# NOTES.

*Some Anilinopyridine Derivatives.* By WILLIAM O. KERMACK and (MISS) ALICE P. WEATHERHEAD.

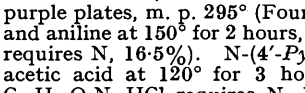
THE following anilinopyridine derivatives have been prepared with the object of obtaining 2 : 3-pyridoquinolines (pyracridines) : 2-*Anilinonicotinic acid*, from 2-chloronicotinic acid and aniline at 160° for 1 hour, recrystallised from alcohol, formed almost colourless plates, m. p. 263° (Found : N, 13·0. $C_{12}H_{10}O_2N_2$ requires N, 13·1%). 2-p-*Anisidinonicotinic acid*, from 2-chloronicotinic acid and *p*-anisidine at 150° for 1 hour, recrystallised from alcohol, formed faintly purple plates, m. p. 295° (Found : N, 11·4. $C_{13}H_{12}O_3N_2$ requires N, 11·5%). 4-*Anilinopyridine*, from 4-chloropyridine and aniline at 150° for 2 hours, recrystallised from benzene, formed white needles, m. p. 173° (Found : N, 16·4. $C_{11}H_{10}N_2$ requires N, 16·5%). N-(4′-*Pyridyl*)*anthranilic acid hydrochloride*, from 4-chloropyridine and anthranilic acid in glacial acetic acid at 120° for 3 hours, recrystallised from alcohol, formed white needles, m. p. 185° (Found : N, 11·4. $C_{12}H_{10}O_2N_2$,HCl requires N, 11·2%). N-(3′-*Pyridyl*)*anthranilic acid*, from 3-aminopyridine and potassium *o*-bromobenzoate in amyl alcohol with a trace of copper bronze at 130° for 6 hours, recrystallised from alcohol in small cubes, m. p. 238° (Found : C, 67·1; H, 4·5. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·6%).

All attempts to cyclise the above carboxylic acids by treatment with sulphuric acid or phosphoryl chloride have so far failed.—RESEARCH LABORATORY, ROYAL COLLEGE OF PHYSICIANS, EDINBURGH. [*Received, October 2nd*, 1942.]

---

*The Preparation of* 1-p-*Aminobenzenesulphonamido*-2 : 5-*dimethylpyrrole.* By E. O'FARRELL WALSH.

ACETONYLACETONE condenses with *p*-acetamidobenzenesulphonhydrazide in hot glacial acetic acid to give 1-*p*-acetamidobenzenesulphonamido-2 : 5-dimethylpyrrole in theoretical yield. The product on alkaline hydrolysis yields 1-p-*aminobenzenesulphonamido*-2 : 5-*dimethylpyrrole* (I, R = $NH_2$), which, it is suggested, may be of therapeutic value. It is essential that pure sulphonhydrazide, free from traces of sulphonyl chloride, be used for the condensation, otherwise uncrystallisable red tars are produced.


(I.)

When a solution of *p*-acetamidobenzenesulphonhydrazide (6 g.) in boiling glacial acetic acid (15 c.c.) containing acetonylacetone (4 c.c.) is heated for a few minutes, crystals begin to separate. The hot solution is diluted with warm water and cooled rapidly, and the crystals separated immediately, washed with cold water, and dried. Yield 8 g., m. p. 240° (decomp.). Deacetylation is effected by refluxing with 20% sodium hydroxide solution until a test portion gives no precipitate with excess of acid (1—1½ hrs.). The solution is diluted, acidified with acetic acid, and neutralised with ammonia; the *sulphanilamide* derivative (I, R = $NH_2$) thus precipitated in 85% yield crystallises from aqueous alcohol in colourless platelets, m. p. 202° (decomp.) (Found : N, 15·8; S, 11·9. $C_{12}H_{15}O_2N_3S$ requires N, 15·85; S, 12·1%).

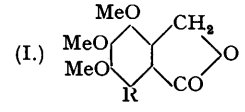
1-p-*Toluenesulphonamido*-2 : 5-*dimethylpyrrole* (I, R = Me), prepared by the above method from *p*-toluenesulphonhydrazide, crystallises from acetic acid or aqueous alcohol in large needles, m. p. 144°, readily soluble in alcohol, acetone, and acetic acid, soluble in chloroform, sparingly in ether, and insoluble in light petroleum (Found : N, 10·6. $C_{13}H_{16}O_2N_2S$ requires N, 10·6%).

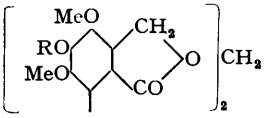
I am indebted to Mr. J. E. Still for the micro-analyses for nitrogen and sulphur.—UNIVERSITY COLLEGE, NOTTINGHAM. [*Received, September 18th*, 1942.]

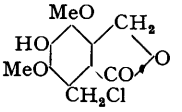
---

*Synthesis of Phthalides from* 3 : 4 : 5-*Trimethoxybenzoic Acid.* By F. E. KING and T. J. KING.

THE phthalide synthesis introduced by Edwards, Perkin, and Stoyle (J., 1925, **127**, 125) for the meconines has been applied to trimethylgallic acid; the published conditions gave rise to 6-*chloromethyl*-3 : 4 : 5-*trimethoxyphthalide* (I, R = $CH_2Cl$). The required phthalide (I, R = H) can, however, be obtained by using considerably less hydrochloric


(I.)


(II).


(III.)

acid, and it was identified by comparison with a specimen prepared by the Fritsche method from the gallic acid, chloral, and sulphuric acid (Alimchandani and Meldrum, J., 1920, **117**, 964). From the formaldehyde reaction a small quantity of the phthalide (II, R = Me) was also isolated.

Before the constitution of the compound (I, R = $CH_2Cl$) had been ascertained, there was a possibility that it arose from syringic acid formed by demethylation with hot mineral acid, but syringic acid actually gave the *chloromethylphthalide* (III), together with 6 : 6′-*methylenebis*-4-*hydroxy*-3 : 5-*dimethoxyphthalide* (II, R = H), which when methylated gave (II, R = Me).

In pyrogallolcarboxylic acid 3 : 4-dimethyl ether the *o*-position is less active, and the formaldehyde–hydrochloric acid reaction gave only 5 : 5′-*methylenebis*-2-*hydroxy*-3 : 4-*dimethoxybenzoic acid.*

3 : 4 : 5-Trimethoxyphthalide reacted with sodium ethoxide and ethyl oxalate, giving *ethyl* 3 : 4 : 5-*trimethoxyphthalidylglyoxylate*, which was conveniently isolated as its sodium salt.

6-*Chloromethyl*-3 : 4 : 5-*trimethoxyphthalide* (I, R = $CH_2Cl$).—A mixture of trimethylgallic acid (10 g.), aqueous formaldehyde (25 c.c. of 40%), and concentrated hydrochloric acid (40 c.c.) was refluxed for 20 minutes in an oil-bath at 140°. On cooling and addition of water, the oily product solidified; recrystallisation from alcohol gave the *chloromethylphthalide* (7 g.) in colourless needles, m. p. 85°, with marked irritant properties (Found : C, 52·8; H, 4·8. $C_{12}H_{13}O_5Cl$ requires C, 52·8; H, 4·8%).

3 : 4 : 5-*Trimethoxyphthalide* (I, R = H).—When the previous experiment was repeated with a smaller amount of hydrochloric acid (10—12 c.c.), the product was 3 : 4 : 5-trimethoxyphthalide, which by two crystallisations from alcohol (charcoal) was obtained in colourless prisms (5·5 g.), m. p. 134—135° alone or mixed with an authentic specimen (Alimchandani and Meldrum, *loc. cit.*). Heating the phthalide (1 g.) with formalin (2·5 c.c. of 40%) and excess of concentrated hydrochloric acid (4—5 c.c.) for 30 minutes gave the above chloromethyl derivative, m. p. and mixed m. p. 85°.

6 : 6′-*Methylenebis*-3 : 4 : 5-*trimethoxyphthalide* (II, R = Me).—Once-crystallised specimens of the trimethoxyphthalide (I, R = H) or of its chloromethyl derivative (I, R = $CH_2Cl$) were treated with boiling alcohol, and the solutions quickly decanted from the sparingly soluble residue (yield, *ca.* 5%). Recrystallisation from alcohol gave the *methylenebisphthalide* in pointed prisms, m. p. 199° (Found : C, 59·5; H, 5·2. $C_{23}H_{24}O_{10}$ requires C, 60·0; H, 5·2%).

6 : 6′-Methylenebis-4-hydroxy-3 : 5-dimethoxyphthalide (*vide infra*) (0·5 g.) was refluxed with potassium carbonate (1 g.) and methyl iodide (2 c.c.) in acetone (20 c.c.) for 8 hours. The product, isolated by evaporation of the solvent and addition of water, when crystallised from alcohol had m. p. and mixed m. p. 199°.

6-*Chloromethyl*-4-*hydroxy*-3 : 5-*dimethoxyphthalide* (III).—The clear solution obtained by heating syringic acid (10 g.) for 10—12 minutes with aqueous formaldehyde (25 c.c. of 40%) and concentrated hydrochloric acid (40 c.c.) on a steam-bath, slowly deposited a dark oil which shortly solidified. The product collected after 30 minutes' heating crystallised from alcohol in long rectangular tablets of the *chloromethylphthalide*, m. p. 185° (Found: C, 50·7; H, 4·3. $C_{11}H_{11}O_5Cl$ requires C, 51·1; H, 4·3%). The phthalide dissolved in aqueous sodium carbonate, giving a slowly fading pink colour; the ferric chloride reaction was a weak green-yellow.

6 : 6′-*Methylenebis*-4-*hydroxy*-3 : 5-*dimethoxyphthalide* (II, R = H).—The formaldehyde–acid solution from which the above phthalide (III) had been collected was diluted with water, and the resinous product crystallised from alcohol (charcoal). It formed opaque bipyramids, m. p. 223—224°, giving an olive-green ferric chloride reaction (Found: C, 58·5; H, 4·7. $C_{21}H_{20}O_{10}$ requires C, 58·3; H, 4·6%).

5 : 5′-*Methylenebis*-2-*hydroxy*-3 : 4-*dimethoxybenzoic Acid*.—Pyrogallolcarboxylic acid 3 : 4-dimethyl ether (5 g.) was heated for 30 minutes with concentrated hydrochloric acid (20 c.c.) and aqueous formaldehyde (12 c.c.) at 140°, and the product precipitated by water. Crystallisation from 80% alcohol gave minute needles, m. p. 252° (efferv.); these gave an intense blue ferric chloride reaction (Found: C, 55·3; H, 5·0. $C_{19}H_{22}O_{10}$ requires C, 55·6; H, 5·3%).

*Ethyl* 3 : 4 : 5-*Trimethoxyphthalidylglyoxylate*.—To a suspension of sodium ethoxide prepared from powdered sodium (1·6 g.) and alcohol (3·2 g.) in toluene (30 c.c.), freshly distilled ethyl oxalate was added. The trimethoxyphthalide (15 g.) was now introduced, and the mixture heated (hydrogen atmosphere) on a steam-bath for 2 hours. The bright yellow insoluble sodium salt of the *phthalidylglyoxylate* was collected from the dark green liquid, washed with ether, and the free ester obtained by trituration with ice-cold aqueous acetic acid. Crystallisation from ethyl acetate–acetic acid gave pale yellow prisms, m. p. 188—189°, exhibiting a steel-blue ferric chloride reaction (Found: C, 55·6; H, 5·1. $C_{15}H_{16}O_8$ requires C, 55·5; H, 4·9%).—Dyson Perrins Laboratory, Oxford. [*Received, August 19th*, 1942.]