

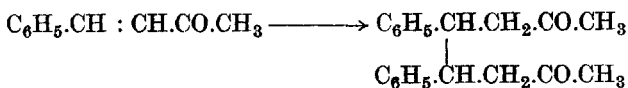
STUDIES IN THE ISOQUINOLINE SERIES.

PART VIII. 1,1'-BIS-TETRAHYDRO-ISOQUINOLINES.

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(Read January 2, 1940.)

As early as 1896, Harries and Eschenbach (*Ber.*, 1896, 29, 380), while reducing benzylidene acetone with moist sodium or aluminium amalgam, observed the formation of a dimolecular reduction product with a coupling at the β -position, thus:



Harries and co-workers (*Ann.*, 1897, 29, 380; *Ber.*, 1898, 31, 1806; *Ann.*, 1904, 330, 235) extended the study of these reductions to benzylidene acetophenone, methyl cyclohexanone, phorone, mesityl oxide and other similar compounds, and in all these cases obtained evidence of the formation of dimolecular reduction products.

Higginbotham and Lapworth (*J.C.S.*, 1923, 129, 594) have advanced the adsorption theory to account for the formation of these dimolecular products. A part of the molecules are supposed to be first adsorbed, and these then attacked by the other molecules still in solution. Two layers of simple molecules would then be formed one above the other, changing ultimately into one layer of double molecules by readjustment of electrons in the whole complex system made up of the molecules as well as the metal and the solvent. Alternatively, the individual molecules of the interacting pairs, which lie side by side, form part of the layer of molecules directly attached to the metal, and by subsequent readjustments of electrons in the systems, unite in pairs.

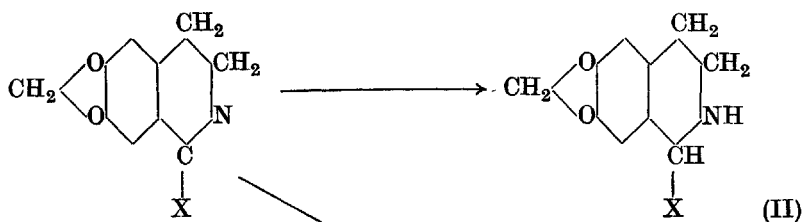
Israel Vogel has accepted the above theory as the most feasible, and as a result of a number of investigations on the reductions with aluminium amalgam of compounds of the type $\text{CR}_1\text{R}_2 = \text{CR}_3\text{R}_4$, where R_1, R_2 are groups or ring systems, and R_3, R_4 are H, CN, COOEt or COOMe (*J.C.S.*, 1927, 129, 594, 1985; *ibid.*, 1928, pp. 1017, 2010, 2032), has arrived at certain general conclusions as follows:—

1. The extent to which dimolecular reduction products are formed depends on the groups R_1, R_2 . The larger the volumes of these groups, the less the chances of dimolecular products being formed.
2. Other conditions being comparable, the nature of the compounds formed and their yields are controlled by the thickness and therefore the surface of the aluminium foil.

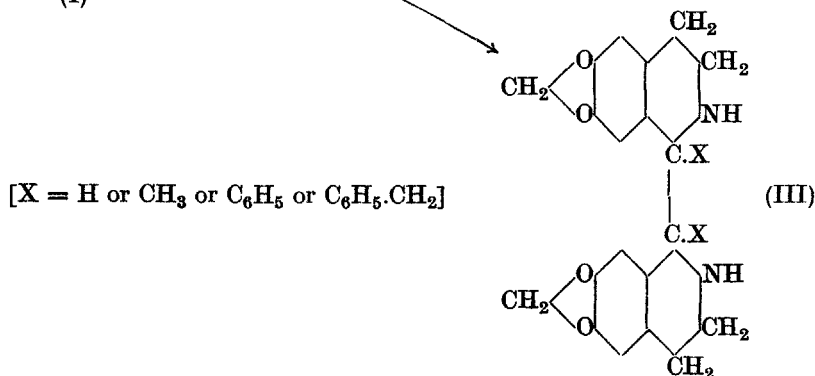
The reduction of substituted 3 : 4 dihydro-isoquinolines with aluminium amalgam, described in this communication, was undertaken with a view to study if such dimolecular products were formed at all during the reduction of the C = N linkage, and if so, how far the yields of these products were controlled by the nature and volume of the substituent attached to C-atom in position 1.

Norhydrastinine (6 : 7-methylene-dioxy-3 : 4-dihydro-isoquinoline) gave only about 15 per cent of the dimolecular products (1,1'-bis-norhydrohydrastinine) and about 55 per cent of the normal tetrahydro base, norhydrohydrastinine, while 1-methyl-norhydrastinine gave as much as 60-70 per cent of 1,1' bis-methyl-norhydrohydrastinine and only 5-10 per cent of 1-methyl-norhydrohydrastinine. On the other hand, with 1-phenyl-norhydrastinine, the normal reduction product, 1-phenyl-norhydrohydrastinine appeared to be exclusively formed (nearly 95 per cent), no evidence of the formation of any dimolecular reduction product being found. Again, 1-benzyl norhydrastinine gave 60 per cent of the dimolecular compound (1-1'-bis-benzyl norhydrohydrastinine) and 30 per cent of the monomolecular product, 1-benzyl norhydrastinine. The analytical data for the latter compounds are not yet complete, and this, together with the reduction of 1-cyclohexyl-, and 1-cyclohexyl methyl-norhydrastinine, will form the subject of a later communication.

The reduction of the various isoquinolines, studied in this paper is represented in the following scheme:—



(I)



[X = H or CH₃ or C₆H₅ or C₆H₅.CH₂]

Norhydrastinine, and the 1,methyl- and 1,phenyl-derivatives appear to have been synthesised by Decker and Becker (*Ann.*, 1913, 395, 313), but complete details have not been given by the authors. They are now described in full.

EXPERIMENTAL.

The aluminium amalgam required in these reductions was prepared according to the method of Vogel (*J.C.S.*, 1927, p. 597) with the difference that a 0.5 per cent instead of a 2 per cent solution of mercuric chloride was used.

Norhydrastinine.

2 gms. of homopiperonylamine were dissolved in 10 c.c. of dry ether and treated drop by drop with 0.6 gm. of anhydrous formic acid. The ether was then distilled off, and the salt heated in a small flask fitted with a cork carrying a CaCl_2 -tube, to 180° - 200° for 2 hours. After cooling, 8 c.c. of dry toluene and then 4 c.c. of phosphoryl chloride were added and the solution was heated on an oil-bath to 120° for one and half hours. On cooling, 15 c.c. of petroleum ether were added, allowed to stand for 15 minutes, and the toluene-petroleum ether layer decanted off. The gummy residue was dissolved in water, extracted with ether to remove non-basic impurities, cooled in ice and basified with caustic soda. The oil that separated was extracted with benzene, the benzene extract dried over solid potash and the benzene distilled off. 1.65 gm. of crude norhydrastinine (M.P. 83° - 85°) were thus obtained. Recrystallisation from ligroin gave 1.4 gm. of the pure product. M.P. 90° - 91° .

Reduction of norhydrastinine with aluminium amalgam.

2 gms. of norhydrastinine were added to 2.5 gms. of aluminium amalgam in 75 c.c. of moist ether. The flask was fitted with a double surface condenser and cooled in a large trough of cold water to minimise loss of ether. The evolution of hydrogen was found to cease immediately after the addition of the isoquinoline but was resumed after what might be called an induction period of 15-20 minutes. The reduction was allowed to proceed for 48 hours, a few drops of water being added at the end of 24 hours. The ether was filtered off, the residue ground thoroughly with more ether, and again filtered. (Residue A.)

The combined ether extracts left on distillation, 1.4 gm. of a mixture of solid and oil. This was treated with 10 c.c. of rectified spirits, warmed slightly, cooled and then filtered. 0.2 gm. of a solid was obtained which, after slow crystallisation from acetone, melted at 226° - 227° . White prismatic blocks.

The alcoholic filtrate gave, on evaporation, 1.15 gm. of oil. Treatment with rectified spirits was repeated if there was any sign of solid particles. The oil gave a nitroso-derivative crystallising in flat square plates. M.P. 226° . This was proved to be identical with the nitroso-derivative of norhydrodra-

stinine prepared by the reduction of norhydrastinine with zinc and sulphuric acid.

Residue A was dissolved in 20 c.c. of 4N HCl, filtered, treated with alkali until the solution remained slightly acidic, and precipitated with picric acid. The picrate (0.25 gm.) melted at 220°-221° after crystallisation from acetic acid (rhombic blocks). This was found to be identical with the picrate of the compound, M.P. 226°-227°, obtained from the ethereal solution and it could be converted into the free base in the usual way.

1-1', bis-norhydrodrastinine, (III, X = H), M.P. 226°-227°.

16.63 mg. of substance dried in vacuum gave 1.2251 c.c. of nitrogen at 33° and 757.6 mm. pressure.

Found : N, 8.19 per cent.

$C_{20}H_{20}O_4N_2$ requires N, 7.90 per cent.

The platinichloride, M.P. 299° (decomp.).

·0536 gm. gave ·0091 gm. of platinum.

Found : Pt, 16.97 per cent.

$[C_{20}H_{20}O_4N_2]_2 \cdot H_2PtCl_6$ requires Pt, 17.5 per cent.

$C_{20}H_{20}O_4N_2 \cdot H_2PtCl_6$ requires Pt, 25.75 per cent.

The nitroso-derivative. Thick rhombic needles from alcohol. M.P. 218° (d.)

11.42 mg. gave 1.1792 c.c. of N_2 at 28° and 764.3 mm.

Found : N, 11.79 per cent.

$C_{20}H_{18}O_6N_4 \cdot 2H_2O$ requires N, 11.66 per cent.

Benzoyl derivative. Clusters of tiny rhombic needles from alcohol. M.P. 263°.

Picrate. Crystallised from acetic acid as thick rhombic plates. M.P. 220°-221° (decomp.).

Methiodide, M.P. 225°—sparingly soluble in alcohol, unlike the methiodide of norhydrodrastinine.

1, methyl-6, 7-methylenedioxy-4, 5-dihydroisoquinoline.

2 gms. of homopiperonylamine were dissolved in 10 c.c. of dry ether, and treated with 1.5 gm. of acetic anhydride drop by drop. The ether was then distilled off, and the thick oil left behind was treated with 8 c.c. of dry toluene and 2 c.c. of $POCl_3$ and kept at 120°-130° for one and a half hours. After cooling, 20 c.c. of petroleum ether were added, allowed to stand for 10 minutes and the toluene-petroleum ether was decanted off. The gummy residue was dissolved in 30 c.c. of water, and extracted with ether to remove non-basic impurities. The acid solution was then strongly cooled and basified with caustic soda. The oil that separated was extracted with benzene dried over caustic potash and the benzene distilled off. The oil that was left behind solidified immediately. Yield, 2.1 gm. M.P. 81°-88° raised to 92° on crystallisation from ligroin.

Reduction of the above isoquinoline with aluminium amalgam.

2 gms. of the isoquinoline were added to 2.5 gms. of aluminium amalgam in 75 c.c. of moist ether and the experiment conducted in the same way as with norhydrastinine. Shiny white crystals began to separate soon after the initial period of induction, during which hydrogen ceased to be evolved, was over, but the reaction was allowed to proceed as usual for 48 hours.

The solid residue in the flask was filtered from the ether, ground up thoroughly with more ether, and again filtered. (Residue A.) The collective ether filtrates left on distillation a mixture of solid and oil. This was treated with about 10 c.c. of rectified spirits. The oil dissolved, and the undissolved solid was filtered off. This melted at 162° and after recrystallisation from acetone, melted at 165°. Rhombic plates. Yield, 0.1 gm. It is practically insoluble in cold alcohol and dissolves sparingly in benzene, ether, ligroin, and more readily in hot acetone and chloroform.

The alcoholic filtrate gave, on evaporation under reduced pressure in a desiccator, only 0.1 gm. of an oil which readily formed a sparingly soluble hydrobromide, M.P. 268°, and a picrate, M.P. 185° identical with the hydrobromide and picrate respectively of 1-methyl 6,7-methylene dioxy-1,2,3,4-tetrahydroisoquinoline.

Residue A was ground up in a mortar with 30 c.c. of 8N HCl, filtered, and the cooled filtrate nearly neutralised with caustic soda solution, and then precipitated with picric acid. The picrate was collected, washed with water, ground up with 20 c.c. of 8N HCl, and the liberated picric acid removed by repeated extraction with ether. The aqueous layer was then strongly cooled and basified with ammonia, the precipitated base was filtered, washed repeatedly with distilled water, and then with cold rectified spirit. Yield, 1.2 gm. M.P. 164°, after softening at 162°. Recrystallisation from acetone gave rhombic plates, M.P. 165°, identical with the solid obtained from the ethereal filtrate.

1-1' bis-methyl-norhydrohydrastinine, (III, X = CH₃), M.P. 165°.

15.98 mg. of substance gave 40.94 mg. of CO₂ and 9.29 mg. of H₂O.

22.38 mg. of substance gave 1.523 c.c. of N₂ at 38° and 756.3 mm.

C₂₂H₂₄O₄N₂ requires C, 69.47; H, 6.32; N, 7.37 per cent.

Found: C, 69.87; H, 6.48; N, 7.46 per cent.

C₂₂H₂₄O₄N₂ requires C, 69.47; H, 6.32; N, 7.37 per cent.

Picrate. Laminated crystals, M.P. 164°.

10.36 mg. gave 1.215 c.c. of nitrogen at 32°C. and 760.8 mm.

Found: N, 13.14 per cent.

C₃₄H₃₀O₁₈N₈ (dipicrate) requires N, 13.37 per cent.

The nitroso-derivative.

0.2 gm. of the bis-isoquinoline was dissolved in 5 c.c. of HCl, cooled in a freezing mixture, and treated with 5 drops of a saturated solution of NaNO₂

with stirring. The white solid which separated was filtered quickly, washed thoroughly with cold distilled water, and dried in a vacuum desiccator over CaCl_2 . It was crystallised from a small amount of hot acetone, avoiding prolonged boiling.

M.P. 160° , with decomposition and evolution of gas.

23.53 mg. gave 2.6876 c.c. of nitrogen at 36° and 755.75 mm.

Found: N, 12.54 per cent.

$\text{C}_{22}\text{H}_{22}\text{O}_6\text{N}_4$ (dinitroso-derivative) requires N, 12.76 per cent.

The platinichloride, M.P. 240° .

.0961 gm. of platinichloride gave .0158 gm. of platinum.

Found: Platinum, 16.44 per cent.

$(\text{C}_{22}\text{H}_{24}\text{O}_4\text{N}_2)_2 \cdot \text{H}_2\text{PtCl}_6$ requires Pt, 16.67 per cent.

$(\text{C}_{22}\text{H}_{24}\text{O}_4\text{N}_2) \cdot \text{H}_2\text{PtCl}_6$ requires Pt, 24.71 per cent.

Although there are two basic nitrogen atoms in the bis-isoquinoline molecule, the analytical values for platinum indicate that two such bis-isoquinoline molecules have combined with one molecule of H_2PtCl_6 , as if it was a mono-acid base.

1-phenyl-norhydrastinine.

2 gms. of homopiperonylamine were benzoylated in the usual way and gave 3.0 gms. of pure benzoyl homopiperonylamine after crystallisation from rectified spirits. M.P. 119° - 120° .

3.0 gms. of benzoyl homopiperonylamine were heated with 8 c.c. of POCl_3 on the boiling water-bath for one and a half hours and then poured on to crushed ice. The solution was filtered, cooled, made alkaline with caustic soda and extracted with benzene. The benzene extract was dried over solid caustic potash and the benzene distilled off. The crude product weighed 2.6 gms. and melted at 134° - 136° . Recrystallisation from ligroin gave 2.1 gms. of the pure isoquinoline. M.P. 138° .

Reduction of 1-phenyl-norhydrastinine with aluminium amalgam.

2 gms. of the above compound were reduced with 2.5 gms. of amalgam in 75 c.c. of moist ether in precisely the same way as before. The usual induction period of 5 minutes was observed also in this case. The ethereal solution was filtered, the residue ground up with more ether, and again filtered. The combined ether filtrates gave 1.95 gm. of a solid, M.P. 97° - 98° , with only slight sintering at 95° . On crystallising from ligroin, it melted at 98° . The hydrochloride, prepared by rubbing the compound with aqueous HCl , melted at 280° - 281° . The substance was proved to be identical with 1-phenyl-norhydrodrastinine in all respects. Not a trace of the dimolecular product could be observed in this case.