II. 8-Propionyl-3,8-diazabicyclo[3.2.1]octane (I; 1 g) was heated at 120° and a sample examined each hr by IR spectrum. After 2 hr a band at 1235 cm^{-1} appeared which is characteristic of the IR spectrum of the 3-propionyl-3,8-diazabicyclo[3.2.1]octane (II). After 5 hr, as soon as the IR analysis showed complete rearrangement, the heating was stopped and the oily compound (0·9 g) distilled to give 0·8 g pure II, b.p. 125–126° (0·2 mm), m.p. 39–40° (sublimed). This compound was identical by IR comparison and by mixed m.p. with synthetic II When I was refluxed in toluene or in benzene, changes in the IR spectra were observed after 5 and 15 hr; the rearrangement completed after 24 and 32 hr respectively.

IX → XII. 8-Benzoyl-3,8-diazabicyclo[3.2.1]octane (IX), m.p. 82–83° (1 g) was heated 5 hr at 120°. On cooling the product solidified and could be crystallized from ether to give 0·85 g of 3-benzoyl-3,8-diazabicyclo[3.2.1]octane (XII), m.p. 122–123°. The IR spectrum in CCl_4 solution showed bands at 1635 cm^{-1} (tertiary amide), 1260 cm^{-1} (characteristic band of 3-acyl-3,8-diazabicyclo[3.2.1]octane) and 707 cm^{-1} (CH out of plane of phenyl group). (Found: C, 71·98; H, 7·59; N, 13·07. $C_{13}H_{16}N_2O$ requires: C, 72·19; H, 7·45; N, 12·95%).

(b) *By base catalysed rearrangement.* I → II. The 8-propionyl-3,8-diazabicyclo[3.2.1]octane (I; 1 g) was suspended in 5 ml 2N NaOH, and a small amount of ethanol was added to obtain a clear solution. After 4 hr at room temp, the solution was concentrated to ½ volume at 25° under red press and extracted with ether. The extract was dried (Na_2SO_4), the solvent evaporated and the residue distilled by the Ronco technique[11] to give 0·75 g of an oil, at 125–130° (0·2 mm) which on standing solidified (m.p. 38–40° after sublimation) and the IR spectrum in CCl_4 was identical with that of pure 3-propionyl-3,8-diazabicyclo[3.2.1]octane (II).

IX → XII. The 8-benzoyl-3,8-diazabicyclo[3.2.1]octane (IX; 1 g) was dissolved in 2 ml ethanol, 5 ml 2 N NaOH was added and the clear solution allowed to stand 4 hr at room temp. The reaction mixture was concentrated and extracted with benzene. The extract was dried (Na_2SO_4) and the solvent evaporated to give 0·72 g of a solid which after crystallization from ether yielded 0·62 g of 3-benzoyl 3,8-diazabicyclo[3.2.1]octane (XII), m.p.122–123°. The IR spectrum of XII was identical with that of the product obtained by thermal rearrangement of IX.

(c) *By thermal-acid rearrangement.* I → II. The 8-propionyl-3,8-diazabicyclo[3.2.1]octane (I; 1 g) was dissolved in 10 ml absolute ethanol, the solution saturated with dry HCl and refluxed 2 hr in a stream of dry HCl. During the reaction 360 mg of a white crystalline product separated which was identified by mixed m.p. and by IR spectra as 3,8-diazabicyclo[3.2.1]octane dihydrochloride (VIII).[9] The alcoholic solution was evaporated *in vacuo* and the viscous residue treated during cooling with excess 20% ethanolic ammonia solution. By adding ether the inorganic salt was precipitated and after filtration the solvent was evaporated at 25° *in vacuo*. The oily residue (0·65 g) was distilled by the Ronco technique[11] to give 0·58 g pure 3-propionyl-3,8-diazabicyclo[3.2.1]octane (II). In separate experiments, compound I was recovered unchanged (a) after refluxing 8 hr in ethanol, thus ruling out a merely thermal rearrangement; (b) after standing 4 days in ethanolic hydrochloric acid, thus excluding a merely acid rearrangement. Moreover, to prove that no acyl migration occurred during the isolation of the product, the compound I was recovered unchanged after standing 1 hr in 20% ethanolic ammonia and after distillation of amounts of 1–5 g by the Ronco technique.[11]

IX → XII. An ethanolic solution of 8-benzoyl-3,8-diazabicyclo[3.2.1]octane (IX; 1 g) was refluxed 2 hr in a stream of HCl. After cooling, 0·3 g VIII was collected by filtration, the filtrate evaporated *in vacuo*, the viscous residue dissolved in ethanolic ammonia and the solution worked up as described for I. The crude product isolated was crystallized from ether to give 0·65 g of XII, m.p. 122–123°.

Behaviour of 8-propionyl-(I) *and 3-propionyl-3,8-diazabicyclo*[3.2.1]*octane* (II) *in aqueous acidic medium*

(a) *At room temperature.* A solution of 0·5 g of I (or II) in 5 ml 5% hydrochloric acid was allowed to stand 24 hr at room temp (20°). The solution was then concentrated to dryness at 35–40° *in vacuo* (1 mm) the oily residue dissolved in a small amount of ethanol and treated during cooling with excess ammonia in ether solution. The inorganic salt was filtered off and the filtrate evaporated to give about 0·4 g of the starting compound.

(b) *On heating*. A solution of 0·5 g of I (or II) in 5 ml 5% hydrochloric acid was refluxed for 2 hr, then concentrated to dryness *in vacuo*. The solid residue was crystallized from 95% ethanol to give 0·4 g of a white crystalline compound which after drying at 100° *in vacuo* melted at 305–310° (dec) and was found identical (IR spectra) with an authentic sample of 3,8-diazabicyclo[3.2.1]octane dihydrochloride (VIII).

Methylation of 3-propionyl-3,8-diazabicyclo[3.2.1]octane. To 0·7 g (0·015 mole) formic acid and 0·81 g (0·005 mole) 3-propionyl-3,8-diazabicyclo[3.2.1]octane obtained by rearrangement of I, 0·79 g 38% formaldehyde (0·01 mole) was added. The mixture was gently refluxed 15 hr, cooled, treated with 1 ml hydrochloric acid and concentrated *in vacuo* at 30–40°. The residue made alkaline by addition of 30% sodium hydroxide solution was extracted with ether. The organic solution, after drying (KOH), was evaporated and the residue distilled *in vacuo* to give 0·54 g 3-propionyl-8-methyl-3,8-diazabicyclo[3.2.1]octane b.p. 100–112° (1 mm), (Found C, 65·93; H, 10·09; N, 15·50. $C_{10}H_{18}N_2O$ requires: C, 65·89; H, 9·95; N, 15·37%).

The IR spectrum of this product was identical with that of 3-propionyl-8-methyl-3,8-diazabicyclo-[3.2.1]octane obtained by propionylation of 8-methyl-3,8-diazabicyclo[3.2.1]octane.[10]

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