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

CONFIGURATION OF DIASTEREOISOMERIC 3-METHOXY-4-HYDROXYPHENYLPROPANOLAMINES

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In a previous communication (1) a synthesis of 1-(3-methoxy-4-hydroxyphenyl)-2-aminopropanol-1 (IVa) was described; this proceeded from isoeugenol benzyl ether *via* IA → IIa → III → IVa (route *A*). The hydrochloride of IVa melted at 205°. Other investigators (2) had prepared an amino alcohol of the same structure by a method analogous to ours, from isoeugenol acetate *via* IB → Va → IV (route *B*), but they recorded m.p. 176° for the hydrochloride of IV. We assumed that the compounds are diastereoisomers (1).

By the same type of synthesis, two closely related starting materials led to two end-products of assumedly different configuration. The reason for this discrepancy remained still to be elucidated. This seemed all the more interesting, as Welsh (3) called our attention to the same problem. He thought that IV obtained by route *B* would possess the same configuration as ephedrine, whereas using method *A*, deacetylation of IIa to III would result in a change of configuration, so that IVa would belong configuratively to ψ-ephedrine.

We record briefly our investigations, which afforded elucidation of the question, as follows. The acetamido derivative IIa was converted by hydrogenolysis into the phenolic compound VIa, and this, in turn, was acetylated to Va. The latter proved to be identical with the diacetyl derivative Va, obtained from isoeugenol acetate by route *B*. Consequently, IIa and Va are of the same configuration. As in our experiments both acetamides IIa and Va underwent an instantaneous N → O acetyl migration by the action of alcoholic hydrogen chloride,[1] they probably are related configurationally to ψ-ephedrine (4, 5).

Change of this configuration could occur either (a) in converting IIa into III, or (b) during deacetylation of Va to IV.

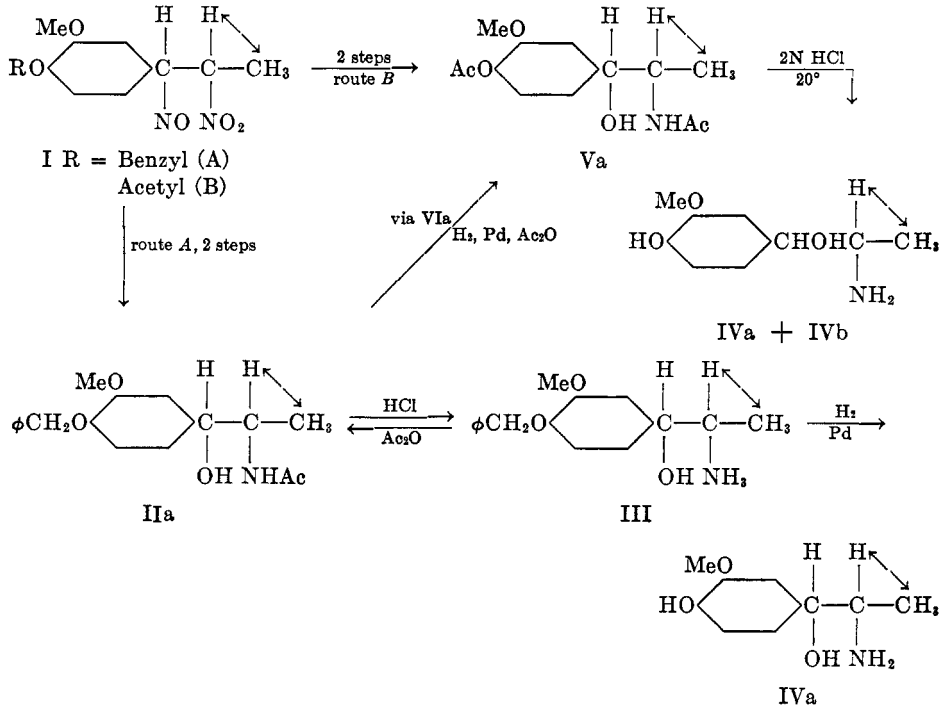
We deacetylated IIa to III, according to (1) by heating the nearly neutral aqueous solution of the corresponding O-acetyl amino alcohol; III was then reacetylated with acetic anhydride in pyridine to give IIa in nearly quantitative yield, but no trace of its diastereoisomer IIb. It was thus proved that the isolated product III (1) of the deacetylation of IIa retained the configuration of ψ-ephedrine. Since III afforded by hydrogenolysis (1) IVa, the latter must have the same configuration, as hydrogenolysis never effects a change of configuration.

In order to determine the correctness of our second assumption (*i.e.*, that deacetylation of bis-acetyl-ψ-ephedrine derivative Va would be associated with Walden inversion, and lead to the hydrochloride of IV of ephedrine configuration)

[1] Bruckner and Krámli (2) carried out an acetyl migration experiment by adding the calculated 1 mole of hydrochloric acid in small portions to an acetone solution of Va in the course of 24 hours to avoid deacetylation. Acyl migration completed, therefore, only after the full amount of acid was added. This slow reaction prompted Welsh (3) to assume ephedrine configuration as well for Va as for the product of its deacetylation, IV.

we synthesized 1-(3-methoxy-4-hydroxyphenyl)-2-aminopropanol-1 by a method which led with analogous compounds selectively (6, 7) to norephedrine derivatives. This end-product should be identical with either the amino alcohol obtained by route *A*, or with that produced by method *B*.

We started with 3-methoxy-4-hydroxypropiophenone[2], prepared in a good yield from guaiacol and propionic acid with boron trifluoride. This ketone was, in turn, converted into the oximino ketone VII. With thionyl chloride the latter underwent secondary Beckmann rearrangement (9) to furnish, after hydrolysis,



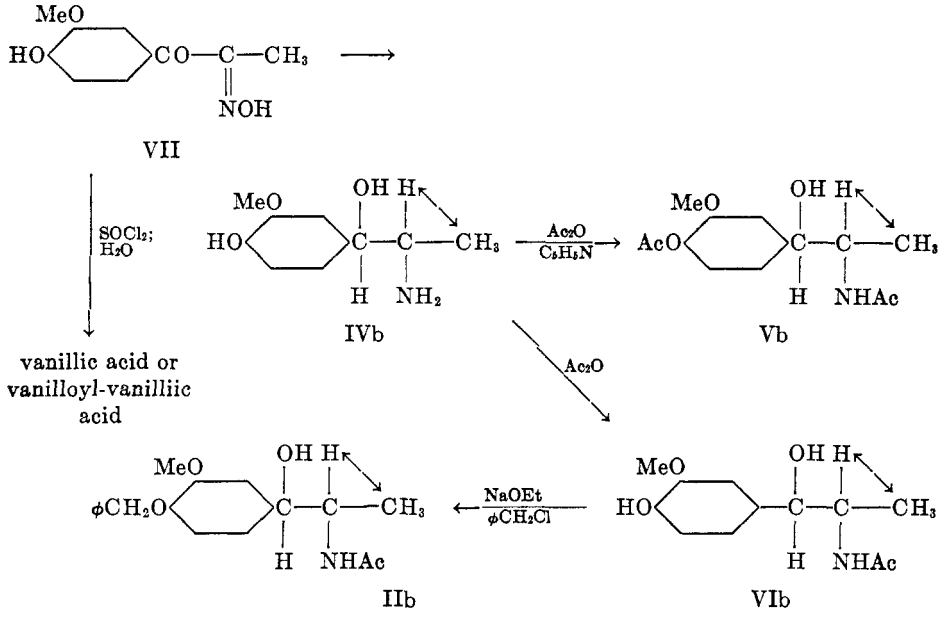
vanillic acid (under more energetic conditions vanilloylvanillic acid was formed. *para*-Position of the ketonic group to the phenolic hydroxyl was therefore proved. Reduction of the oximino ketone under Hartung's conditions furnished the hydrochloride of IVb, m.p. 217°, which gave a strong m.p. depression with IVa-hydrochloride from isoeugenol benzyl ether, m.p. 206°. The free base showed m.p. 170°; IVa melted at 149–150°. Methylation with diazomethane gave 3,4-dimethoxynorephedrine (10) while IVa gave on similar treatment 3,4-dimethoxynor-ψ-ephedrine (1), obtained also from the corresponding 1-nitroso-2-nitro compound (11).[3]

[2] Marshall (8) recorded Fries rearrangement of guaiacol propionate to this ketone in the presence of $AlCl_3$.

[3] Regarding the configuration of some amino alcohols produced by this type of synthesis compare (6).

Acetylation of IVb with 2 moles of acetic anhydride in pyridine yielded a 4,N-diacetyl derivative Vb, not identical with Va obtained from isoeugenol acetate and from isoeugenol benzyl ether through the corresponding 1-nitroso-2-nitro compounds. This acetamide, under mild conditions, did not undergo acyl migration N → O, proving thus its ephedrine configuration (4, 5).

Acetylation of IVb with one mole of anhydride gave rise to an alkali-soluble N-monoacetyl derivative VIb, which, in turn, was benzylated to IIb, not identical with IIa, produced by route *A*. Compound IIb did not undergo acyl migration spontaneously.



All these facts suggest that: 1. Synthesis of IVa starting from the nitroso-nitro compound IA led to a compound which is related configurationally to ψ-ephedrine, whereas reduction of oximino ketone VII produced the appropriate ephedrine derivative IVb. Therefore our earlier paper (1) must be modified, as the therein described compounds are "synthetic ψ-norephedrine derivatives" and not "synthetic norephedrine derivatives".

2. Synthesis of Va from nitroso-nitro derivative IB led similarly to a ψ-ephedrine derivative. However, this latter underwent an inversion during its hydrolysis to IV, so that the hydrochloride m.p. 176° (2) must therefore consist of a difficultly separable mixture of both diastereoisomeric amino alcohols IVa (m.p. 206°), and IVb (m.p. 217°).

EXPERIMENTAL

3-Methoxy-4-hydroxypropiophenone. A solution of 12.4 g. (0.1 mole) of guaiacol in 14.8 g. (0.2 mole) of propionic acid was saturated with boron trifluoride while cooling with ice.

In five hours the weight increased 15 g. The sirupy reddish mixture was heated at 70° for 90 min. in a water-bath, then poured with stirring into a solution of 22 g. of anhydrous sodium acetate in 90 cc. of water; the separated oil was extracted with a total of 150 cc. of ether. The solvent was then evaporated and the residual oil distilled *in vacuo*, b.p. 165–175° (5–7 mm.). Thirteen grams (77.4%) of crystals, m.p. 48–50°, was obtained, suitably pure for the preparation of the oximino ketone. Marshall *et al.* (8) recorded m.p. 60–62°.

3-Methoxy-4-hydroxy-α-oximinopropiophenone (*VII*). To a solution of 26 g. (0.14 mole) of 3-methoxy-4-hydroxypropiophenone in 120 cc. of benzene, 23.8 g. (0.13 mole) of 20% hydrogen chloride in dry ether, then 16.7 g. (0.16 mole) of isobutyl nitrite, were added in 30 min. while cooling with ice. After standing for a few hours in the ice-box, 20 g. of crystals was obtained; evaporation of benzene *in vacuo* furnished a further crop, 2 g., (a total of 84%); m.p. 144° after recrystallization from 50% ethanol.

Anal. Calc'd for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3.
Found: C, 57.1; H, 5.4.

Degradation. (a) Treatment of 1 g. (0.048 mole) of oximino ketone with 5 cc. (0.071 mole) of thionyl chloride under stirring caused a rise in temperature; the reddish-brown solution was evaporated, and the residual oil heated with 50 cc. of water. One cc. (0.005 mole) of 5 *N* sodium hydroxide was added and the undissolved part, 0.2 g., was filtered and the filtrate acidified; the radial needles which separated, 0.3 g., melted at 222–223°. Analysis gave data corresponding to those for vanilloylvanillic acid.

Anal. Calc'd for $C_{16}H_{14}O_7$: C, 60.4; H, 4.4.
Found: C, 60.1; H, 4.55.

(b) The above experiment was repeated, but addition of thionyl chloride was carried out dropwise under cooling with ice, and removal of excess thionyl chloride took place at 15–20°. The crystalline residue yielded on recrystallization from water pale yellow needles, 0.76 g. (94.5%) of vanillic acid, m.p. 205–206°, which was raised by further purification to 207–208° (12).

Anal. Calc'd for $C_8H_8O_4$: C, 57.1; H, 4.8.
Found: C, 56.8; H, 5.1.

3-Methoxy-4-hydroxy-dl-norephedrine (*IVb*). A solution of 31.5 g. (0.15 mole) of oximino ketone in 380 cc. of absolute alcohol was hydrogenated in the presence of 69 cc. of 5 *N* hydrogen chloride in absolute alcohol and 10 g. of Pd-charcoal (7% PdO). Absorption of hydrogen: 6750 STP-cc. (2 moles) in six hours. The excess of hydrogen chloride was neutralized with 20% sodium hydroxide solution, the catalyst-free solution evaporated to 60 cc. volume, and diluted with 170 cc. of water and hydrogenated with 5 g. of Pd-charcoal; uptake of hydrogen: 3350 STP-cc. in 5 hours. The residue from the solution was dissolved in 150 cc. of anhydrous alcohol, filtered from sodium chloride and concentrated to a 20–30 cc. volume; the crystals of IVb-hydrochloride were transferred to a filter with 20 cc. of ether, and washed with alcohol-ether; 19 g., 55%, m.p. 217° (dec.). Fodor (1) recorded m.p. 206° for IVa; a mixture melted from 184–192°.

Anal. Calc'd for $C_{10}H_{15}NO_3 \cdot HCl$: C, 51.37; H, 6.90.
Found: C, 51.53; H, 7.52.

Free base. Liberation was carried out in absolute alcohol using sodium ethoxide, and the resulting base was recrystallized from toluene; yellowish crystals, m.p. 169–170°.

Anal. Calc'd for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.7.
Found: C, 60.5; H, 7.7.

3,4-Dimethoxy-dl-norephedrine (*methyl ether of IVb*). To a solution of 0.8 g. of base IVb in 20 cc. of absolute methanol an ethereal diazomethane solution was added until nitrogen evolution ceased. The methylated amino alcohol, 0.8 g., was recrystallized from benzene; after washing with alkali, nearly colorless crystals were obtained, m.p., alone and in mixture with an authentic specimen (10) 139–140°.

N-Acetyl-3-methoxy-4-acetoxy-dl-norephedrine (*Vb*). To a solution of 0.6 g. (0.003 mole) of amino alcohol IVb in 20 cc. of pyridine, 0.65 cc. of acetic anhydride (0.0065 mole) was added. The solvent was removed after a day; the residue gave white needles from benzene, 0.52 g., m.p. 135–136°. The diastereoisomer melted at 164–165° (2).

Anal. Calc'd for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.8.
Found: C, 60.0; H, 6.9.

From 0.28 g. of Vb, 0.22 g. was recovered unchanged after standing ten hours with 0.2 cc. of 4 *N* alcoholic HCl in 2 cc. of absolute alcohol.

N-Acetyl-3-methoxy-4-hydroxy-dl-norephedrine (VIb). To 0.805 g. (0.004 mole) of the amino alcohol IVb, 0.86 cc. (0.008 mole) of acetic anhydride was added; an immediate reaction took place and the temperature rose to 40°. The crystals were collected after keeping the mixture for a day at room temperature; yield 0.758 g., m.p. 138–141°, raised to 142–143° after recrystallization from toluene.

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.2.
Found: C, 60.15; H, 7.2.

N-Acetyl-3-methoxy-4-benzyloxy-dl-norephedrine (IIb). A solution containing 0.24 g. (0.0012 mole) of the acetamido alcohol VIb, 25 cc. of anhydrous ethanol, 0.15 cc. (0.0012 mole) of benzyl chloride, and 0.024 g. (0.0012 atom) of sodium was refluxed for 20 hours and the filtered solution evaporated to dryness. The residue was recrystallized from 30 cc. of benzene to give 0.16 g. of white plates, m.p. 145–146°, mixed m.p. with IIa (m.p. 138°) 125–130°, From 0.15 g. of IIb, 0.13 g. was recovered unchanged after standing ten hours with 0.2 cc. of alcoholic 4 *N* HCl in 2 cc. of anhydrous alcohol.

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0.
Found: C, 69.4; H, 7.2.

Conversion of IIa into Va. One gram of N-acetyl derivative IIa in 15 cc. of absolute alcohol absorbed 70 cc. of hydrogen (calc'd for 1 mole, 68 STP-cc.) in the presence of 0.4 g. of Pd-charcoal in 30 min. The filtrate was evaporated, the residue, 0.32 g. of amorphous VIa, was dissolved in 1 cc. of dry pyridine, 0.15 cc. of acetic anhydride was added, and kept for 24 hours at room temperature. The solvent and acetic acid were removed *in vacuo* at 25° and the crystalline residue, 0.2 g., was recrystallized from alcohol; m.p. 163°, also in mixture with authentic Va from isoeugenol acetate (2). *Acyl migration* N → O. A solution of 0.1 g. of diacetyl product Va in 2 cc. of absolute alcohol was treated with 0.1 cc. of 4 *N* HCl in alcohol and the solution evaporated after 15 min. to dryness. The residual crystalline hydrochloride showed m.p. 192° (2). *Acyl migration* O → N. This hydrochloride (0.05 g.) was dissolved in 3 cc. of water and the N-acetyl derivative, 0.03 g., precipitated by sodium carbonate.

N-Acetyl-3-methoxy-4-benzyloxy-dl-nor-ψ-ephedrine (IIa) from 3-methoxy-4-benzyloxy-nor-ψ-ephedrine (III). Three tenths gram of III, prepared according to (1) with 40% yield, m.p. 129°, was added to 1 cc. of acetic anhydride with shaking. An exothermic reaction took place and the acetyl derivative crystallized from the solution, yield 0.25 g. after washing with a small amount of cold acetic acid, m.p. 138°, also in mixture with an authentic specimen of IIa (1).

Deacetylation of Va. 1. According to (2), 0.25 g. of Va, m.p. 165°, prepared by route *B* from isoeugenol acetate *via* IB, was added to 2.5 cc. of 2 *N* HCl and kept for 4 days at room temperature with occasional shaking. In 2 days the amide dissolved completely. The solution was evaporated *in vacuo* at 25° and 5 mm.; the amorphous residue could, however, not be crystallized. 2. A solution of 0.113 g. of Va in 0.86 cc. of *N* HCl (1.1 mole) was kept for 20 hours at room temperature, then heated for an hour on a steam-bath. Evaporation under 1–2 mm. pressure afforded a crystalline residue which could be recrystallized from alcohol-ether to furnish colorless prisms, m.p. 184–187°. This mixture of the assumed diastereoisomers proved to be unseparable by recrystallization.

Action of alcoholic hydrogen chloride upon IVb. 1. To a solution of 0.185 g. of IVb hydrochloride, m.p. 217°, in 20 cc. of alcohol, 0.6 cc. of 4 *N* HCl (3 moles) in absolute alcohol was added and the mixture refluxed for 3 hours. Evaporation gave 200 mg. of ammonium chloride, formed by a hydramine cleavage during the heating. 2. A solution of 0.032 g. of IVb-HCl in 10 cc. of absolute alcohol was refluxed for 46 min. with 0.06 cc. (1.5 mole) of 4 *N* HCl in absolute alcohol. Evaporation afforded an assumed mixture of diastereoisomers, m.p. 184–188°. Longer heating yielded a product, m.p. 170–184°.

The phenolic amino alcohol is obviously very sensitive towards acids, and apparently tends to undergo inversion easily.

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SUMMARY

Analogous syntheses (1, 2) of IV led to different products. It could be proved by synthesis of the ephedrine derivative of IVb and by several interconversions that both syntheses starting with 1-nitroso-2-nitro compounds Ia and Ib, respectively, led primarily to nor-ψ-ephedrine derivatives IIa and Va, respectively.[3] However, deacetylation of Va resulted in a partial inversion, leading to a mixture of IVa and IVb, whereas hydrolysis of IIa and subsequent hydrogenolysis of III furnished with retention of configuration the ψ-ephedrine derivative IVa.

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