CCCLXVII.—*Nor*-d-ψ-*ephedrine, a Convenient Base for the Resolution of externally compensated Acids. Resolution of* dl-*Benzenesulphonylalanine and of* dl-N-*Phenylalanineamide-4-arsinic Acid.*

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IN addition to *l*-ephedrine and *d*-ψ-ephedrine

(OH·CHPh·CHMe·NHMe),

Smith has shown that Ma Huang, the Chinese drug from an *Ephedra* species, contains *l*-methylephedrine (OH·CHPh·CHMe·NMe_2) (J., 1927, 2056) and nor-*d*-ψ-ephedrine (OH·CHPh·CHMe·NH_2) (J., 1928, 51). In the form of its sulphate, nor-*d*-ψ-ephedrine is obtained from the residues remaining after the extraction of the *l*-ephedrine and is easily obtained pure. It was suggested to one of us by Dr. F. L. Pyman that this fairly strong base of low molecular weight might prove useful for the resolution of externally compensated acids, and two examples of its application for this purpose are now given.

dl-Benzenesulphonylalanine (Hedin, *Ber.*, 1890, **23**, 3197), which could not be resolved by Gibson and Simonsen (*J. Roy. Asiatic Soc. Bengal*, 1917, **13**, 191) by previously described methods (Pope and Gibson, J., 1912, **101**, 939; Gibson and Simonsen, J., 1915, **107**, 798; Colles and Gibson, J., 1924, **125**, 2505; 1928, 99) for resolving externally compensated acyl derivatives of amino-acids, was readily resolved by means of nor-*d*-ψ-ephedrine. It has $[M]^{20°}_{5461} = \pm 76{\cdot}3°$ as sodium salt in water as compared with $[M]^{20°}_{5461} = \pm 80{\cdot}0°$ for the corresponding benzoylalanine under approximately the same conditions. The externally compensated and the optically active methyl esters and amides have also been prepared, the latter compounds from the former by the action of an aqueous solution of ammonia. Few amides of this series of acids have been described and they have been obtained by the action of acyl chlorides on the amide (compare Koenigs and Mylo, *Ber.*, 1908, **41**, 4432). It is also shown that *l*-benzenesulphonylalanine is a derivative of *d*-alanine.

dl-N-Phenylalanineamide-4-arsinic acid has been previously resolved by means of quinine (Gibson, Johnson, and Levin, this vol., p. 479). Its resolution by means of nor-*d*-ψ-ephedrine, whilst perhaps not quite so simple, indicates the possibility of this base being used for the resolution of analogous types of externally compensated acids.

The use of nor-*d*-ψ-ephedrine in stereochemical investigations is being continued.

EXPERIMENTAL.

*Purification of Nor-*d*-ψ-ephedrine Sulphate.*—The crude sulphate as supplied had $[\alpha]_{5461}^{20°} = +38{\cdot}9°$ * in aqueous solution. It was crystallised three times from water, after which its rotatory power was constant: $c = 1{\cdot}0608$, $\alpha = +2{\cdot}07°$, $[\alpha] = +48{\cdot}7°$.

The free base was obtained by the addition of a slight excess of potassium hydroxide solution to an aqueous solution of the pure sulphate. A portion of the base which crystallised from the cooled solution was removed, and the filtrate extracted thoroughly with ether. The ethereal solution was washed, dried with potassium carbonate, and evaporated, and the residue was recrystallised from benzene. The base crystallised in colourless plates, m. p. 77°. In methyl alcohol, $c = 0{\cdot}6566$, $\alpha = +0{\cdot}98°$, $[\alpha] = +37{\cdot}5°$. In water, $c = 1{\cdot}1992$, $\alpha = +1{\cdot}19°$, $[\alpha] = +24{\cdot}7°$.†

Resolution of dl-*Benzenesulphonylalanine.*—The *dl*-benzenesulphonylalanine was prepared in the usual manner from *dl*-alanine, benzenesulphonyl chloride, and sodium hydroxide. It was recrystallised from water and obtained in colourless needles, m. p. 124—125°. Its properties agreed with those described by Hedin (*loc. cit.*).

To a warm solution of *dl*-benzenesulphonylalanine (4·58 g.) in sodium hydroxide (5·59 c.c., 1·79*N*), nor-*d*-*ψ*-ephedrine (1·51 g.) in water (10 c.c.) was added. The *salt* began to crystallise almost immediately and, after 24 hours, it was filtered off (3·2 g.) and recrystallised from hot water (10 c.c.). It was obtained in colourless prisms or fine needles and, after two crystallisations, its rotatory

* All rotatory powers in this work were carried out at 20°, 4 dm. tubes and the mercury green line (λ 5461) being used.

† These values for the rotatory powers of nor-*d*-*ψ*-ephedrine sulphate and for nor-*d*-*ψ*-ephedrine itself differ appreciably from those previously given (Smith, J., 1928, 51). We accordingly consulted with Dr. Sydney Smith, who confirmed our value for the sulphate and writes as follows:

"It has been found necessary to redetermine the rotatory powers of nor-*d*-*ψ*-ephedrine and its derivatives, as the previous measurements were made with the mercury yellow line (λ 5790) and not with the mercury green line (λ 5461) as recorded. The values at 20° for the line λ 5461 are as follows:

Nor-*d*-*ψ*-ephedrine sulphate, $[\alpha] = +48{\cdot}7°$ ($c = 1{\cdot}4$ in water).
Nor-*d*-*ψ*-ephedrine, $[\alpha] = +37{\cdot}9°$ ($c = 3{\cdot}0$ in methyl alcohol).
d-*ψ*-Methylephedrine methiodide, $[\alpha] = +42{\cdot}3°$ ($c = 2{\cdot}3$ in water).
Nor-*d*-*ψ*-ephedrine hydrogen tartrate, $[\alpha] = +49{\cdot}5°$ ($c = 2{\cdot}3$ in water).
Dibenzoylnor-*d*-*ψ*-ephedrine, $[\alpha] = +32{\cdot}8°$ ($c = 2{\cdot}2$ in methyl alcohol).
N-Benzoylnor-*d*-*ψ*-ephedrine, $[\alpha] = +67{\cdot}2°$ ($c = 1{\cdot}2$ in methyl alcohol).
O-Benzoylnor-*d*-*ψ*-ephedrine hydrochloride, $[\alpha] = -37{\cdot}6°$ ($c = 1{\cdot}0$ in water).

"In the original paper (*loc. cit.*), '5461' should be corrected to '5790' throughout.—S. SMITH."

power was constant: In water, $c = 0{\cdot}3744$, $\alpha = +0{\cdot}70°$, $[\alpha] = +46{\cdot}6°$. The salt had m. p. 147—148° (Found: N, 7·5. $C_{18}H_{24}O_5N_2S$ requires N, 7·4%).

d-*Benzenesulphonylalanine* was obtained from an aqueous solution of the above nor-*d*-ψ-ephedrine salt by addition of an aqueous solution of ammonia. The mixture was thoroughly extracted with chloroform to remove the base and the aqueous solution was then acidified with concentrated hydrochloric acid. The acid separated as an oil which rapidly solidified. It was recrystallised from water and obtained in colourless prisms, m. p. 126—127°, which were found to be optically pure (Found: N, 6·6. $C_9H_{11}O_4NS$ requires N, 6·1%). In aqueous solution as the sodium salt: $c = 0{\cdot}3994$, $\alpha = +0{\cdot}53°$, $[\alpha] = +33{\cdot}4°$.

l-*Benzenesulphonylalanine*.—After the above *d*A*d*B salt had been separated, the mother-liquor was treated with an excess of aqueous ammonia and extracted thoroughly with chloroform to remove the alkaloid. The aqueous solution was evaporated on the water-bath and then acidified with concentrated hydrochloric acid. The benzenesulphonylalanine so obtained had $[\alpha] = -9{\cdot}8°$ as sodium salt in aqueous solution, and this rotatory power was unaffected on further recrystallisation from water. This acid (3·0 g.) was dissolved in sodium hydroxide solution (4·71 c.c., 1·79*N*—sufficient to neutralise the *l*-acid present) and nor-*d*-ψ-ephedrine (0·706 g.—sufficient to neutralise the *d*-acid present) and water (10 c.c.) were added. Complete solution was effected on warming. The crystalline salt which had separated after 24 hours was filtered off; on further standing, more crystalline salt separated. The mother-liquor from this salt was worked up in the usual way; the acid obtained (1·1 g.) was optically pure after one crystallisation from water. It had m. p. 126—127° and was superficially indistinguishable from its optical isomeride (Found: N, 6·3. $C_9H_{11}O_4NS$ requires N, 6·1%). As the sodium salt in water it had the following rotatory power: $c = 0{\cdot}3326$, $\alpha = -0{\cdot}44$, $[\alpha] = -33{\cdot}1°$.

The same compound was prepared from *d*-alanine. The amino-acid (1·0 g.), dissolved in an equivalent quantity of sodium hydroxide solution (6·3 c.c., 1·79*N*), was treated with a further quantity of the alkali (18·8 c.c.) and the requisite amount of benzenesulphonyl chloride, added in small quantities, the mixture being vigorously shaken and warmed towards the end of the reaction. The solution was evaporated to about half its original volume and the acid was precipitated on acidification with hydrochloric acid. The product (1·6 g.; yield, 65%) was recrystallised from water and proved to be pure *l*-benzenesulphonylalanine identical in all respects with that described above. As sodium salt in water ($c = 0{\cdot}4120$), it had

$\alpha = -0{\cdot}55°$, whence $[\alpha] = -33{\cdot}6°$. In ethyl alcohol; $c = 0{\cdot}4031$, $\alpha = -0{\cdot}17°$, $[\alpha] = -10{\cdot}5°$.

dl-*Benzenesulphonylalanine Methyl Ester.*—*dl*-Benzenesulphonylalanine (7·5 g.) in pure methyl alcohol (42 c.c.) containing concentrated sulphuric acid (1·5 c.c.) was boiled for 2 hours, and the mixture poured into water. The precipitated oil solidified after 2 days. The *ester* (6 g.; yield, 80%) crystallised from aqueous methyl alcohol in colourless rhombs, m. p. 52° (Found: N, 6·1. $C_{10}H_{13}O_4NS$ requires N, 5·8%).

dl-*Benzenesulphonylalanineamide.*—The methyl ester (3 g.) was added to ammonia solution (15 c.c., *d* 0·880) cooled in ice and the well-stirred mixture was kept for 24 hours. The crystalline *amide* was filtered off and recrystallised from methyl alcohol, forming long colourless needles, m. p. 179—180° (yield, 92%) (Found: N, 12·4. $C_9H_{12}O_3N_2S$ requires N, 12·3%).

Methyl Esters of d- *and* l-*Benzenesulphonylalanine.*—These compounds were prepared from the corresponding optically active amino-acids in the same way as the externally compensated compound. They were both recrystallised from aqueous methyl alcohol and obtained in colourless needles, m. p. 65—67° (Found: *d*-ester, N, 5·7; *l*-ester, N, 6·0. $C_{10}H_{13}O_4NS$ requires N, 5·8%). The rotatory powers were determined in ethyl alcohol solution. *d*-Ester: $c = 0{\cdot}4023$, $\alpha = +0{\cdot}685°$, $[\alpha] = +42{\cdot}6°$. *l*-Ester: $c = 0{\cdot}2815$, $\alpha = -0{\cdot}48°$, $[\alpha] = -42{\cdot}3°$.

d- and l-*Benzenesulphonylalanineamides* were prepared from the corresponding optically active methyl esters in the same way as the externally compensated compound. When recrystallised from methyl alcohol, the two compounds were superficially indistinguishable and were obtained in colourless needles. Both compounds had m. p. 211—212° (Found: *d*-amide, N, 12·4; *l*-amide, N, 12·4. $C_9H_{12}O_3N_2S$ requires N, 12·3%). They are sparingly soluble in cold acetone and in water but readily soluble in the hot solvents. In ethyl alcohol, the *d*-amide ($c = 0{\cdot}3626$) had $\alpha = +0{\cdot}60°$, whence $[\alpha] = +41{\cdot}3°$, and the *l*-amide ($c = 0{\cdot}3580$) had $\alpha = -0{\cdot}60°$, whence $[\alpha] = -41{\cdot}9°$. In water, the *l*-amide ($c = 0{\cdot}2206$) had $\alpha = -0{\cdot}66°$, whence $[\alpha] = -75{\cdot}0°$.

Resolution of dl-N-*Phenylalanineamide*-4-*arsinic Acid* (compare Gibson, Johnson, and Levin, *loc. cit.*).—The amide-acid (43·2 g.) was dissolved in sodium hydroxide solution (83·8 c.c., 1·79*N*) and water (167 c.c.). To the boiling solution, nor-*d*-ψ-ephedrine sulphate (15 g.) was added, a clear solution being obtained from which the *lAdB* salt crystallised in colourless soft needles after standing for 4 hours in the ice chest. The *salt* (24 g.) was recrystallised from water (225 c.c.) and obtained in colourless well-formed prisms, m. p.

217—223° (decomp.). The rotatory power was not increased by further recrystallisation (Found : N, 9·45; As, 17·4. $C_{18}H_{26}O_5N_3As$ requires N, 9·55; As, 17·1%). In aqueous solution, $c = 1·0790$, $\alpha = +0·39°$, $[\alpha] = +8·97°$.

l-*N*-Phenylalanineamide-4-arsinic acid was liberated from the above *l*A*d*B salt in the usual manner, 2·4 g. being obtained from 4 g. of salt. It was optically pure after one crystallisation; as sodium salt in water, $[\alpha] = -18·6°$ ($c = 0·7804$). It had m. p. 247° (decomp.).

From the mother-liquor from the above *l*A*d*B salt the optically impure *d*-*N*-phenylalanineamide-4-arsinic acid was obtained in the manner described above. After one crystallisation from water, it had, as sodium salt in water, $[\alpha] = +9·82°$, and further recrystallisation from water seemed to have little or no effect on the rotatory power.

The above optically impure *d*-*N*-phenylalanineamide-4-arsinic acid (6 g.) was dissolved in sodium hydroxide solution (8·71 c.c., 1·79*N*), and nor-*d*-ψ-ephedrine (0·793 g.—to neutralise the calculated amount of *l*-acid present) added. On warming, a homogeneous solution was obtained, which was kept for 20 hours at the ordinary temperature. The crystalline precipitate (pure *l*A*d*B salt) was filtered off, and the mother-liquor worked up in the usual manner. The crude acid, as sodium salt, had $[\alpha] = +13·4°$. After four crystallisations from water this acid, as sodium salt in aqueous solution ($c = 0·3271$), had $[\alpha] = +17·12°$, approximating to the specific rotatory power of the sodium salt of pure *d*-*N*-phenylalanineamide-4-arsinic acid.

We desire to thank Messrs. Boots Pure Drug Co., Ltd., for the crude nor-*d*-ψ-ephedrine sulphate used in this work. The other expenses have been met from a grant from the Government Grant Committee of the Royal Society, which is gratefully acknowledged. One of us (B. L.) is indebted to the Department of Scientific and Industrial Research for a grant which is enabling him to take part in this investigation.

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