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SYNTHESIS OF THE ISOMERIC SULPHONIC ACIDS OF 2,6-DI-TERT.-BUTYLPYRIDINE

H.C. van der Plas and H.J. den Hertog
Laboratory of Organic Chemistry of the
Agricultural University, Wageningen, The Netherlands

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SOME time ago we have shown that the sulphonic acid obtained in the remarkable sulphonation of 2,6-di-tert.-butylpyridine (I) with sulphur trioxide in liquid sulphur dioxide at -10° according to Brown and Kanner [1] is not the 4-derivative (III) as suggested by these investigators but the 3-derivative (II) [2]. Recently our conclusion was affirmed by the results of an examination of the nuclear magnetic resonance spectrum of the sulphonic acid by Muller and Wallace [3]. In this letter a definitive proof is given by syntheses of both II and III from 4-ethoxypyridine (IV) and 4-thiomethylpyridine (V) respectively.

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[1] H.C. Brown and B. Kanner, J. Am. Chem. Soc. 75, 3865 (1953).

[2] H.C. van der Plas and H.J. den Hertog, Chem. Weekblad 53, 560 (1957).

[3] N. Muller and W.J. Wallace, J. Org. Chem. 24, 1151 (1959).

Synthesis of 2,6-di-tert.-butylpyridine-3-sulphonic acid (II).

4-Ethoxypyridine (IV) was converted with *tert.*-butyl lithium into 2-*tert.*-butyl-4-ethoxypyridine (VI. B.p. 115-116° (15 mm), n_D^{20} 1.494. Found: C, 73.7; H, 9.7. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56. Picrate m.p. 121-122°. Found: C, 50.2; H, 4.6; N, 13.6. $C_{11}H_{17}NO.C_6H_3N_3O_7$ requires C, 50.00; H, 4.94; N, 13.72).

By reacting VI with *tert.*-butyl lithium again, the 2,6-di-*tert.*-butyl derivative of 4-ethoxypyridine (VII) was obtained (b.p. 141-142°/21 mm. $HAuCl_4$ compound m.p. 193-194°. Found: C, 31.4; H, 4.4; Au, 34.0; N, 2.6. $C_{15}H_{25}NO.HAuCl_4$ requires C, 31.39; H, 4.56; Au, 34.27; N, 2.44).

Heating of VII with 25% aqueous hydrochloric acid solution yielded 2,6-di-*tert.*-butylpyridone-4 (VIII. M.p. 170.5-172°. Found: C, 75.2; H, 10.3; N, 6.7. $C_{13}H_{21}NO$ requires C, 75.31; H, 10.21; N, 6.77. $HAuCl_4$ compound m.p. 199-201°. Found: C, 41.5; H, 5.6; Au, 26.1. $(C_{13}H_{21}NO)_2.HAuCl_4$ requires C, 41.38; H, 5.74; Au, 26.13).

From the UV absorption spectra of VIII in absolute methanol (λ_{max}, 258 mμ; log ε, 4.17), in 0.1 N methanolic hydrochloric acid solution (λ_{max}, 240 mμ; log ε, 3.97) and in 0.1 N methanolic sodium methylate solution (λ_{max}, 232 mμ; log ε, 3.91) it seems probable that VIII chiefly occurs in the pyridone structure.

By heating with a mixture of phosphorus pentachloride and phosphorus oxychloride, VIII was converted into 2,6-di-*tert.*-butyl-4-chloropyridine (IX. B.p. 110-112°/12 mm. Found: C, 69.5; H, 8.9. $C_{13}H_{20}NCl$ requires C, 69.16; H, 8.93. $HAuCl_4$ compound m.p. 252-254°. Found: 27.8; H, 3.9; Au, 34.5. $C_{13}H_{20}NCl.HAuCl_4$ requires C, 27.45; H, 3.72; Au, 34.67).

IX could be sulphonated according to the procedure of Brown and Kanner. The reaction rate was slow, however, the sulphonic acid X being formed in a yield of 12% only when XIII was allowed to stand with an excess of sulphur trioxide in liquid sulphur dioxide at -10° for 20 hrs. The sodium salt of 2,6-di-tert.-butyl-4-chloropyridine-3-sulphonic acid was isolated and melted at 304-305° (Found: C, 47.7; H, 6.0; Cl, 11.1. $C_{13}H_{19}ClNO_3SNa$ requires C, 47.64; H, 5.84; Cl, 10.82).

The chlorine atom in X was replaced by hydrogen by refluxing this substance in alkaline ethanolic solution with a Raney nickel catalyst for 4 hrs. The reaction product, 2,6-di-tert.-butylpyridine-3-sulphonic acid (II. M.p. 333-334° (with decomp.)) was identified as S-benzylthiuronium derivative (m.p. 213-215°. Found: C, 57.9; H, 7.5; N, 9.8. $C_{21}H_{31}N_3S_2O_3$ requires C, 57.64; H, 7.14; N, 9.60) with the corresponding compound of II obtained by sulphonation of 2,6-di-tert.-butylpyridine (I) with sulphur trioxide in liquid sulphur dioxide.

Synthesis of 2,6-di-tert.-butylpyridine-4-sulphonic acid (III).

4-Thiomethylpyridine (V) was converted with tert.-butyl lithium into 2-tert.-butyl-4-thiomethylpyridine (XI. B.p. 105-107° /10 mm. Found: C, 66.5; H, 8.3. $C_{10}H_{15}NS$ requires C, 66.24; H, 8.34. Picrate m.p. 113-114°. Found: C, 47.1; H, 4.4. $C_{10}H_{15}NS.C_6H_3N_3O_7$ requires C, 46.82; H, 4.42).

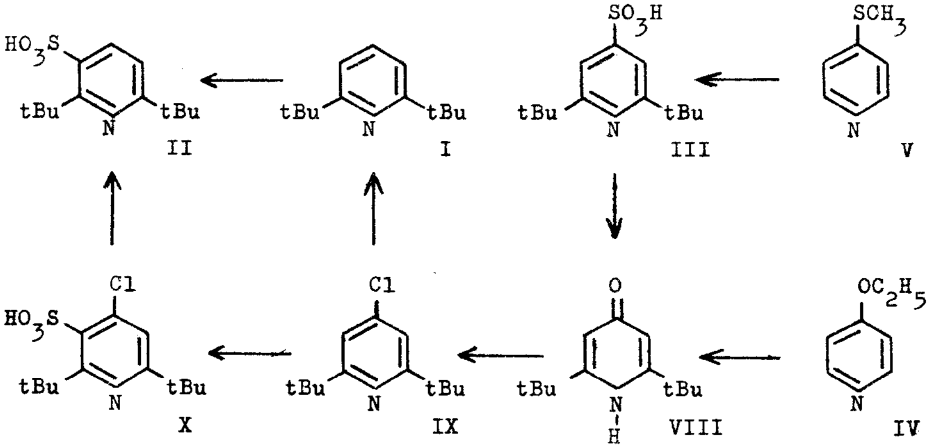
By reacting XI again with tert.-butyl lithium a complicated reaction product was obtained, containing possibly 2,6-di-tert.-butylpyridine-4-thiol (XII) and inter alia 4,4'-di-(2,6-di-tert.-butylpyridyl)sulfide (XIII, m.p. 125-126°. Found: C, 75.9; H, 9.8;

N, 6.6; S, 7.6. $C_{26}H_{40}N_2S$ requires C, 75.67; H, 9.77; N, 6.79; S, 7.77).

After removing XIII from the reaction product and oxidising the residue with a mixture of 30% aqueous hydrogen peroxide solution and acetic acid, 2,6-di-tert.-butylpyridine-4-sulphonic acid (III) was obtained.

III is a colourless substance, m.p. 344-346° (with decomp.) from a mixture of benzene and ethanol. Found: C, 57.2; H, 7.5. $C_{13}H_{21}NO_3S$ requires C, 57.51; H, 7.78 . Its S-benzylthiuronium derivative melts at 210-212° (Found: C, 58.1; H, 7.3; N, 9.4. $C_{21}H_{31}N_3O_3S$ requires C, 57.64; H, 7.14; N, 9.60).

Proof of the structures of the isomeric sulphonic acids of I:



The positions of the tert.-butyl groups in both II and III are the same as in IX, the structure of which is established by the formation of this substance from 4-ethoxypyridine (IV) and its conversion by catalytical reduction into 2,6-di-tert.-butylpyridine(I).

The position of the sulphonic acid group in II follows from its formation (via X) from IX in which compound hydrogen is available for substitution only at positions 3 and 5.

The position of the sulphonic acid group in III follows from the synthesis described and the conversion of III by heating with water for 10 hrs at 240° in a sealed tube into VIII.

The conclusions given above are affirmed by the following facts:

II does not react when heated with aqueous ammonia at 160°, but yields 2,6-di-tert.-butyl-3-hydroxypyridine when heated with potassium hydroxide at 330° [4].

III is converted by heating with aqueous ammonia at 180° into 4-amino-2,6-di-tert.-butylpyridine (XV. Picrate m.p. 146-150° (with decomp.). Found: C, 52.4; H, 5.5; N, 15.9. $C_{13}H_{22}N_2 \cdot C_6H_3N_3O_7$ requires C, 52.41; H, 5.79; N, 16.09).

The UV absorption spectrum of a solution of the picrate of XV in 96% ethanol corresponds with that of 4-aminopyridine picrate solution.

The microanalyses were carried out in this laboratory by Mr. W.P. Combé.

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[4] Cf. the paper cited in note 2.