146. *Some Derivatives of* d-*Nor-ψ-ephedrine.*

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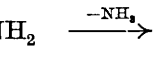
OUR intention was to prepare an active semicarbazide, *d*-nor-ψ-ephedrinoformylhydrazide, $CHPh(OH)\cdot CHMe\cdot NH\cdot CO\cdot NH\cdot NH_2$, and to utilise it for the resolution of benzoin (compare Hopper and Wilson, J., 1928, 2483) and of *p*-methoxyhydratropaldehyde (compare Betti, *Ber.*, 1930, **63**, 874). The hydrochloride of this hydrazide was prepared, but was found to be unsuitable for the purpose, since oily products only were obtained when the resolutions were attempted. It seems desirable, however, to report on some derivatives of *d*-nor-ψ-ephedrine obtained in the course of the work.

It was expected that a semicarbazone, when heated with *d*-nor-ψ-ephedrine (Gibson and Levin, J., 1929, 2754), would conform to the normal reaction, $CRR'{:}N\cdot NH\cdot CO\cdot NH_2 + HO\cdot CHPh\cdot CHMe\cdot NH_2 =$ (I) $CRR'{:}N\cdot NH\cdot CO\cdot NH\cdot CHMe\cdot CHPh\cdot OH + NH_3$, giving a nor-ψ-ephedrinoformylhydrazone (I), hydrolysis of which with hydrochloric acid would give *nor-ψ-ephedrinoformylhydrazide hydrochloride* (II). With acetonesemicarbazone an oil, which would not solidify, resulted; this with hydrochloric acid gave (II), which had the

formula $3HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2,4HCl,H_2O$. Acetophenonesemicarbazone also gave an oily non-crystallisable product which with hydrochloric acid gave hydrazine hydrochloride and a substance (III) identified later as *5-phenyl-4-methyl-2-oxazolidone*. Benzaldehydesemicarbazone, however, yielded a solid product, *benzaldehyde*-d-*nor-ψ-ephedrinoformylhydrazone* (I; R = Ph, R′ = H), which when boiled with very dilute hydrochloric acid gave (II); more concentrated acid (1%), however, gave in addition hydrazine hydrochloride and (III).

When boiled with concentrated hydrochloric acid, (II) gave hydrazine and *d*-nor-*ψ*-ephedrine salts (with a trace of ammonium chloride); a quantitative estimation showed that the hydrazine amounted to $\frac{2}{3}$ of the total nitrogen in the compound, which is in accordance with the formula for the hydrazide.

Substance (III) had the molecular formula $C_{10}H_{11}O_2N$. Hydrolysis by heating in a sealed tube with concentrated hydrochloric acid gave *d*-nor-*ψ*-ephedrine. When heated with syrupy phosphoric acid, it evolved carbon dioxide, a quantitative estimation showing that $\frac{1}{10}$ of the total carbon was thus liberated. The substance was synthesised by heating *d*-nor-*ψ*-ephedrine sulphate with urea, (III) being formed instead of the mono- or di-substituted urea which would have been expected (Davis and Blanchard, *J. Amer. Chem. Soc.*, 1923, **45**, 1816). Another synthesis was accomplished by heating *d*-nor-*ψ*-ephedrine sulphate with potassium cyanate (compare the synthesis of 2-oxazolidone by Knorr and Rössler, *Ber.*, 1903, **36**, 1280). This reaction proved that (III) was 5-phenyl-4-methyl-2-oxazolidone, formed thus: $HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH_2 + HNCO = HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH{\cdot}CO{\cdot}NH_2 \xrightarrow{-NH_3}$  The synthesis from *d*-nor-*ψ*-ephedrine sulphate and urea would then be as follows: $HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH_2 + CO(NH_2)_2 \xrightarrow{-NH_3}$ $HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH{\cdot}CO{\cdot}NH_2 \xrightarrow{-NH_3}$ (III). Hydrolysis of (III) would proceed thus: (III) + $H_2O \longrightarrow HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH_2 + CO_2$, one-tenth of the total carbon appearing as carbon dioxide. Although sparingly soluble in cold water, (III) dissolved readily in sodium hydroxide solution, probably owing to formation of the sodium salt of the amino-acid.

The hydrochloride (II) could not be dehydrated without decomposition; when heated under reduced pressure, it gave (III), hydrazine dihydrochloride, and hydrazine monohydrochloride: (II) = $2(N_2H_4,HCl) + N_2H_4,2HCl + 3$(III). The hydrochloride tended to decompose spontaneously in this way, for addition of picric acid to an alcoholic solution gave hydrazine picrate.

Probably, then, acetonesemicarbazone and acetophenonesemicarbazone reacted normally with *d*-nor-*ψ*-ephedrine, the oily products containing the expected nor-*ψ*-ephedrinoformylhydrazone, which is then hydrolysed by hydrochloric acid to give (II) or the decomposition product (III). The appearance of (III) in the hydrolysis of benzaldehyde-*d*-nor-*ψ*-ephedrinoformylhydrazone when the acid is too concentrated is due to the same reason.

d-Nor-*ψ*-ephedrine can be conveniently characterised by its N-*benzenesulphonyl* derivative. All the substances mentioned were dextrorotatory in alcoholic solution ($\lambda = 5461$) except (III), which was lævorotatory.

It is rather remarkable that the hydrochloride (II), when being formed from benzaldehyde-*d*-nor-*ψ*-ephedrinoformylhydrazone by hydrolysis with hot acid, rapidly reforms the benzaldehyde derivative as the solution cools, whereas the isolated and purified hydrochloride reacts with benzaldehyde much more slowly. Possibly there may be an equilibrium, $HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}NH_2 \rightleftharpoons HO{\cdot}CHPh{\cdot}CHMe{\cdot}NH{\cdot}C(OH)\langle\begin{smallmatrix}NH\\|\\NH\end{smallmatrix}$, the first substance predominating during the hydrolysis.

EXPERIMENTAL.

The *d*-nor-*ψ*-ephedrine used had $[\alpha]_{5461}^{21\cdot5^\circ}$ + 25·2° in water (c = 1·6368). N-*Benzenesulphonyl*-d-*nor-ψ-ephedrine* was prepared in the usual way from the base and benzenesulphonyl chloride with sodium hydroxide solution. It was precipitated from the acidified solution, washed with water, and crystallised from alcohol or benzene by addition of water or light petroleum, respectively, forming long prisms, m. p. 103—104° insoluble in water and light petroleum (Found: N, 4·8. $C_{15}H_{17}O_3NS$ requires N, 4·8%); $[\alpha]_{5461}^{17^\circ}$ + 8·9° in alcohol (c = 4·4788).

With acetonesemicarbazone. Equimolecular quantities of the semicarbazone and *d*-nor-*ψ*-ephedrine were heated in toluene for 12 hours at 110—120°, ammonia being evolved. Removal of the toluene under reduced pressure left a viscid yellow non-crystallisable oil which, after standing for a considerable time with a little concentrated hydrochloric acid, deposited *d*-nor-*ψ*-ephedrinoformylhydrazide hydrochloride (II); after being washed with ether, this crystallised from alcohol–ether in prismatic needles, m. p. 156°.

With acetophenonesemicarbazone. Equimolecular quantities of this semicarbazone and the amine were heated in toluene at 115—125°; solution with evolution of ammonia occurred. After 9 hours the solvent was removed under reduced pressure and the viscid yellow oil remaining was dissolved in ether. A trace of unaltered

semicarbazone slowly separated; evaporation of the filtered solution left a non-crystallisable oil. After this had stood in contact with a little hydrochloric acid for some days, some hydrazine hydrochloride separated and was removed; the residue was steam-distilled under reduced pressure, and the resulting solution concentrated to small bulk under reduced pressure. The pale brown, mealy solid remaining crystallised from benzene, on addition of light petroleum, in long prisms grouped in rosettes, m. p. 123°; it was 5-phenyl-4-methyl-2-oxazolidone (III).

With benzaldehydesemicarbazone. This substance and the amine (equimolecular quantities) were heated in toluene at 110—120°, ammonia being evolved. After 60 hours the cooled solution was poured into a flask previously moistened with water; this induced a rapid separation of crystals. The filtrate was evaporated under reduced pressure, and the residue recrystallised by addition of light petroleum to a benzene solution; the two crops were then recrystallised together from the same solvent mixture. *Benzaldehyde*-d-*nor-ψ-ephedrinoformylhydrazone* formed long prisms, m. p. 118° (yield, 83%) (Found: C, 69·0; H, 6·5; N, 14·1. $C_{17}H_{19}O_2N_3$ requires C, 68·7; H, 6·4; N, 14·1%). It gave a high rotation, $[\alpha]_{5461}^{19°}$ + 290·5° in alcohol (c = 1·9926).

d-*Nor-ψ-ephedrinoformylhydrazide hydrochloride* (II). The benzaldehyde derivative (12 g.) just described was boiled with 250 c.c. of hydrochloric acid (0·7%) and steam-distilled for 10 hours until all the aldehyde was removed. The residue left on evaporation of the aqueous solution dissolved completely in cold alcohol; evaporation of this solution in an evacuated desiccator gave a viscid yellow mass, which solidified somewhat on addition of light petroleum and evacuation at the pump but became sticky again on exposure to the air. It was purified by precipitation from alcoholic solution by addition of ether; the d-*nor-ψ-ephedrinoformylhydrazide hydrochloride* so obtained, m. p. 156°, formed prismatic needles soluble in water and alcohol and was identical with the specimen previously obtained. It reformed the benzaldehyde derivative on treatment with this aldehyde in aqueous-alcoholic solution, but the reaction was slow. In alcohol it gave $[\alpha]_{5461}^{17°}$ + 37·8° (c = 2·842) (Found: C, 45·4, 45·4; H, 6·5, 6·4; N, 15·9, 16·2; Cl, 17·9. $3C_{10}H_{15}O_2N_3,4HCl,H_2O$ requires C, 45·5; H, 6·4; N, 15·9; Cl, 18·0%).

The hydrochloride (II) was boiled for 5 hours with concentrated hydrochloric acid. After removal of some hydrazine hydrochloride which separated on cooling, the solution was evaporated, and the residue extracted with cold absolute alcohol to remove a further quantity of hydrazine hydrochloride. The alcoholic extract on

concentration deposited a trace of ammonium chloride; the filtrate on evaporation gave a residue, identified as *d*-nor-*ψ*-ephedrine by means of the benzenesulphonyl derivative. A quantitative estimation of the hydrazine was carried out by boiling a weighed quantity of the hydrochloride (II) with concentrated hydrochloric acid for 3 hours. After concentration the solution was made alkaline and heated with Fehling's solution; the nitrogen evolved was $\frac{2}{3}$ of the total nitrogen in the salt, so that the ratio hydrazine residue : amine residue = 1 : 1.

5-Phenyl-4-methyl-2-oxazolidone (III) was soluble in alcohol, ether, benzene, chloroform and hot water, sparingly soluble in cold water, and insoluble in light petroleum; it dissolved in cold caustic soda solution. It melted at 123° and was lævorotatory in alcoholic solution, $[\alpha]_{5461}^{19°} - 18{\cdot}0°$ ($c = 4{\cdot}9764$) [Found: C, 68·1, 68·1; H, 6·4, 6·2; N* (micro-Dumas), 8·0, 7·9, (micro-Kjeldahl) 7·9, 7·8; *M* (cryoscopic in camphor), 201, 209, 204. $C_{10}H_{11}O_2N$ requires C, 67·8; H, 6·2; N, 7·9%; *M*, 177]. When it was heated in a sealed tube with concentrated hydrochloric acid at 135° for 5 hours, *d*-nor-*ψ*-ephedrine (identified as the benzenesulphonyl derivative) and a trace of ammonium chloride were formed. Carbon dioxide was liberated on warming with syrupy phosphoric acid (Found: C, 6·7. $C_{10}H_{11}O_2N$ requires for C_1, 6·8%).

The oxazolidone was synthesised in two ways. (1) *d*-Nor-*ψ*-ephedrine sulphate (5 g.) and urea (0·8 g.) were heated in a flask with an air condenser (the oxazolidone is somewhat volatile) at 170—180° for 3 hours, ammonia being evolved. The cold residue was heated with water on a boiling water-bath; the solution after filtration from a small amount of oil deposited, on cooling, crystals of 5-phenyl-4-methyl-2-oxazolidone, m. p. 123° after recrystallisation from benzene–light petroleum. (2) An aqueous solution of the sulphate of the amine (6 g.) and potassium cyanate (2·3 g.) was heated for several hours and then concentrated on the water-bath, potassium sulphate being removed during the evaporation. The residual viscid, slightly greenish oil was heated to 120—130°; ammonia was evolved, and a hard glassy mass formed on cooling. This was extracted with absolute alcohol to remove potassium sulphate, and the alcoholic solution distilled, the temperature being gradually raised to 200—210°; the thick brown oil then frothed vigorously, ammonia being copiously evolved. When the evolution of gas had slackened, the heating was continued at 250° under somewhat reduced pressure. The oil obtained solidified rapidly on cooling, and was then extracted with boiling water; the extract, after

* Macro-estimations (Dumas) tended to give high results even with use of copper oxide–cobalt oxide mixture or of lead chromate on copper oxide.

filtration from a small quantity of oil, deposited the oxazolidone on cooling, m. p. 123°. The oxazolidone obtained by these two methods was identical with the substance, m. p. 123°, previously obtained.

Dehydration of the hydrochloride (II). Only a very small loss of weight occurred on heating at 100° for 3 hours under reduced pressure. A weighing tube containing some of the salt was placed in a glass bottle and heated at 140° at 7 mm. pressure till the frothing of the molten mass abated. A sublimate formed; extraction of this with cold water removed hydrazine hydrochloride, leaving a residue of the oxazolidone (III). Treatment of the residue in the weighing tube with benzene dissolved out the oxazolidone, leaving a mixture of unaltered hydrochloride, which was dissolved out by alcohol, and hydrazine monohydrochloride, identified as such by melting point (89°) and by comparison with an authentic specimen. The 5-phenyl-4-methyl-2-oxazolidone formed in this experiment was identical with the specimen previously obtained.

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