[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

USE OF ACYL MIGRATION IN SEPARATING DIASTEREOISOMERIC AMINO ALCOHOLS

GÁBOR FODOR, V. BRUCKNER, J. KISS, AND GÉZA ÓHEGYI

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In a recent communication (1) we reported that under the same experimental conditions *dl*-1-(3,4-diethoxyphenyl)-2-acetamido-1-propanol (IIf), synthesized from 1-(3,4-diethoxyphenyl)-1-nitroso-2-nitropropane (If), reacted instantly with hydrogen chloride in absolute alcohol to form the salt of the corresponding O-acetylamino alcohol (IIIf), whereas the N-acetyl derivative of the diastereoisomeric aminopropanol, obtained by reduction of 3,4-diethoxy-α-isonitrosopropiophenone (VIf), remained unchanged. Welsh (2) had previously observed a difference between the rates of the acetyl migration reaction of N-acetyl-*dl*-ephedrine and N-acetyl-*d*-ψ-ephedrine.

This paper deals with a comparative study on acyl migration in three different diastereoisomeric pairs of amino alcohols.

dl-Norephedrine (VIIj) was prepared from α-oximinopropiophenone (VIj) (3). *dl*-Nor-ψ-ephedrine was synthesized from propenylbenzene *via* 1-phenyl-1-nitroso-2-nitropropane and 1-phenyl-2-nitro-1-acetoxypropane, according to the principle of Bruckner's synthesis (4); the formation of norephedrine could not be detected. The *N*-benzoyl derivatives of these diastereoisomers behave differently towards alcoholic hydrogen chloride; N-benzoyl-*dl*-norephedrine did not undergo acyl migration in the course of three days at room temperature, whereas N-benzoyl-*dl*-nor-ψ-ephedrine yielded the calculated amount of O-benzoyl-*dl*-nor-ψ-ephedrine hydrochloride (5). This behavior prompted us to attempt the separation of these diastereoisomers by the acyl migration reaction. For this purpose *dl*-norephedrine was converted into a mixture of the two diastereoisomers, benzoylated and treated subsequently with hydrogen chloride in absolute alcohol. The salt of O-benzoyl-*dl*-nor-ψ-ephedrine which was formed could be separated easily from the unchanged N-benzoyl-*dl*-norephedrine through its far greater solubility in water; it was then converted by reverse acyl migration into N-benzoyl-*dl*-nor-ψ-ephedrine. The separated N-benzoylated diastereoisomers gave rise on acetylation to different O-acetyl-N-benzoyl derivatives. Their formation without inversion is at variance with the assumption of Kanao (6), *i.e.*, that esterification in the ephedrine series must always be combined with a Walden inversion. Our results are in agreement with those of Welsh (2) and of Bretschneider (7) who have conducted esterification with retention of configuration in the acetylation of ephedrine hydrochloride.

This new method for separation is all the more interesting in view of the results of Hoover and Hass (8), who were unable to separate satisfactorily *dl*-norephedrine from *dl*-nor-ψ-ephedrine.

We wanted to extend this method to the separation of acylated ephedrines

from acylated ψ-ephedrines. For this purpose N-benzoyl-*dl*-ψ-ephedrine and the corresponding derivative of *dl*-ephedrine were prepared. In alcoholic hydrogen chloride, the former showed a spontaneous benzoyl shift yielding O-benzoyl-*dl*-ψ-ephedrine hydrochloride. N-benzoyl-*dl*-ephedrine gave on similar treatment varying amounts of O-benzoyl-*dl*-ψ-ephedrine hydrochloride, depending upon the time it was kept in alcoholic hydrogen chloride. For example, on adding this reagent to N-benzoyl-*dl*-ephedrine, evaporating the solvent after a few minutes, and allowing the residue to crystallize, the main bulk of the amide was recovered; a smaller part, however, was converted into O-benzoyl-ψ-ephedrine hydrochloride because of an inversion prior to acyl migration.[1] However, the presence of an appreciable amount of inverted material was not evidenced on inoculation of the residue immediately after evaporation of the solvent.

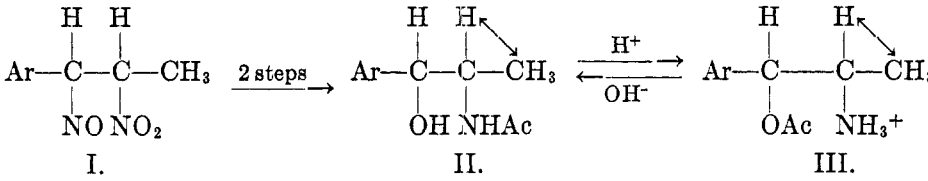
Several attempts were undertaken to separate a mixture of N-benzoyl-ephedrine from N-benzoyl-ψ-ephedrine by treating the mixture with an excess of alcoholic hydrogen chloride for a few minutes, cautiously removing the solvent, and allowing the residual sirup to crystallize; on keeping the sirupy mixture for several days in a desiccator, only O-benzoyl-*dl*-ψ-ephedrine hydrochloride could be isolated because of an inversion of N-benzoylephedrine. However, if the mixture was extracted with water immediately after removal of alcohol, the unchanged crystalline ephedrine derivative was obtained, whereas the O-benzoyl-ψ-ephedrine salt went into solution. In this case inversion of the acylated ephedrine derivative took place to only a small extent. A still more successful separation of the diastereoisomers was achieved by adding only the amount of alcoholic hydrogen chloride equivalent to the quantity of ψ-ephedrine derivative present. This procedure should be useful in the separation of mixtures of optically active derivatives in which the content of ψ-ephedrine derivative can be calculated from rotation data.

Finally, the behavior of a diastereoisomeric pair containing a phenyl group instead of the methyl group of norephedrine was investigated. *dl*-1,2-Diphenyl-2-aminoethanol (Type VII), prepared by reduction of benzoin oxime (10), was isomerized to a mixture of the two diastereoisomers, then acetylated and treated with alcoholic hydrogen chloride. As expected, *dl*-1,2-diphenyl-2-acetamidoethanol (11a) was recovered besides *dl*-1,2-*iso*-diphenyl-2-amino-1-acetoxyethane hydrochloride (Type III) (11b). The different solubilities of the amide and the salt rendered separation easy. The hydrochloride was then converted into the neutral *dl*-1,2-*iso*-diphenyl-2-acetamidoethanol (11b), formulated erroneously as an O-acetyl base (12). The same results were obtained in the separation of mixtures of known composition which were prepared from the pure diasteroisomeric acetyl derivatives.

These examples illustrate the possibilities given by the new method of separation. Attempts to extend and to refine it are in progress.

[1] Similar changes of configuration combined with an N → O acyl shift have been recorded in the cases of other N-acylephedrines; e.g., N-*p*-nitrobenzoyl-*l*-ephedrine by the action of cold aqueous hydrochloric acid gave O-*p*-nitrobenzoyl-*d*-ψ-ephedrine hydrochloride (9). On the other hand, N-acetyl-*dl*-ephedrine yielded, under other experimental conditions, the salt of O-acetyl-*dl*-ephedrine (2).

The reason for the great difference between N-acylated norephedrine and nor-ψ-ephedrine derivatives from the point of view of acyl migration must be sought in the configurations of the two series of compounds. Similar differences are



I. II. III.

Substituents of Ar

4-methoxy (a) (19a)

3,4-dimethoxy (b) (4)

3-methoxy-4-acetoxy (c) (19a)

3-methoxy-4-benzyloxy (d) (19c)

3,4-dibenzyloxy (e) (19b)

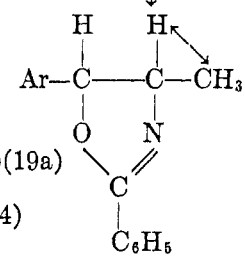
3,4-diethoxy (f) (1)

3,4-dihydroxy (g) (19b)

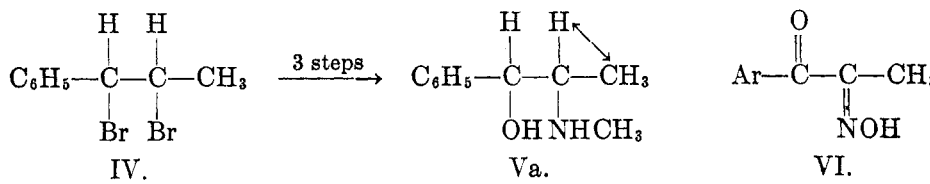
3-methoxy-4-hydroxy (h)(19a)

3,4-methylenedioxy (i) (4)

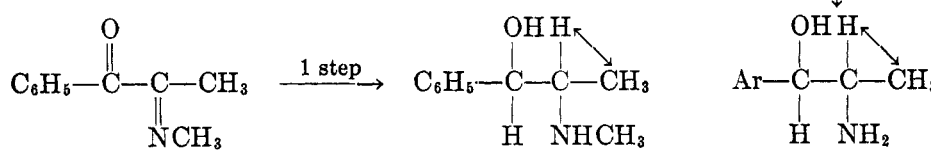
Ar = phenyl (j) (3)



IX f, j.



IV. Va. VI.



VIII. Vb. VII.

Substituents of Ar

3,4-dimethoxy (b) (20a)
3,4-diethoxy (f) (1)
3,4-dihydroxy (g) (20b)

3-methoxy-4-hydroxy (h) (20c)
Ar = phenyl (j)

observed in their behavior in forming an oxazoline ring. N-benzoyl-*dl*-nor-ψ-ephedrine gives by the action of cold thionyl chloride (5) the corresponding oxazoline derivative (IXj) with retention of configuration, whereas similar treatment of the appropriate norephedrine derivative results in a Walden inversion prior to condensation, and yields an oxazoline derivative related to ψ-ephedrine. In our experiments, N-benzoyl-3,4-diethoxy-*dl*-nor-ψ-ephedrine readily furnished an

oxazoline (IXf) salt as a result of the action of thionyl chloride. From the analogous diastereoisomer we were, however, unable to isolate any crystalline product. These facts may be perhaps explained by supposing that a case of restricted rotation (13, 14) occurs, in which the acylamino and hydroxyl groups are more frequently *cis* in acyl (nor)-ψ-ephedrines and *trans* in acyl (nor) ephedrines. The hydroxyl group of N-benzoylephedrine may assume a position of proximity to the acylamino group (which position is needed for acyl migration) more easily by inversion than by rotation.

Regarding ephedrine and ψ-ephedrine, Späth (15) speculated that in the molecule of ψ-ephedrine the hydroxyl and methylamino groups are placed spatially nearer to each other than in the molecule of ephedrine. Possible evidence for this supposition is presented by the fact that ψ-ephedrine, unlike ephedrine, does not form a hydrate. This difference in behavior was explained by Emde (16) as due to interaction of residual affinities of the functional groups in the ψ-isomer. The presence of a hydrogen bridge (17) between the propanol oxygen and the neighboring nitrogen of the methylamino group seems to us a better explanation; this suggestion must, however, be supported by infra red data. It is also of interest to consider that syntheses of aminopropanols (Ia-i; j; Va) starting with propenylbenzene derivatives always lead to ψ-(nor)ephedrines (18, 19). A *cis* addition of nitroso and nitro groups (or of bromine IV) to the propene double bond is more favored than a *trans* addition; if these groups are exchanged by amino and hydroxyl groups (assuming no Walden inversion takes place) the latter ought to retain the same relative positions. On the other hand, reduction of oximino or alkimino ketones (VIII) leads exclusively to (nor)-ephedrine derivatives VII or Vb (20, 21). Manske and Johnson (21) assumed that in alkimino ketones the nitrogen and oxygen atoms are spatially on opposite sides of the carbon chain, because of a repulsive effect, and that they respectively predestine the positions of the succeeding alkamino and hydroxyl groups.

All mentioned facts seem to support the validity of Späth's suggestion for ephedrine and ψ-ephedrine. However, the ready formation of different oxazolidines from ephedrine (22) and from ψ-ephedrine (23) is at variance with the behavior of acylated (nor)ephedrine derivatives. We must, however, take into consideration that restricted rotation does not exclude the possibility for rotation; it signifies only that certain steric positions are energetically more stable, and that the shift into another position requires an amount of energy (14).

The elucidation of the relative steric position of the hydroxyl and of the substituted amino groups does not give any evidence regarding the relative steric position of H and of CH_3 in the molecule of ephedrine and ψ-ephedrine, respectively (24). We suggest new projection formulas which are more in agreement with the results of acyl migration experiments. The positions of the hydrogen atom and the methyl group on carbon atom number 2, however, still remain to be settled (25, 26).

EXPERIMENTAL

A. *dl-Norephedrine and -nor-ψ-ephedrine derivatives. O-acetyl-dl-nor-ψ-ephedrine hydrochloride from propenylbenzene.* To a mixture consisting of 30 g. (0.254 mole) of propenyl-

benzene in 150 cc. of ether and 80 g. of sodium nitrite in 100 cc. of water, 150 cc. of 20 per cent by volume sulfuric acid was added drop by drop in the course of an hour. The crystalline 1-phenyl-1-nitroso-2-nitropropane was isolated in the usual manner (4) and could be recrystallized from chloroform; yield, 40%; m.p. 129–130°.

Anal. Calc'd for $C_9H_{10}N_2O_3$: C, 55.7; H, 5.2. Found: C, 55.8; H, 5.3.

1-Phenyl-1-acetoxy-2-nitropropane. From 30 g. of the nitroso-nitro compound was obtained 26 g. of the oily nitro ester suitable for electrolytic reduction.

O-acetyl-dl-nor-ψ-ephedrine hydrochloride. An amorphous N-acetyl derivative was prepared from 11.2 g. of the nitro ester by the method of reduction described elsewhere (4). The product was converted by the action of absolute ethereal hydrogen chloride into colorless needles of the amino ester hydrochloride; m.p. 183° after recrystallization from ethyl acetate.

Anal. Calc'd for $C_{11}H_{17}ClNO_2$: C, 57.5; H, 7.0. Found: C, 57.5; H, 7.0.

dl-Norephedrine. This substance was prepared according to Hartung and Munch (3) from propiophenone via α-oximinopropiophenone. Reduction to norephedrine was carried out in two steps, as described by Hartung, *et al.* (20b) for other aryl propanolamines; yield, 91%.

N-Benzoyl-dl-norephedrine. This hydroxy amide was prepared under Schotten-Baumann conditions (5); m.p. 143°. To a solution of 0.2 g. of compound in 12 cc. of anhydrous ethanol was added 0.23 cc. of 5 *N* alcoholic hydrochloric acid. The mixture was allowed to stand for five days at room temperature in a desiccator during which time the solvent slowly evaporated. The dry residue was then dissolved in 100 cc. of hot water, the solution was cooled, the crystals separated, and the liquid concentrated; a total of 0.189 g. (94.5%) of crystals was obtained; m.p. 142–144°, alone and mixed with N-benzoylnorephedrine. The mother liquid yielded 8 mg. of crystals. Consequently, no appreciable acyl migration occurred under these experimental conditions.

Conversion of dl-norephedrine into dl-nor-ψ-ephedrine. A solution of 2 g. (0.0107 mole) of *dl*-norephedrine hydrochloride in 50 cc. of hydrochloric acid (14 g. HCl per 100 cc. water) was refluxed for twelve hours. The solvent was removed and the residue was dissolved in absolute alcohol; evaporation afforded 1.96 g. of colorless crystals, consisting of a mixture of the hydrochlorides of the two diastereoisomers; m.p. 100–135°.

Separation of dl-norephedrine from dl-nor-ψ-ephedrine. (*a*). The mixture obtained above (1.95 g., 0.0104 mole) was dissolved in 40 cc. of water, and 6 cc. of 5 *N* sodium hydroxide and 1.75 g. (0.0128 mole) of benzoyl chloride in 2 cc. of benzene were added at 40°; 2.4768 g. of a mixture of the diastereoisomeric N-benzoyl derivatives, m.p. 85–110°, was thus obtained. This was dissolved in 25 cc. of anhydrous ethanol, 3.2 cc. of 4.4 *N* hydrogen chloride (0.0141 mole) in anhydrous alcohol was added and the solution was kept for three days at room temperature. Evaporation of the alcohol *in vacuo* gave a crystalline residue, which was extracted twice with a total of 300 cc. of water. The undissolved part weighed 0.18 g., m.p. 132–136°, and was identical with N-benzoylnorephedrine (5). Concentration of the aqueous solution to 100 cc. furnished a further crop, 0.807 g. of crystals, m.p. 136–140°, identical with N-benzoylnorephedrine. Yield, 0.987 g. (40%, based upon the mixture of benzoyl derivatives). Recrystallization from benzene afforded colorless plates, m.p. 143° (5).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.3; H, 6.2.

The mother liquor was evaporated to dryness. The residue (1.213 g., 43%, based upon the mixture of benzoyl derivatives) melted at 205–210°, and was identical with O-benzoyl-*dl*-nor-ψ-ephedrine hydrochloride (5). Recrystallization of a sample from ethyl acetate gave colorless needles, m.p. 220°.

Anal. Calc'd for $C_{16}H_{18}ClNO_2$: C, 65.8; H, 6.2. Found: C, 65.5; H, 6.2.

It was further identified by reverse acyl migration (O → N), which yielded 1 g. N-benzoyl-*dl*-nor-ψ-ephedrine, m.p. 128°; recrystallized from benzene, m.p. 128°, alone and in admixture with an authentic specimen. Mixed m.p. with N-benzoyl-*dl*-norephedrine 85–110°.

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.71. Found: C, 75.45; H, 6.7.

(*b*). *n*-Benzoyl-*dl*-norephedrine (0.20 g., 0.00082 mole) and 0.20 g. of N-benzoyl-*dl*-nor-ψ-ephedrine were dissolved in 30 cc. of anhydrous alcohol, 0.47 cc. (3 moles per 2 moles amide) of 5 *N* hydrochloric acid in anhydrous alcohol was added. The solution was kept for three days at room temperature, and finally evaporated *in vacuo*. The dried product was treated with 150 cc. of hot water, and the separated crystals were filtered off. The mother liquor gave on concentrating to 20–30 cc. a further crop of crystals. The total yield was 0.1633 g. (81.6%) of pure N-benzoyl-*dl*-norephedrine, m.p. 140–144°. The filtrate was evaporated to dryness. The residual crystals (0.20 g., 82%) showed m.p. 215–216°, alone and in admixture with O-benzoyl-*dl*-ψ-ephedrine hydrochloride.

O-Acetyl-N-benzoyl-dl-norephedrine. One-half gram (0.0049 mole) of acetic anhydride was added to a solution of 0.2 g. (0.00082 mole) of N-benzoyl-*dl*-norephedrine (obtained in the above separation) in 4 cc. of anhydrous pyridine, and the whole was allowed to stand overnight at room temperature. The solvent was then evaporated *in vacuo*, and the residual gum recrystallized from 1.5 cc. of benzene: yield, 0.11 g., m.p. 143–144°; mixed m.p. with the starting material 110–115°.

Anal. Calc'd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4. Found: C, 72.7; H, 6.4.

O-acetyl-N-benzoyl-dl-nor-ψ-ephedrine. The crude ester was obtained from 0.4 g. (0.00164 mole) of N-benzoyl-*dl*-nor-ψ-ephedrine (obtained from the mixture of diastereoisomers) and 1 cc. (0.0098 mole) of acetic anhydride in 4 cc. of pyridine. Recrystallization from a mixture of 2 cc. of benzene and 10 cc. of petroleum ether afforded colorless plates, 0.337 g. (73%), m.p. 130–131°. On admixture with O-acetyl-N-benzoyl-*dl*-norephedrine, m.p. 104–120°; mixed with N-benzoyl-*dl*-nor-ψ-ephedrine, m.p. 99–120°.

Anal. Calc'd for $C_{18}H_{19}NO_3$: C, 72.7; H, 6.4. Found: C, 73.1; H, 6.45.

B. *dl-Ephedrine and -ψ-ephedrine derivatives. N-Benzoyl-dl-ψ-ephedrine.* This substance was obtained by using the Schotten-Baumann procedure given for the diastereoisomeric form. From 2.47 g. (0.015 mole) of ψ-ephedrine, 3.65 g. (90.3%) of this amide was secured, m.p. 116–116.5° after recrystallization from benzene-petroleum ether.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1. Found: C, 75.9; H, 6.9.

Acyl migration N → O. To 3.077 g. (0.0126 mole) of this amide in 30 cc. of absolute ethanol was added 3.64 cc. (0.0175 mole) of 4.8 *N* hydrogen chloride in absolute ethanol and the whole was evaporated *in vacuo* after twenty minutes. The crystalline product (2.958 g., m.p. 193–197°) was recrystallized from absolute alcohol. It was identical with O-benzoyl-*dl*-ψ-ephedrine hydrochloride.

Anal. Calc'd for $C_{17}H_{20}ClNO_2$: C, 66.75; H, 6.6. Found: C, 66.1; H, 6.4.

Acyl migration O → N. To 2.49 g. (0.0084 mole) of this hydrochloride in 40 cc. of water, 5 *N* sodium hydroxide was added; 2.08 g. (91.7%) N-benzoyl-*dl*-ψ-ephedrine was thus obtained, m.p. 116.5°.

N-Benzoyl-dl-ephedrine. To a stirred solution of 2.47 g. (0.015 mole) of *dl*-ephedrine in 44 cc. of 0.5 *N* hydrochloric acid maintained at 40–50° were added, first, 1.8 cc. (0.0154 mole) of benzoyl chloride in 2 cc. of benzene, and subsequently 10 cc. of 20% sodium hydroxide. The yield was 3.7 g. (91.8%) of N-benzoyl-*dl*-ephedrine, m.p., 109–110°, after recrystallization from benzene petroleum ether.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1. Found: C, 75.6; H, 7.2.

Experiments on acyl migrations. (*a*). To a solution of 1.35 g. (0.0052 mole) of N-benzoylephedrine in 10 cc. of anhydrous ethanol was added 1.56 cc. (1.5 moles per mole) of 4.8 *N* HCl in ethanol and the solution was evaporated at 25° after 20 minutes. The sirupy residue crystallized on standing for a few days in a desiccator. After treatment with 10 cc. of water, the crystals were filtered off; they consisted of 0.8784 g. (65%) of the starting material, m.p. 105–109°. The filtrate was evaporated *in vacuo* to dryness, the sticky residue was heated with 10 cc. of benzene and the mixture was filtered. The crystals, 0.353 g., showed m.p. 192–197°; they were identical with O-benzoyl-*dl*-ψ-ephedrine hydrochloride.

(*b*). N-benzoyl-*dl*-ephedrine (0.538 g.) was dissolved in 5 cc. of absolute alcohol, 0.5 cc. of 4.1 *N* HCl in absolute alcohol was added, and, after 15 minutes, the solution was evapo-

rated to dryness at 25° *in vacuo*. The sirupy residue was taken up in 2 cc. of absolute alcohol, and evaporated again. The now crystalline residue was first extracted with 15 cc. of cold water, then with 10 cc. of warm water; the undissolved part weighed 0.4722 g. (87%); m.p. 108–110°, alone and mixed with N-benzoylephedrine. The aqueous solution was evaporated; the crystalline residue (0.0258 g.) did not show a sharp m.p. (150–175°).

(*c*). On allowing 0.538 g. of the benzoyl derivative to react with 2 molecular proportions (0.978 cc.) of 4.1 *N* HCl in absolute alcohol, and working up the mixture exactly as described under (*b*), 0.4424 g. (82%) of unchanged benzoylephedrine, m.p. 108–110°, was recovered; 0.056 g. underwent acyl migration.

Attempts to separate N-benzoyl-dl-ephedrine from N-benzoyl-dl-ψ-ephedrine. (*a*). A mixture consisting of 2.69 g. (0.0105 mole) of each diastereoisomer was dissolved in 20 cc. of absolute alcohol, and 5.37 cc. of 5.6 *N* hydrogen chloride (0.0301 mole) in absolute alcohol was added. After 20 minutes, the solvent was removed at 25°, under 18 mm. pressure, and the sirupy residue was treated with a few cc. of absolute ethanol, then kept for several days in a desiccator until it became solid and no more traces of hydrochloric acid could be observed. To the crystals 40 cc. of cold water was added; filtration of the mixture yielded a crop of O-benzoyl-*dl*-ψ-ephedrine hydrochloride which weighed, after washing with 40 cc. of water, 2.899 g.; m.p. 195–199°. The filtrate, on concentrating to half of its volume, yielded a further crop, 1.365 g.; m.p. 195–198°. The dry residue weighed 1.675 g., m.p. as above. Total yield, 5.89 g. (99.8% based on the mixture of the benzoylated diastereoisomers). The excess of hydrogen chloride therefore exerted in the course of several days a configurational change in benzoylephedrine prior to acyl migration. The hydrochloride thus obtained was converted into N-benzoyl-*dl*-ψ-ephedrine by dissolving it in 50 cc. of water and treating with 5 *N* sodium hydroxide. The product, 5.05 g., showed m.p. 105–112°. After recrystallization from benzene and petroleum ether the m.p. rose to 116–116.5°, alone and in admixture with N-benzoyl-*dl*-ψ-ephedrine.

(*b*). To a solution of 0.538 g. of N-benzoyl-*dl*-ephedrine and 0.538 g. of N-benzoyl-*dl*-ψ-ephedrine in 10 cc. of absolute alcohol, 1 cc. of 4 *N* HCl in absolute ethanol was added and the mixture was kept for 15 minutes at room temperature. The solvent was then removed under reduced pressure at 25°, and the sticky residue was dissolved in a few cc. of absolute alcohol. On evaporating again, a partly crystalline residue resulted, which was extracted with 20 cc. and subsequently with 15 cc. of cold water. The undissolved crystals weighed 0.4398 g. (91%), and were identical with N-benzoyl-*dl*-ephedrine. The aqueous solution afforded on evaporation 0.6214 g. (102%) of O-benzoyl-*dl*-ψ-ephedrine hydrochloride, m.p. 197–200°.

(*c*). To a solution of 1.35 g. (0.0052 mole) of N-benzoyl-*dl*-ephedrine and 1.35 g. of N-benzoyl-*dl*-ψ-ephedrine in 10 cc. of absolute alcohol, 1.1 cc. of 4.7 *N* hydrogen chloride (0.0052 mole) in absolute alcohol was added. After 20 minutes the solvent was evaporated at 25° and 18 mm. pressure, and the residue was taken up in 2–3 cc. of absolute ethanol and evaporated again. The crystalline residue was dried over calcium chloride overnight, then triturated with 30 cc. of water, filtered, and washed with 30 cc. of water. The undissolved portion weighed 1.3 g. (96%); m.p. 104–107°, also in admixture with N-benzoyl-*dl*-ephedrine; mixed m.p. with N-benzoyl-*dl*-ψ-ephedrine: 85–95°. The aqueous filtrate afforded on evaporation 1.48 g. (96%) of the hydrochloride of O-benzoyl-*dl*-ψ-ephedrine, m.p. 195–197°.

C. *Derivatives of 1,2-diphenyl-2-aminoethanol. dl-1,2-Diphenyl-2-acetamidoethanol.* *dl*-1,2-Diphenyl-2-aminoethanol was prepared from benzoin oxime (10). From 0.5 g. of the amino alcohol and 0.28 g. of acetic anhydride in 9 cc. of dry pyridine at room temperature was obtained 0.523 g. (98.9%) of the amide, m.p. 196–197° (11a).

Attempt to effect acyl migration. To 0.3 g. (0.0012 mole) of the amide in 25 cc. of anhydrous ethanol, was added 0.35 cc. (0.0018 mole) of 5 *N* hydrogen chloride and the solution was kept for three days at room temperature. Evaporation of the solvent furnished 0.295 g. of product insoluble in water, m.p. 196°, identical with the starting material. Acyl migration therefore did not occur.

Conversion of dl-1,2-diphenyl-2-aminoethanol into its diastereoisomer. A solution of 5 g. of the hydrochloride of the amino alcohol in 150 cc. of hydrochloric acid (25 g. HCl per 100 cc. of water) was refluxed for twenty hours, decolorized with charcoal, and evaporated to dryness. The white crystalline residue was dissolved in a few cc. of water, and then alkalized. The mixture of diastereoisomeric free bases so obtained (2.4 g.) melted at 110–140°.

Separation of the acetyl derivatives of dl-1,2-diphenyl-2-aminoethanol and dl-1,2-iso-diphenyl-2-aminoethanol. Two and four-tenths grams (0.011 mole) of the mixture of the diastereoisomers obtained above was dissolved in 40 cc. of dry pyridine, and 1.2 cc. (0.012 mole) of acetic anhydride was added. The resulting greenish solution was kept for 24 hours at 25°, then was evaporated *in vacuo* almost to dryness, and the product filtered off; yield, 2.3 g., m.p. 105–150°.

(*a*). To a solution of 1.66 g. (0.0065 mole) of this mixture in 40 cc. of absolute ethanol, 1.3 cc. of 5.5 *N* hydrochloric acid (0.0071 mole) in anhydrous alcohol was added and the mixture was worked up after 24 hours. After removal of the solvent *in vacuo* at 40–45°, the residue was treated with 75 cc. of boiling water. The undissolved part weighed 0.73 g., m.p. 165–172°, and consisted of *dl*-1,2-diphenyl-2-acetamidoethanol. After recrystallization from 3.5 cc. of ethanol, the yield amounted to 0.56 g., m.p. 192–194°. For analysis it was repeatedly recrystallized from ethanol; the m.p. rose to 198° (11a).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.15; H, 7.0.

The 75 cc. of aqueous filtrate gave on alkalization 0.69 g. of white crystals of *dl*-1,2-*iso*-diphenyl-2-acetamidoethanol. Recrystallization from benzene afforded 0.48 g. of crystals, m.p. 147–149°. After one more recrystallization, the m.p. rose to 155° (11b).

Anal. Calc'd for $C_{16}H_{17}NO_2$: C, 75.3; H, 6.7. Found: C, 75.1; H, 7.2.

(*b*). To a solution of 0.21 g. (0.0008 mole) of *iso*-acetamide and 0.21 g. of the acetamide (m.p. 192°) in 9 cc. of absolute alcohol-benzene (8:1), was added 0.41 cc. of 5.6 *N* HCl in absolute alcohol and the mixture was kept at room temperature for 24 hours. The separated colorless needles, 0.146 g., showed m.p. 192–196°. The hydrochloride of *dl*-1,2-*iso*-diphenyl-2-amino-1-acetoxyethane, obtained from a similar experiment, was recrystallized for analysis from absolute ethanol and formed white radial needles, m.p. 204–205° (11b).

Anal. Calc'd for $C_{16}H_{18}ClNO_2$: C, 65.8; H, 6.2. Found: C, 65.5; H, 6.5.

The evaporation of alcohol from the filtrate at 40° furnished a crystalline residue, which was extracted with three 10-cc. portions of hot water; the undissolved part weighed 0.196 g. (93%), was free of chlorine and had m.p. 196–197°, alone and mixed with 1,2-diphenyl-2-acetamidoethanol.

The previously obtained hydrochloride, 0.146 g., was dissolved in 30 cc. of water, then alkalized; the precipitated amide, 0.174 g. (83%), showed m.p. 146–147° and was identical with *dl*-1,2-*iso*-diphenyl-2-acetamidoethanol.

D. *Oxazoline derivatives from N-benzoyl-3,4-diethoxy-dl-nor-ψ-ephedrine.* (*a*). To 0.5 g. of the corresponding benzamide (1), was added 1.6 cc. of thionyl chloride; the mixture melted and became yellow with simultaneous evolution of hydrogen chloride. The whole was kept for three hours at room temperature, then 70 cc. of dry ether was added and the solution was allowed to stand at −5° to −10° for three days. The separated crystals were collected on a filter, washed with a few cc. of dry ether, then recrystallized from petroleum ether; yield, 0.3 g., m.p. 107°. The product contained ionic chlorine. The analytical data agree with those calculated for 2-phenyl-4-methyl-4,5-dihydro-5-(3,4-diethoxyphenyl)oxazole hydrochloride (IX).

Anal. Calc'd for $C_{20}H_{24}ClNO_3$: C, 66.4; H, 6.7. Found: C, 66.5; H, 6.8.

(*b*). Treatment of 0.5 g. of N-benzoyl-3,4-diethoxy-*dl*-norephedrine (1) exactly in the above described manner did not give rise to a crystalline salt. A reddish-brown oil was secured, which could not be crystallized from petroleum ether.

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SUMMARY

A new method has been described for the separation of diastereoisomeric amino alcohols based upon the different reactivity of N-acylephedrines and N-acyl-ψ-ephedrines towards alcoholic hydrogen chloride. The latter series of compounds form salts of O-acylated amino alcohols, which because of their far greater solubility in water can be separated easily from the unchanged amides of ephedrine series. Acylated norephedrine, *dl*-ephedrine and 1,2-diphenyl-2-aminoethanol have been separated from their diastereoisomers by use of the method.

The different reactivities of the diastereoisomers (2, 1) is supposedly due to restricted rotation, in consequence of which the hydroxyl and acylamido groups are in proximity to each other only in the case of acylated ψ-ephedrines. New projection formulas have been proposed in view of these experimental facts. The configuration of ephedrine at the nitrogen bearing carbon atom remains to be settled (25).

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