NOTES.

Preparation of Nuclear-substituted Dimethylanilines. By DAVID P. EVANS and REGINALD WILLIAMS.

NUCLEAR-SUBSTITUTED dimethylanilines have usually been prepared by methylation of the appropriate aniline with methyl iodide (see, *e.g.*, Davies, *Bull. Soc. chim.*, **1935**, **2**, 295; Davies and Cox, J., **1937**, 615; Laidler, J., **1938**, 1786). Methyl sulphate has been used by Ullmann and Wenner (*Ber.*, **1900**, **33**, 2476), Banús and Tomás (*Anal. Fís. Quím.*, **1921**, **19**, 293), van Duin (*Rec. Trav. chim.*, **1932**, **51**, 878), and Groenewoud and Robinson (J., **1934**, 1692).

We have used van Duin's method for the preparation of several dimethylamino-compounds. The tertiary amine was usually obtained directly by treatment of the primary amine with methyl sulphate and sodium hydroxide, but in some cases the initial product consisted of the metho-sulphate, from which the desired tertiary amine was isolated by suitable treatment. Only in the methylation of 2-aminodiphenyl ether did we isolate a mixture of the tertiary amine and the quaternary hydroxide (compare Bell and Kenyon, J., **1926**, 2705). The yields obtainable by this method are usually about 50%, but reaching 80% and 90% in favourable instances, and the procedure is convenient and expeditious.

The methylation of the primary amine involves the addition of a small excess of methyl

sulphate in small amounts to the amine, followed each time by sufficient 30% sodium hydroxide solution to render the mixture alkaline as shown by the colour of some phenolphthalein. The reaction is moderated by cooling in ice–salt or cold water. Two liquid layers are obtained which on warming (or standing) become completely miscible and form a homogeneous layer containing the amine sulphate or the methosulphate. Addition of excess of alkali then precipitates either the amine or the methosulphate. The latter is converted by addition of potassium iodide into the quaternary iodide, and this is changed into the tertiary amine by boiling with sodium hydroxide in amyl alcohol or by heating with moist silver oxide in alcohol and then decomposing the hydroxide so formed by heating; the former method gives by far the better yield. The table gives the primary products of the methylation of the primary amines together with the final yields and m. p.'s or b. p.'s of the pure tertiary amines. In each case the product was treated with acetic anhydride to remove secondary and primary amines.

Substituted aniline.	Primary product.	M.p. or b.p. of tert. amine.	Yield, %, calc. on amine.
o-Fluoro	Tert. amine	75°/20 mm.	50
p- ,,	,, ,,	35·2 (35°; *a*)	40
p-Chloro	,, ,,	32·8 (35·5; *a*)	50
p-Nitro	,, ,,	164·5 (162; *b*)	50
o-Methoxy	Quaternary sulphate (*c*)	113/18 mm.	40
p- ,,	Methosulphate	47	40
o-Phenyl	Tert. amine	145·5/11 mm.	94
p- ,,	Methosulphate (*d*)	122 (123; *f*)	80
o-Phenoxy	Tert. amine + hydroxide	34·5	42
p- ,,	Methosulphate (*e*)	34	54

(*a*) Davies and Cox, *loc. cit.* (*b*) Davies, *loc. cit.*

(*c*) When the mixture was made alkaline, an oily layer separated which dissolved on warming and was not thrown out on cooling. It appears that the substance in solution was then the quaternary sulphate, which, as implied by Groenewoud and Robinson (*loc. cit.*), is probably stable to the action of hot alkali. The yield of the dimethylanisidines (*idem, ibid.*) could be improved by converting the iodide into the tertiary amine by treatment with sodium hydroxide in amyl alcohol; we converted the iodide into the hydroxide, which was thermally decomposed.

(*d*) and (*e*) Quaternary iodide was converted into tertiary amine by boiling with sodium hydroxide in amyl alcohol.

(*f*) Bell and Kenyon, *loc. cit.*

2-*Dimethylaminodiphenyl*.—2-Aminodiphenyl (obtained from nitro-compound in good yield by the method of Turner and Roberts, J., 1925, **127**, 2008) was treated with methyl sulphate and 30% sodium hydroxide solution in the way described above, the reaction being moderated when necessary by cooling in water. The tertiary *amine* was liberated by addition of excess of alkali, extracted in ether, dried over potassium hydroxide, and distilled; b. p. 143—147°/12—14 mm., yield 94%. Treatment with acetic anhydride and fractionation in a vacuum gave a pale yellow liquid, b. p. 145·5°/11 mm. (Found: C, 85·4; H, 7·7; N, 7·3. $C_{14}H_{15}N$ requires C, 85·3; H, 7·6; N, 7·1%).

2-*Dimethylaminodiphenyl Ether*.—The primary amine obtained by reduction of 2-nitrodiphenyl ether (compare Turner and Roberts, *loc. cit.*) was distilled in a vacuum and methylated in the prescribed manner. Addition of excess of alkali to the homogeneous liquid caused the separation of an oil, which solidified on cooling. When this solid was washed with water, the major portion dissolved (quaternary hydroxide). The residue crystallised from aqueous alcohol as a white solid (tertiary amine). Addition of alkali to the aqueous solution reprecipitated the hydroxide, which was separated and dried. The crystallised amine was distilled in a vacuum and the dry hydroxide was then introduced into the distillation flask and decomposed by heating. The *amine* distilled at a constant temperature; yield 42%. The product was treated with acetic anhydride and distilled in a vacuum; b. p. 161—162°/13 mm. The colourless oil slowly solidified to a white solid, m. p. 34·5° after crystallisation from alcohol (Found: C, 79·0; H, 7·0, N, 6·6. $C_{14}H_{15}ON$ requires C, 78·9; H, 7·0; N, 6·6%).

4-*Dimethylaminodiphenyl Ether*.—After methylation of 4-aminodiphenyl ether, addition of excess of alkali gave the solid methosulphate. This was dissolved in water, and potassium iodide added. The precipitated quaternary iodide was boiled with sodium hydroxide in amyl alcohol, the solvent removed, and the residue distilled in a vacuum. The *amine* was obtained as a colourless liquid, b. p. 185°/13 mm., which solidified on standing. Crystallisation from alcohol gave a white solid, m. p. 34° (Found: C, 79·0; H, 6·9; N, 6·65%).

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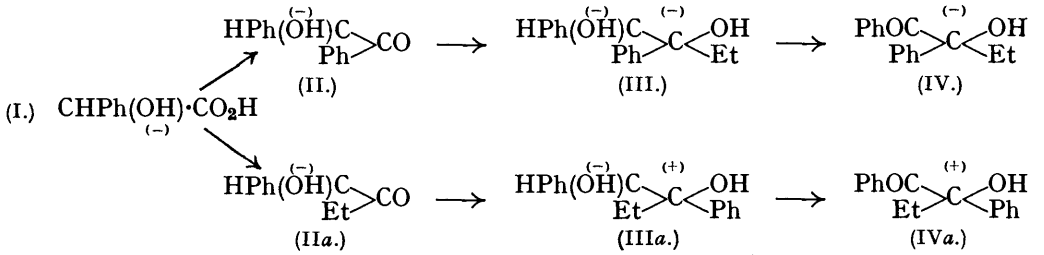
The Influence of the Route chosen for an Asymmetric Synthesis upon the Configuration of the Resulting Enantiomorph. By S. M. PARTRIDGE.

ROGER (this vol., p. 108), dealing with an asymmetric synthesis of a type similar to that described by Kenyon and Partridge (J., 1936, 1313), has shown that both (+) and (−) ethylbenzoin may be obtained from a single optically active form of mandelic acid, the sign of the resulting enantiomorph being dependent upon the route chosen for the synthesis :



From this apparently anomalous behaviour Roger is led to draw conclusions as to the influence of the radicals attached to the ketonic groups in (II) and (II*a*) upon the path of the system.

If the ketonic double bond opens in the same sense in (II) and (II*a*) during the formation of the ethylhydrobenzoins, the ethyl group is embodied in (III) in the same position as the phenyl group in (III*a*). It follows that, since the relative positions of phenyl and ethyl have been reversed, (III) and (III*a*) would appear as diastereoisomerides. This was found to be the case.

The difference in configuration between the ethylbenzoins produced by the two routes is a necessary consequence of the order in which the phenyl and the ethyl group have been embodied.

Thus the relative configuration of the product of such a system is determined, not only by the sense of the specific orientation taking place during the rupture of a ketonic double bond, but also by the order in which the groups are successively built up around the new centre of asymmetry. In the above system the production of opposite enantiomorphs is due to the initial substitution of phenyl and ethyl in stages I ⟶ II and I ⟶ II*a* respectively; the experimental results proving, contrary to the conclusion of Roger, that the influence of the common lævorotatory inducing centre in (II) and (II*a*) has been in the same direction in both cases. The closely similar synthesis of (+) and (−) anisylmethylglycollic acid by McKenzie and Ritchie (*Biochem. Z.*, 1932, **250**, 376) is subject to the same comment.—BATTERSEA POLYTECHNIC, LONDON. S.W.11. [*Received, May 8th*, 1939.]

Smilagenone : A Correction. By GEORGE A. R. KON, HENRY R. SOPER, and AUBREY M. WOOLMAN.

HAVING recently isolated a large quantity of smilagenin, we have repeated the preparation of smilagenone (Askew, Farmer, and Kon, J., 1936, 1399) and have found that the pure compound has m. p. 187—189° and not 157° as previously stated (Found : C, 78·3; H, 10·2. $C_{27}H_{42}O_3$ requires C, 78·2; H, 10·3%). The specimen previously prepared in small amount was apparently contaminated with smilagenin and gave a low value for carbon on analysis.

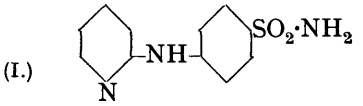
The properties of smilagenone are remarkably close to those of *iso*sarsasapogenone (Fieser and Jacobsen, *J. Amer. Chem. Soc.*, 1938, **60**, 28); the melting points of *iso*sarsasapogenin and its derivatives, lately prepared by Marker and Rohrmann (*ibid.*, 1939, **61**, 846), are also very close to those of the corresponding smilagenin compounds and suggest the identity of the two series of compounds.

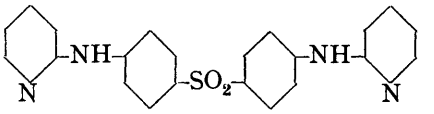
The *o*-bromobenzoates have been found suitable for the characterisation of smilagenin and sarsasapogenin; *smilagenin o-bromobenzoate* has m. p. 196—197° (Found : C, 68·0; H, 8·1. $C_{34}H_{47}O_4Br$ requires C, 68·1; H, 7·9%) and *sarsasapogenin o-bromobenzoate*, m. p. 178—179° (Found : C, 68·1; H, 8·1%).—IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7. [*Received, June 10th*, 1939.]

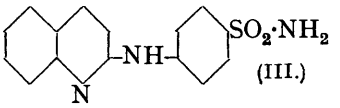
Heterocyclic Derivatives of p-*Aminobenzenesulphonamide and* 4 : 4′-*Diaminodiphenylsulphone.*

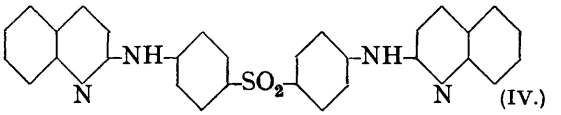
By W. H. Gray.

As part of a scheme to study the effect, on the chemotherapeutic action of antibacterial agents, of inserting heterocyclic basic nuclei into the amino-groups, the following substances have been prepared.









Their constitution is proved by the fact that they give no diazo-reaction.

The pharmacological action has been tested by Dr. Buttle of the Wellcome Physiological Research Laboratories. They have a low toxicity but are inactive in streptococcal and pneumococcal infections of mice. In the latter respect (I) is in marked contrast to 2-*p*-aminobenzenesulphonamidopyridine, $NH_2 \cdot C_6H_4 \cdot SO_2 \cdot NH \cdot C_5H_4N$, where the 2-pyridyl group is attached to the amido-nitrogen, instead of the amino-nitrogen, of *p*-aminobenzenesulphonamide.

The results are published at this stage owing to the appearance of a paper by Bobrański (*Arch. Pharm.*, **1939**, **277**, 75) in which the preparation of (III) is described.

p-(2-*Pyridylamino*)*benzenesulphonamide* (I).—*p*-Aminobenzenesulphonamide (3·4 g.) was heated at 140° for 15 hours with 2-chloropyridine (6 c.c.; 3·2 mols.). The solid part of the product was dissolved in water and treated with sodium carbonate, precipitating the *base*, which was pure after one crystallisation from alcohol. It formed stout plates, m. p. 235°, sparingly soluble in alcohol and less soluble in water (Found : C, 52·8; H, 4·3; N, 16·9; S, 12·8. $C_{11}H_{11}O_2N_3S$ requires C, 53·0; H, 4·5; N, 16·9; S, 12·9%).

pp′-*Bis*-(2-*pyridylamino*)*diphenylsulphone* (II).—*pp*′-Diaminodiphenylsulphone (2·5 g.) was treated with 2-chloropyridine (5·7 c.c.; 6 mols.) similarly. The product was soluble in a little water, but further dilution gave the *base* as a solid, which crystallised from alcohol in clusters of very thin plates, m. p. 241°, sparingly soluble in alcohol (Found : C, 65·0; H, 4·5; N, 13·9; S, 7·8. $C_{22}H_{18}O_2N_4S$ requires C, 65·6; H, 4·5; N, 13·9; S, 8·0%).

p-(2-*Quinolylamino*)*benzenesulphonamide* (III).—*p*-Aminobenzenesulphonamide (3·4 g.) was heated at 160° for 8 hours with 2-chloroquinoline (8·5 g.; 2·6 mols.), the excess of the latter removed by light petroleum, and the residue crystallised from alcohol, forming needles, m. p. 279°, of the *hydrochloride* (Found : C, 53·9; H, 3·5; N, 12·6; S, 9·4; Cl, 10·5. $C_{15}H_{13}O_2N_3S$,HCl requires C, 53·7; H, 4·2; N, 12·5; S, 9·6; Cl, 10·6%). The *base* was obtained from this by heating an aqueous suspension on the water-bath for an hour with a slight excess of sodium carbonate. It crystallised from alcohol in tablets, m. p. 263°, sparingly soluble in water or alcohol (Found : C, 60·1; H, 4·2; N, 14·5; S, 10·7. $C_{15}H_{13}O_2N_3S$ requires C, 60·2; H, 4·4; N, 14·0; S, 10·7%).

pp′-*Bis*-(2-*quinolylamino*)*diphenylsulphone* (IV).—*pp*′-Diaminodiphenylsulphone (2·2 g.) was heated at 160° for 12 hours with 2-chloroquinoline (8·6 g.; 5·9 mols.), the excess of chloroquinoline removed as above, and the residue (5·5 g.) dissolved by gentle warming in an equal weight of pyridine and treated with 4 vols. of alcohol. The crystals which quickly separated were again dissolved in pyridine, and alcohol added; masses of small plates, m. p. 306°, then formed (Found : C, 71·5; H, 4·5; N, 11·2; S, 6·3. $C_{30}H_{22}O_2N_4S$ requires C, 71·7; H, 4·4; N, 11·2; S, 6·4%).—The Wellcome Chemical Research Laboratories, London, N.W.1.

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