

*Quassin and neoQuassin. Part II.**

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[Reprint Order No. 5469.]

A phenol formed by the dehydrogenation of *neoquassin* with selenium (Part I, *loc. cit.*) has been shown to be 3 : 4 : 5-trimethylguaiacol (V).

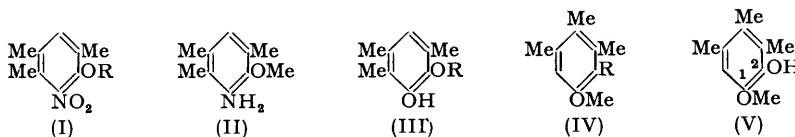
ON being heated with selenium *neoquassin*, a reduction product of quassin, gave rise to the monomethyl ether of a dihydric phenol. This had the formula $C_9H_{11}O \cdot OMe$, m. p. 70° , and gave a greenish-yellow ferric reaction (Part I, *J.*, 1950, 3431). Apparently an integral part of the quassin and *neoquassin* molecule, this product was considered to be a derivative of guaiacol or of resorcinol monomethyl ether, but did not appear to be identical with any of the known isomeric C_3 derivatives of these phenols.

In the present work, since the ferric reaction was more in keeping with that of a guaiacol than of a resorcinol derivative, attention was primarily directed to the preparation of the unknown C_3 alkylguaiacols. Of the eight propylguaiacols the hitherto unknown 4- and 6-*isopropylguaiacol* have been synthesised by standard methods, but neither was identical with the dehydrogenation product.

Whilst these experiments were in progress the small amount of the phenol, m. p. 70° , available was re-examined and found to give a blue-violet colour with 2 : 6-dichloroquinone chloroimide (Gibbs's reagent), indicating the absence of a substituent in the *p*-position to the hydroxyl group, and to couple with the *p*-nitrobenzenediazonium chloride. Subsequently, the dehydrogenation of *neoquassin* was carried out on a larger scale and from the phenolic fraction, which was isolated and purified by a somewhat modified procedure (cf. Part I, *loc. cit.*), there was obtained a phenol, $C_9H_{11}O \cdot OMe$, m. p. 74.5° , with a pale green ferric

* Part I, *J.*, 1950, 3431.

reaction, which on admixture did not depress the melting point of the earlier specimen. This product, however, gave a negative fluorescein and Gibbs's reaction, and did not react with toluene-*p*-diazonium chloride under the usual conditions; the positive reactions given by the earlier specimen appear to have been due to traces of impurities, probably arising by the distillation of the crude dehydrogenation product over sodium. On demethylation the phenol, m. p. 74.5°, gave a dihydric phenol, m. p. 93°, which had a deep green ferric reaction and on being kept decomposed in aqueous solution. From these results it appeared likely that the phenol was either a trimethyl-, type (III) or (V), or an ethylmethyl-guaiacol.



The precursor (I; R = Me) required for the preparation of (III; R = Me) and (III; R = H) has been obtained from ψ -cuminol by Auwers (*Ber.*, 1884, **17**, 2979; 1885, **18**, 2658; 1896, **29**, 1105) but, as difficulties were encountered in the nitration of ψ -cuminol to the required intermediate quinitrol, the compound (III; R = Me) was prepared from 6-nitro- ψ -cumidine by way of the stages (I; R = H), (I; R = Me), and (II). The guaiacol (III; R = Me) and the parent catechol (III; R = H) were similar to, but not identical with, the phenol, m. p. 74.5°, and its demethylation product respectively. By a similar procedure (IV; R = NO₂), obtained from 3 : 4 : 5-trimethyl-2-nitrophenol, was converted by way of (IV; R = NH₂) into 3 : 4 : 5-trimethylguaiacol (V) which was identical with the dehydrogenation product, m. p. 74.5°, giving the same carbanilate and the same ultra-violet absorption spectra.

The two isomeric monomethyl ethers of 4-*n*-propylresorcinol were synthesised by standard methods in the course of comparing the phenol from *neoquassin* with some of the isomeric alkylresorcinols.

EXPERIMENTAL

2-Amino-3 : 4 : 6-trimethylanisole (II).—6-Nitro- ψ -cumidine (Heunder, *Rec. Trav. chim.*, 1915, **34**, 11) (5 g.), dissolved in 20% sulphuric acid (50 ml.), was diazotised at 0–5° with a solution of sodium nitrite (2 g.) in water (25 ml.) and the mixture added to a boiling saturated solution of copper sulphate in water (100 ml.) during 5 min. Next day the product was isolated with ether and purified by means of dilute aqueous sodium hydroxide and then by crystallisation from dilute alcohol, giving 6-nitro- ψ -cuminol in orange prisms (1.9 g.), m. p. 46–47°, which with diazomethane gave the monomethyl ether, m. p. 39–40° (cf. Auwers, *loc. cit.*). Decomposition of the diazonium salt with steam, with boiling sulphuric acid containing sodium sulphate, or by the methods of Orton *et al.* (*J.*, 1907, **91**, 35) gave poor yields (*ca.* 10%) of the required phenol, probably owing in part to a tendency to indazole formation.

Reduction of this ether (4.2 g.), in methanol (70 ml.), with hydrogen and palladium-charcoal furnished 6-amino-2 : 4 : 5-trimethylanisole as a colourless oil (1.9 g.), b. p. 132°/12 mm. (Found : N, 8.5; OMe, 18.5. C₉H₁₂N·OMe requires N, 8.4; OMe, 18.2%).

3 : 4 : 6-Trimethylcatechol (III; R = H).—Prepared at 0–5° from 6-amino-2 : 4 : 5-trimethylanisole (1.6 g.), dissolved in a mixture of concentrated sulphuric acid (2 ml.) and water (14 ml.), with a solution of sodium nitrite (0.7 g.) in water (10 ml.), the solution of the diazonium salt was added dropwise to a boiling saturated solution of copper sulphate (*ca.* 50 ml.) in a distilling flask. From the distillate 3 : 4 : 6-trimethylguaiacol was isolated with ether and purified by means of aqueous sodium hydroxide and then by crystallisation from dilute methanol, forming rods (0.85 g.), m. p. 84° (Found, in specimen sublimed at 60°/0.1 mm.: C, 72.4; H, 8.5. C₁₀H₁₄O₂ requires C, 72.3; H, 8.4%). This phenol gives a green ferric reaction in alcohol and a blue colour with Gibbs's reagent. On demethylation with boiling concentrated hydriodic acid and acetic acid for 30 min. the compound furnished 3 : 4 : 6-trimethylcatechol which on repeated sublimation at 80°/0.001 mm. formed colourless needles, m. p. 118–120°, with a green ferric reaction in alcohol.

2-Amino-3 : 4 : 5-trimethylanisole (IV; R = NH₂).—Methylated with ethereal diazomethane, 3 : 4 : 5-trimethyl-2-nitrophenol (Auwers, *Fortschr. Chem.*, 1926, 18, 26) (2.4 g.) gave 3 : 4 : 5-trimethyl-2-nitroanisole which separated from methanol in pale yellow rods (2.1 g.), m. p. 162—164° (Found : N, 7.5; OMe, 16.1. C₉H₁₀O₂N·OMe requires N, 7.2; OMe, 15.9%). Reduction of this compound (2 g.) with hydrogen and palladium-charcoal furnished *2-amino-3 : 4 : 5-trimethylanisole* as a colourless oil (0.82 g.), b. p. 155—160/15 mm. (Found : N, 8.6; OMe, 18.8. C₉H₁₂N·OMe requires N, 8.4; OMe, 18.2%). Purified by sublimation in a high vacuum, the *acetyl* derivative had m. p. 154° (Found : OMe, 14.7. C₁₆H₁₆ON·OMe requires OMe, 15.0%).

3 : 4 : 5-*Trimethylguaiacol* (V).—(a) 2-Amino-3 : 4 : 5-trimethylanisole (0.8 g.) was diazotised and converted into 3 : 4 : 5-trimethylguaiacol by the procedure employed for the preparation of 3 : 4 : 6-trimethylguaiacol. Purified by sublimation in a vacuum and then by crystallisation from dilute methanol, 3 : 4 : 5-trimethylguaiacol formed slender needles (436 mg.), m. p. 74°, λ_{max.} 284 (log ε 3.37), λ_{min.} 253 (log ε 2.52) (Found : C, 72.3; H, 8.4; OMe, 18.7. C₉H₁₁O·OMe requires C, 72.3; H, 8.4; OMe, 18.7%). The *carbanilate* of this phenol separated from light petroleum (b. p. 60—80°) in prisms, m. p. 142—143° (Found : N, 5.1. C₁₇H₁₉O₃N requires N, 4.9%).

(b) The product obtained by heating a mixture of *neoquassin* (20 g.) and selenium (30 g.) at 295—305° for 20 hr. (Part I, *loc. cit.*) was distilled and a solution of the fraction, b. p. 100—200°/15 mm., in light petroleum (b. p. 40—60°) was extracted with several small portions of 2N-sodium hydroxide, and the combined extracts were acidified. From this an oil was isolated with ether which on distillation gave a semi-solid fraction (0.2 g.), b. p. 100—150°/15 mm. Recrystallised from light petroleum (b. p. 40—60°) and then dilute methanol this product furnished 3 : 4 : 5-trimethylguaiacol in needles, m. p. 74.5—75° undepressed on admixture with synthetic material, λ_{max.} 285 (log ε 3.38), λ_{min.} 253 (log ε 2.49) (Found : C, 72.6; H, 8.4%). Like the synthetic compound, the phenol gave a pale green ferric reaction and a negative Gibb's and fluorescein reaction. The *carbanilate* had m. p. and mixed m. p. 142—143°.

Demethylation of 3 : 4 : 5-trimethylguaiacol (35 mg.) by the method employed for 3 : 4 : 6-trimethylguaiacol gave 3 : 4 : 5-trimethylcatechol which was purified by distillation in a high vacuum and then crystallisation from light petroleum (b. p. 40—60°), having m. p. 86—89° and a green ferric reaction.

2-Nitro-4-isopropylanisole.—Nitric acid (37 g., diluted with 37 g. of water) was added to a well-stirred solution of *p-isopropylphenol* (25 g.) in benzene (50 g.) at 20° in 1 hr., and an hour later the benzene solution was separated, washed, and distilled with steam. A dried ethereal extract of the distillate was evaporated, leaving an oil which on distillation gave *2-nitro-4-isopropylphenol* as a pale yellow oil (19.8 g.), b. p. 131—133°/19 mm. (Found : N, 7.9. C₉H₁₁O₂N requires N, 7.7%). Purified by chromatography from benzene on aluminium oxide and then from light petroleum (b. p. 40—60°), the *benzoate* formed colourless needles, m. p. 61° (Found : N, 5.0. C₁₆H₁₈O₄N requires N, 4.9%).

Methylation of 2-nitro-4-isopropylphenol (19.5 g.) was effected with methyl sulphate (28 g.) and potassium carbonate (38.5 g.) in boiling xylene (30 ml.) for 22 hr. After the removal of the solvent with steam the product was isolated with ether, washed with 2N-sodium hydroxide, and distilled, giving *2-nitro-4-isopropylanisole* as a pale yellow oil (15.1 g.), b. p. 166—168°/11 mm. (Found : N, 7.5. C₁₀H₁₃O₂N requires N, 7.2%).

4-isopropylguaiacol.—2-Nitro-4-isopropylanisole (15 g.) was reduced in methanol (100 ml.) with hydrogen and palladium-charcoal (from 1 g. of charcoal and 0.5 g. of palladium chloride), and the product purified by way of the hydrochloride and then by distillation, giving 2-amino-4-isopropylanisole as a colourless wax-like solid (8.4 g.), b. p. 138°/15 mm., m. p. 36—37°. Purified by chromatography from benzene on aluminium oxide and then from aqueous methanol, the *benzoyl* derivative formed needles, m. p. 67—68° (Found : N, 5.2; OMe, 12.6. C₁₆H₁₆ON·OMe requires N, 5.2; OMe, 11.5%).

A solution of 2-amino-4-isopropylanisole (8.2 g.) in 50% sulphuric acid (16 g.) and water (80 ml.) at 0° was treated with sodium nitrite (4 g.) in water (40 ml.), and the mixture added drop-wise to boiling 60% sulphuric acid (400 ml.). Isolated with steam, followed by extraction with ether, the resulting *4-isopropylguaiacol* was purified by way of the sodium salt, then by distillation and by crystallisation from dilute methanol, forming large micaceous plates (4.7 g.), m. p. 39°, with a pale green ferric reaction in alcohol (Found : C, 71.9; H, 8.3; OMe, 18.3. C₉H₁₁O·OMe requires C, 72.3; H, 8.4; OMe, 18.7%). Purified by chromatography from benzene and then by crystallisation from dilute methanol, the *benzoate* formed shining rectangular plates, m. p. 66° (Found : C, 75.1; H, 6.5; OMe, 11.6. C₁₆H₁₅O₂·OMe requires C, 75.5; H, 6.7; OMe, 11.5%).

6-isoPropylguaiacol.—Prepared from 2-isopropylphenol (Niederl and Storch, *J. Amer. Chem. Soc.*, 1933, **55**, 292), 6-nitro-2-isopropylphenol (Fileti, *Gazzetta*, 1886, **16**, 121) (5.2 g.) was esterified with diazomethane, giving 6-nitro-2-isopropylanisole as an oil, b. p. 140°/15 mm. (Found: N, 7.4; OMe, 15.4. $C_9H_{10}O_2N \cdot OMe$ requires N, 7.2; OMe, 15.9%). Catalytic reduction of this compound (4.1 g.) furnished 6-amino-2-isopropylanisole as a pale yellow oil (2.4 g.), b. p. 117—120°/15 mm., which gave a benzoyl derivative forming irregular plates, m. p. 100—101°, from aqueous methanol after having been chromatographed from benzene on aluminium oxide (Found: N, 5.2; OMe, 11.5. $C_{16}H_{16}ON \cdot OMe$ requires N, 5.2; OMe, 11.5%).

6-Amino-2-isopropylanisole (2.3 g.) was diazotised and converted into 6-isopropylguaiacol by the procedure employed for 2-amino-4-isopropylanisole. The phenol separated from light petroleum (b. p. 40—60°) in needles (0.7 g.), m. p. 63—64°, having a very faint green ferric reaction (Found: C, 72.2; H, 8.3; OMe, 18.8%).

5-Methoxy-2-n-propylphenol.—A mixture of 2:4-dihydroxy-n-propiophenone (Brewster and Harries, *J. Amer. Chem. Soc.*, 1930, **52**, 4866) (7 g.), methyl iodide (6 ml.), potassium carbonate (13 g.), and acetone (50 ml.) was heated under reflux for 2½ hr. On isolation the resulting 2-hydroxy-4-methoxy-n-propiophenone formed plates (4.2 g.), m. p. 58°, from alcohol (cf. Tahara, *Ber.*, 1892, **25**, 1298). Reduction of this ketone (2 g.) with amalgamated zinc (10 g.) and 15% hydrochloric acid (20 ml.) at room temperature for 16 hr. and then under reflux for 2 hr. gave 5-methoxy-2-n-propylphenol, forming plates (1.7 g.), m. p. 45°, from light petroleum (b. p. 40—60°), with a negative ferric reaction (Found: C, 72.4; H, 8.6. $C_{10}H_{14}O_2$ requires C, 72.3; H, 8.4%).

3-Methoxy-4-n-propylphenol.—Partial benzylation of 2:4-dihydroxy-n-propiophenone (6 g.), with benzyl chloride (6.8 g.) and potassium carbonate (12 g.) in boiling acetone for 2 hr., gave 4-benzyloxy-2-hydroxy-n-propiophenone, forming plates (7.0 g.), m. p. 112—114°, from methanol, with a red-purple ferric reaction (Found: C, 74.7; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%). The 2:4-dinitrophenylhydrazone separated from ethyl acetate in bright red needles, m. p. 203° (Found: N, 13.0. $C_{22}H_{20}O_6N_4$ requires N, 12.8%).

Methylation of the benzyl ether (5 g.) by the methyl iodide-potassium carbonate method for 36 hr. gave 4-benzyloxy-2-methoxy-n-propiophenone, forming long needles (4.8 g.), m. p. 59—60°, from light petroleum (b. p. 60—80°) (Found: C, 75.3; H, 6.5. $C_{17}H_{18}O_3$ requires C, 75.6; H, 6.7%). The 2:4-dinitrophenylhydrazone separated from methanol in orange needles, m. p. 129—131° (Found: N, 12.4. $C_{23}H_{22}O_6N_4$ requires N, 12.4%).

Debenzylation of this ether (4 g.) with acetic acid (40 ml.) and concentrated hydrochloric acid (27 ml.) at 100° for ½ hr. gave 4-hydroxy-2-methoxy-n-propiophenone which was distilled at 140°/0.001 mm. and then crystallised from ethyl acetate-light petroleum (b. p. 60—80°), forming prisms, m. p. 114—116° (Found: C, 66.4; H, 6.7; OMe, 17.1. $C_9H_9O_2 \cdot OMe$ requires C, 66.6; H, 6.7; OMe, 17.2%). Reduction of this ketone (1 g.) by the Clemmensen method gave 3-methoxy-4-n-propylphenol, which on distillation at 110°/0.002 mm. followed by crystallisation from light petroleum (b. p. 40—60°) formed micaceous plates (0.6 g.), m. p. 51—53°, with a negative ferric reaction (Found: C, 72.1; H, 8.3; OMe, 18.7. $C_9H_{11}O \cdot OMe$ requires C, 72.3; H, 8.4; OMe, 18.7%).