CCCLXVIII.—*Compounds of the Tryparsamide Type. Part II. Resolution of* dl-N-2-*Methylphenylalanineamide*-4-*arsinic Acid.*

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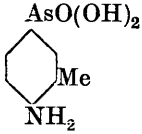
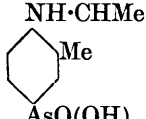
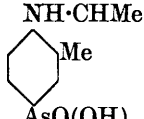
ANOTHER example of a compound of the tryparsamide type which is capable of being resolved into its optically active components is dl-N-2-*methylphenylalanineamide*-4-*arsinic acid* [dl-N-o-*tolylalanineamide*-5-*arsinic acid*] (III). This compound has been made by condensing α-bromopropionamide with 6-amino-*m*-tolylarsinic acid (I) and also by the action of ammonia on the *methyl* ester of dl-N-2-*methylphenylalanine*-4-*arsinic acid* (II), which itself was made by condensing α-bromopropionic acid with compound (I).



(I.)



(II.)



(III.)

The externally compensated acid (II) was not resolved directly; it has, however, been obtained optically active (see below). The *dl*-amide-acid (III) was easily resolved by nor-*d*-ψ-ephedrine (compare Gibson and Levin, preceding paper), the *l*A*d*B salt separating in an almost pure condition from an aqueous solution containing the amide-acid (2 equivs.), the *d*-base (1 equiv.), and sodium hydroxide (1 equiv.). The above salt gave the pure *l*-amide-acid, and the pure *d*-amide-acid was obtained from the mother-liquor after further treatment with nor-*d*-ψ-ephedrine to remove a further quantity of the *l*A*d*B salt. The optically active amide-acids (III) on hydrolysis with an excess of sodium hydroxide yielded the sodium salt of the corresponding dibasic acid (II) having the opposite optical rotatory sign, and there is strong evidence that the hydrolysis of the amide-acid is accompanied by racemisation, as was found in the conversion of *l*-*N*-phenylalanineamide-4-arsinic acid into *d*-*N*-phenylalanine-4-arsinic acid (Gibson, Johnson, and Levin, this vol., p. 482).

The compounds of the tryparsamide type described in the present paper and in Part I (Gibson, Johnson, and Levin, *loc. cit.*, p. 479) have been examined for therapeutical activity by Professor Warrington Yorke of the University of Liverpool on behalf of the Chemotherapy Committee, under whose auspices this work is being carried out, and we are greatly indebted to him for his help. From his results it appears that there is little difference in therapeutic activity towards *Trypanosoma equiperdum* and *T. rhodesiense* between the

externally compensated and the optically active forms. In general, it may be stated that none of these compounds of the tryparsamide type has anything like the therapeutical activity of tryparsamide itself and therefore it is not necessary to quote the quantitative data but only to give Professor Warrington Yorke's general conclusion in each case :

dl-N-Phenylalanine-4-arsinic acid	Definite, but transient, action.
d-N-Phenylalanine-4-arsinic acid	No action.
l-N-Phenylalanine-4-arsinic acid	No action.
dl-N-Phenylalanineamide-4-arsinic acid	Definite, but transient, action.
d-N-Phenylalanineamide-4-arsinic acid	Definite, but transient, action.
l-N-Phenylalanineamide-4-arsinic acid	Slight, but transient action.
dl-N-2-Methylphenylalanine-4-arsinic acid	No action.
dl-N-2-Methylphenylalanineamide-4-arsinic acid	No action.
l-N-2-Methylphenylalanineamide-4-arsinic acid	Slight action.

The carboxylic esters of the dibasic acids which were examined were reported upon as having no therapeutic action.

Experimental.

dl-N-2-*Methylphenylalanine*-4-*arsinic Acid* (II).—A solution of the sodium salt of 6-amino-*m*-tolylarsinic acid (38·5 g.) in water (175 c.c.) was mixed with a solution of α-bromopropionic acid (35 g.) in water (40 c.c.), and the mixture boiled for 8 hours. The resulting solution was kept for 2 days, and the precipitate recrystallised from boiling water (charcoal) (yield, 12·5 g. or 27%). The *acid* crystallised in colourless needles, m. p. 170° (decomp.) (Found : N, 4·6; As, 24·6. $C_{10}H_{14}O_5NAs$ requires N, 4·6; As, 24·75%). On titration with 0·1*N*-sodium hydroxide solution and phenolphthalein it appeared to be rather less than dibasic.

dl-N-2-*Methylphenylalanine*-4-*arsinic Acid Ethyl Ester*.—The above acid (6 g.) was dissolved in absolute ethyl alcohol (40 c.c.) and concentrated sulphuric acid (1 c.c.) and boiled for 4 hours. A portion of the alcohol having been removed by distillation, the remainder of the solution was poured into water (150 c.c.); the *ester* was at once precipitated (5·5 g.; yield, 85%). On crystallisation from 60% alcohol, it was obtained in colourless needles, m. p. 214—216° (decomp.). It is sparingly soluble in cold but readily soluble in hot alcohol (Found : N, 4·3; As, 22·8. $C_{12}H_{18}O_5NAs$ requires N, 4·2; As, 22·7%). This ethyl ester does not show a sharp end-point when titrated with 0·1*N*-sodium hydroxide and phenolphthalein.

The corresponding *methyl* ester was prepared in an analogous manner, pure methyl alcohol being used. It crystallised from 60% alcohol in colourless needles, m. p. 215° (decomp.) (yield, 85%)

(Found: N, 4·8; As, 23·5. $C_{11}H_{16}O_5NAs$ requires N, 4·4; As, 23·7%).

dl-N-2-*Methylphenylalanineamide*-4-*arsinic Acid* (III).—This was prepared in two ways. (*a*) The above methyl ester (4 g.) was added in small quantities to concentrated ammonia solution (*d* 0·880) cooled in ice; it dissolved fairly readily. After the solution had been kept for 48 hours at the ordinary temperature, the excess of ammonia was removed under reduced pressure over sulphuric acid. The solid residue was dissolved in water and acidified with acetic acid. The precipitated *amide* was recrystallised from the minimum quantity of hot water and was obtained in colourless needles, m. p. 211° (decomp.) after previous softening (yield, 58%) (Found: N, 9·0; As, 25·0. $C_{10}H_{15}O_4N_2As$ requires N, 9·3; As, 24·8%).

(*b*) A solution containing α-bromopropionamide (20 g.) and the sodium salt of 6-amino-*m*-tolylarsinic acid (25 g.) in water (90 c.c.) was boiled for 1 hour. The crystalline precipitate was washed with 10% hydrochloric acid to remove unchanged aminotolylarsinic acid and then recrystallised from boiling water (charcoal). It was obtained in colourless needles, the highest melting point of which was 219—220° (decomp.); yield, 21 g. (70%) (compare Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1919, **41**, 1589). The compound is sparingly soluble in cold water and soluble in hot water and in 50% alcohol (Found: N, 8·8; As, 24·6%). The crystalline ammonium salt may be obtained by adding 95% alcohol to a solution of the amide-acid in concentrated ammonia solution.

Quinine and strychnine did not yield crystalline salts with *dl*-2-methylphenylalanine-4-arsinic acid. The brucine salt was crystalline but the less soluble portion proved to be a partial racemate, since the acid obtained from it in the usual way was optically inactive. Nor-*d*-ψ-ephedrine was also tried as a resolving base, but the less soluble fraction of the salt gave an acid which was but feebly optically active (lævorotatory).

Resolution of dl-N-2-*Methylphenylalanineamide*-4-*arsinic Acid*.—*l*-α-Phenylethylamine was first tried as the resolving base, but no crystalline salt was obtained. Preliminary experiments having indicated that it was preferable to use nor-*d*-ψ-ephedrine rather than the sulphate, the partly resolved amide-acid was recovered and mixed with a further amount of inactive amide-acid, and the mixture (7·67 g.), having $[\alpha] = +3·8°$, used for the resolution now described. This amide-acid was dissolved in sodium hydroxide solution (1·79*N*, 7·84 c.c.—sufficient to neutralise the *d*-amide-acid present), and nor-*d*-ψ-ephedrine (1·72 g.—sufficient to combine with the *l*-amide-acid present) in water (10 c.c.) added. On warming, a clear solution was obtained, which was kept at the ordinary temperature for 12

hours. The crystalline *salt* was filtered off and after one crystallisation from boiling water it was optically pure. It crystallised in colourless needles (4·9 g.), m. p. 205—208° (decomp.). This *l*A*d*B salt had $[\alpha] = -2{\cdot}46°$ * in aqueous solution ($c = 1{\cdot}180$, $\alpha = -0{\cdot}11°$) (Found : N, 9·3; As, 16·7. $C_{19}H_{28}O_5N_3As$ requires N, 9·3; As, 16·6%).

l-N-2-*Methylphenylalanineamide*-4-*arsinic Acid.*—The nor-*d*-ψ-ephedrine salt (3·5 g.) was ground with an excess of concentrated aqueous ammonia, and the solution extracted thoroughly with chloroform to remove the organic base. The aqueous solution after evaporation was acidified with concentrated hydrochloric acid, and the precipitated *amide-acid* recrystallised from boiling water. It was obtained in long colourless needles (2·75 g.), m. p. 267—268° (decomp.) after darkening from 260°. Obtained in the manner described, it was optically pure and, as sodium salt (made up with the calculated quantity of sodium bicarbonate), it had $[\alpha] = -34{\cdot}9°$ ($c = 0{\cdot}661$ in water; $\alpha = -0{\cdot}92°$) (Found : N, 9·3; As, 25·3. $C_{10}H_{15}O_4N_2As$ requires N, 9·3; As, 24·8%).

d-N-2-*Methylphenylalanineamide*-4-*arsinic Acid.*—The impure *d*-amide-acid, isolated from the mother-liquor from the above *l*A*d*B salt in the usual manner, had $[\alpha] = +23{\cdot}4°$ as sodium salt and therefore contained approximately 85% of the *d*-amide-acid. This rotatory power was but little affected by recrystallisation of the amide-acid from water. The amide-acid (2·75 g.) was dissolved in sodium hydroxide solution (1·79*N*, 4·21 c.c.), and nor-*d*-ψ-ephedrine (0·24 g.) added. On warming, a homogeneous solution was obtained and this rapidly deposited the *l*A*d*B salt, which was filtered off after 24 hours. The *amide-acid* was obtained from the mother-liquor in the usual way and it had, after one recrystallisation, as sodium salt, $[\alpha] = +30{\cdot}8°$. After two further recrystallisations from water, it was optically pure. Made up in the usual way as sodium salt, it had $[\alpha] = +33{\cdot}4°$ ($c = 0{\cdot}1811$ in water; $\alpha = +0{\cdot}24°$). This optically active amide-acid, like its enantiomorph, crystallises from water in colourless needles, m. p. 267°. Their solubility is markedly lower than that of the *dl*-amide-acid (Found : As, 24·9%).

Hydrolysis of l-N-2-*Methylphenylalanineamide*-4-*arsinic Acid.*—50 C.c. of an aqueous solution containing 0·3552 g. of the *l*-amide-acid had $[\alpha] = -34{\cdot}4°$. 40 C.c. of this solution together with 1 g. of sodium hydroxide were boiled for 10 minutes; it was then free from ammonia. The residue was cooled and made up to 50 c.c. with water; it had $[\alpha] = +20{\cdot}3°$. The same experiment was repeated with a larger quantity of the *l*-amide-acid. The dibasic acid,

* The rotatory powers recorded in this paper were determined at 20° in 4 dcm. tubes, the mercury green line (λ 5461) being used in all cases.

recovered from the final alkaline solution by addition of hydrochloric acid (Congo-red), was recrystallised twice from the minimum quantity of boiling water. This acid had $[\alpha] = +12{\cdot}3°$ (as sodium salt, $c = 0{\cdot}6534$, $\alpha = +0{\cdot}32°$). This rotatory power is much less than the former, indicating that some externally compensated acid (less soluble than the optically active acid) is formed during the hydrolysis of the optically active amide.

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