Researches on the constitution of physostigmine. Pt. 3 / by Arthur H. Salway.

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RESEARCHES
ON THE
CONSTITUTION OF PHYSOSTIGMINE
PART III

BY

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CCXI.—*Researches on the Constitution of Physostigmine. Part III. The Formation of Substistuted Indoles from* m-4-*Xylidine, and the Reduction of* 3-*Nitro*-p-*tolylacrylic Acid.*

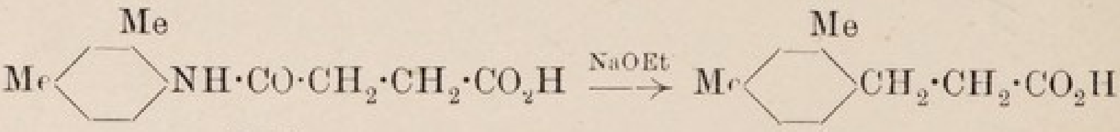
By Arthur Henry Salway.

In continuation of the author's previous investigations (T., 1912, **101**, 978; **103**, 351) on physostigmine (eserine), $C_{15}H_{21}O_2N_3$, some synthetic experiments have been conducted with the object of obtaining a further insight into the constitution of the alkaloid. Although these experiments have not resulted in the synthesis of the desired compounds, and are of no value for the solution of the problem under consideration, they are not entirely devoid of interest, and it is therefore proposed to place them on record, and to describe the characters of the new compounds which have been prepared.

It has recently been shown by Madelung (*Ber.*, 1912, **45**, 1128, 3541) that *o*-toluidides, $C_6H_4\Big<\substack{NH\cdot CO\cdot R\\ Me}$, can be converted into indole derivatives, $C_6H_4\Big<\substack{NH\\ CH}\Big>C\cdot R$, by heating with dry sodium ethoxide. By applying such a reaction to acyl derivatives of *m*-4-xylidine it was thought that substituted 5-methylindoles might be obtained, and a suitable choice of the acyl radicle would enable one to prepare compounds of service in helping to elucidate the constitution of physostigmine. Consequently it was necessary, in the first place, to ascertain whether the simplest xylidides could be converted by the above method into indole derivatives, and accordingly aceto-*m*-4-xylidide (I) was investigated in this direction, when a good yield of 2 : 5-dimethylindole (II) was obtained:

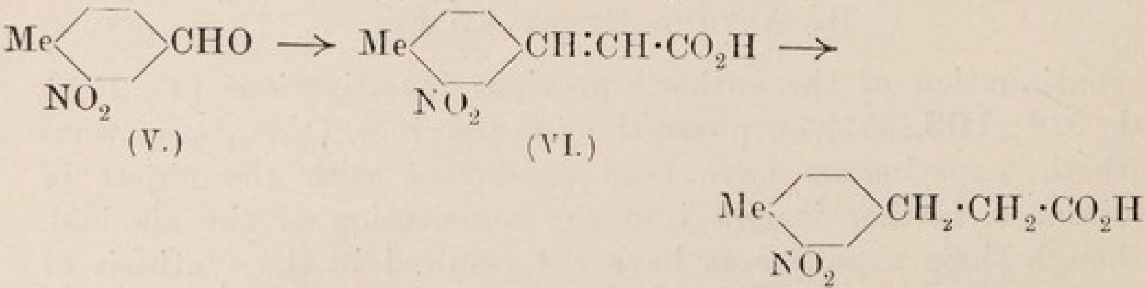
(I.) (II.)

Unfortunately, the reaction was not generally applicable to other derivatives of *m*-4-xylidine, since the compound of chief interest to the author, namely, 2 : 4-*xylylsuccinamic acid* (III), suffers disruption under the influence of dry sodium ethoxide, and the principal product of the reaction was *β*-2 : 4-xylylpropionic acid (IV):



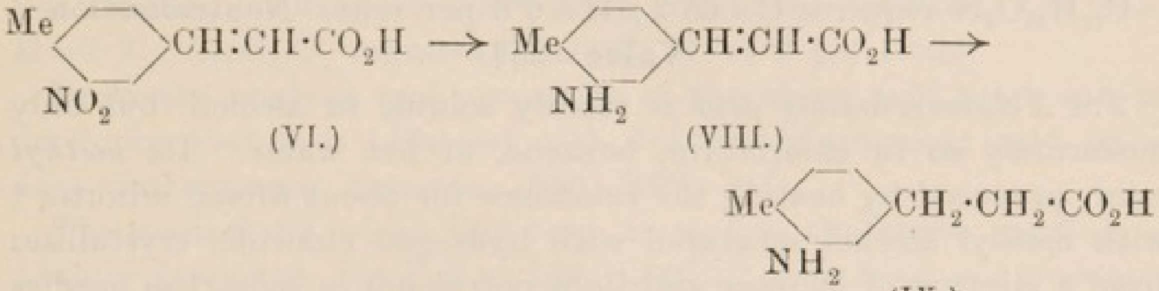
(III.) (IV.)

The second part of this investigation arose out of an attempt to prepare *β*-3-nitro-*p*-tolylpropionic acid (VII). For this purpose *p*-tolualdehyde was first nitrated, and the resulting *m*-nitro-*p*-tolualdehyde (V) converted into 3-nitro-*p*-tolylacrylic acid (VI); it was then assumed that the latter would yield the required compound on reduction, according to the following scheme:



(V.) (VI.) (VII.)

It was observed, however, that the nitro-group of 3-nitro-*p*-tolylacrylic acid (VI) was more readily attacked by reducing agents than the cinnamyl residue, so that the first product of the reaction was not a substituted propionic acid (VII), but 3-*amino*-p-*tolylacrylic acid* (VIII), which by further reduction then became converted into β-3-*amino*-p-*tolylpropionic acid* (IX):


(VI.) (VIII.) (IX.)

Under no condition of reduction investigated by the author was it possible to reduce the 3-nitro-*p*-tolylacrylic acid (VI) without affecting the nitro-group.

EXPERIMENTAL.

I. *Preparation of* 2:5-*Dimethylindole from* m-4-*Xylidine.*

In order to ascertain whether *m*-4-xylidine could be converted into 2:5-dimethylindole, a quantity of the former was acetylated, and the resulting acetyl derivative (m. p. 129°; b. p. 170°/10 mm.) heated for a short time at 250—300° with an equal weight of dry sodium ethoxide in the absence of air. After the vigorous reaction which ensued had subsided, water was added, and the mixture distilled in a current of steam. The first portion of the distillate contained xylidine, but subsequently a solid compound began to pass over into the receiver. This was collected separately, and purified by crystallisation from a mixture of benzene and light petroleum, when glistening leaflets melting at 114° were obtained (Found, C=82·7; H=7·7. $C_{10}H_{11}N$ requires C=82·8; H=7·6 per cent.). This substance readily gave the pine-shaving colour reaction typical of indoles, and was evidently identical with 2:5-dimethylindole (compare Raschen, *Annalen*, 1887, **239**, 227). The yield of the latter amounted to 40 per cent. of the acetoxylidide employed in the reaction.

2:4-*Xylylsuccinamic Acid* (III, p. 1989).

For the preparation of this compound six parts of *m*-4-xylidine were added to a solution of five parts of succinic anhydride in hot chloroform, and the mixture allowed to cool. In a very short time colourless, slender needles of the succinamic acid were deposited, the yield amounting to 80 per cent. of the theoretical. The substance was collected and purified by crystallisation from chloroform, when it was found to sinter at 160° and to become completely melted at 164°:

0·0965 gave 0·2299 CO_2 and 0·0614 H_2O. C=65·0; H=7·1.

0·1063 required for neutralisation 4·85 c.c. *N*/10-KOH. Neutralisation Value=256.

$C_{12}H_{15}O_3N$ requires C=65·2; H=6·8 per cent. Neutralisation Value=254.

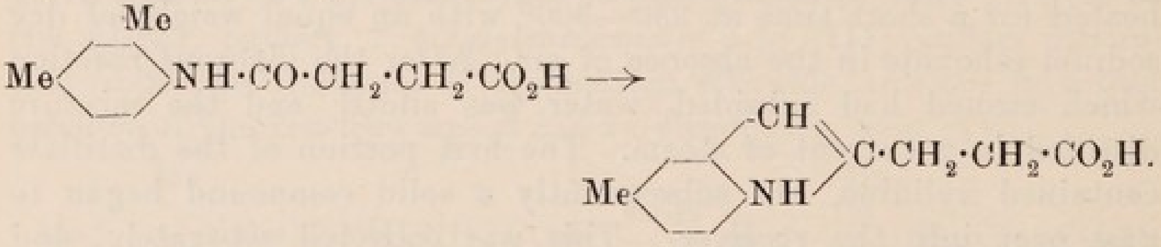
2:4-*Xylylsuccinamic acid* is readily soluble in alcohol, but only moderately so in chloroform, benzene, or hot water. Its *methyl* ester, prepared by heating the substance for about fifteen minutes * with methyl alcohol saturated with hydrogen chloride, crystallises from a mixture of benzene and light petroleum in colourless needles melting at 107°.

Found: C=66·7; H=7·2.

$C_{13}H_{17}O_3N$ requires C=66·4; H=7·2 per cent.

Action of Sodium Ethoxide on 2:4-Xylylsuccinamic Acid. Formation of β-2:4-Xylylpropionic Acid.

The object of this experiment was to ascertain whether 2:4-xylylsuccinamic acid could be converted into an indole derivative according to the following scheme:



Fifty grams of the acid, in convenient portions of 10 grams each, were added to an equal weight of sodium ethoxide in a capacious flask, and the mixture heated for a short time (fifteen minutes) at a temperature of about 300° in the absence of air. The dark-coloured solid thus obtained was digested with water, and the alkaline mixture extracted with ether, which removed some xylidine and a small quantity (3 grams) of a neutral oil. The alkaline liquid was next filtered from some insoluble resin, and then acidified with dilute hydrochloric acid, when a considerable quantity of acidic substance was precipitated. The mixture was extracted with ether, the ethereal solution being washed, dried, and the solvent removed. The residue thus obtained was found to contain a large proportion of unchanged 2:4-xylylsuccinamic acid, which

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* Prolonged heating of this mixture causes hydrolysis, with the formation of xylidine and succinic acid.

was separated from the other acids present by treatment with cold chloroform (2:4-xylylsuccinamic acid is almost insoluble in this solvent), and filtering the mixture. The filtrate, on evaporation, yielded a residue, which slowly crystallised. The crystalline substance was separated from some oily matter by drying on a porous tile, and was then recrystallised from dilute alcohol, when colourless needles, melting at 106°, were obtained. (Found, C=74·3; H=7·9. $C_{11}H_{14}O_2$ requires C=74·2; H=7·9 per cent.)

From the analysis and properties of the above acid there can be no doubt that it is identical with β-2:4-xylylpropionic acid (compare Gattermann, *Annalen*, 1906, **347**, 347).

The neutral oil, which had been formed in the above reaction as already described, distilled at 150—200°/15 mm., and was evidently a mixture. It gave a scarlet coloration in contact with a pine shaving which had previously been moistened with concentrated hydrochloric acid, and therefore contained some compound of an indolic character. The yield of this material was, however, too small to enable it to be further investigated.

It is evident from the results of the above experiment that sodium ethoxide at a high temperature effects the disruption of 2:4-xylylsuccinamic acid with the formation of β-2:4-xylylpropionic acid, and no appreciable quantity of a substituted indole is produced.

2:4-*Xylylsuccinamide*, $C_6H_3Me_2\cdot NH\cdot CO\cdot CH_2\cdot CH_2\cdot CO\cdot NH_2$.

This substance was prepared by the addition of concentrated aqueous ammonia to an alcoholic solution of methyl 2:4-xylylsuccinamate. In a short time the acid amide was deposited from the liquid in glistening leaflets, which melted at 203° and were pure. The compound was also obtained directly from 2:4-xylylsuccinamic acid by heating the latter for a short time with methyl alcohol containing hydrogen chloride, and then adding to the mixture an excess of concentrated aqueous ammonia, when the amide was precipitated in almost a pure condition. The yield of pure substance amounted to 80—90 per cent. of the acid employed in the reaction:

0·1503 gave 0·3598 CO_2 and 0·0987 H_2O. C=65·3; H=7·3.
$C_{12}H_{16}O_2N_2$ requires C=65·5; H=7·3 per cent.

2:4-*Xylylsuccinamide* is readily soluble in alcohol, but only sparingly so in benzene, ethyl acetate, or water. It is also soluble in concentrated hydrochloric acid, but is reprecipitated from this solution on the addition of water. When the substance is heated with aqueous potassium hydroxide, ammonia is rapidly evolved, with the formation of 2:4-xylylsuccinamic acid, which is further resolved, on prolonged heating with the alkali, into xylidine and succinic acid.

An attempt was made to convert the above amide into an indole derivative by heating with sodium ethoxide in a manner similar to that described in connexion with 2:4-xylylsuccinamic acid, but without success, since the only compounds that could be isolated from the reaction mixture were xylidine and 2:4-xylylsuccinamic acid.

II. *Reduction of 3-Nitro-*p*-tolylacrylic Acid* (VI, p. 1989).

The 3-nitro-*p*-tolylacrylic acid required for these experiments was prepared from *p*-tolualdehyde in the manner already described by Hanzlik and Bianchi (*Ber.*, 1899, **32**, 1288, 2285). In order to ascertain, in the first place, whether reduction could be effected by means of sodium amalgam, 800 grams of the latter (4 per cent. Na) were added in small quantities, with continuous mechanical stirring, to a solution of the acid in dilute sodium hydroxide. After the amalgam had been completely decomposed, the alkaline liquid was filtered, then acidified, and the acidic substance, which was precipitated, was collected. The greater part of the latter was found to consist of unchanged material, but a small quantity of an indefinite acid of high melting point was isolated, which appeared to be formed from the original acid by polymerisation under the influence of the alkali. No evidence was obtained of the formation of any β-3-nitro-*p*-tolylpropionic acid (VII, p. 1989) in the reaction.

*3-Amino-*p*-tolylacrylic Acid* (VIII, p. 1990).

This compound was obtained as the first reduction product of 3-nitro-*p*-tolylacrylic acid when the latter was heated for a short time at 100° with an excess of hydriodic acid (D 1·7) and red phosphorus. As soon as the vigorous initial reaction had subsided, water was added, and the mixture filtered to remove the red phosphorus. The filtrate, on concentration, yielded well-formed crystals of a hydriodide, which were collected and dissolved in a little water. Aqueous sodium carbonate was then cautiously added to the solution, when the amino-acid was deposited as a yellow precipitate. It was purified by crystallisation from alcohol, and thus obtained in lemon-yellow, elongated needles, melting at 184°:

0·0984 gave 0·2443 CO_2 and 0·0548 H_2O. C=67·7; H=6·2.

$C_{10}H_{11}O_2N$ requires C=67·8; H=6·2 per cent.

It is evident from the above analysis that the cinnamyl residue has remained intact during the reduction, whilst the nitro-group has been converted into an amino-group with the formation of 3-amino-*p*-tolylacrylic acid.

3-*Amino*-p-*tolylacrylic acid* is very sparingly soluble in chloroform, ether, or benzene, and moderately so in hot water or hot alcohol. It separates from the latter solvents, on cooling, in well-formed needles. It possesses both acid and basic properties, and is converted by further reduction into the following compound.

β-3-*Amino*-p-*tolylpropionic Acid* (IX, p. 1990).

This compound was prepared by heating 3-nitro-*p*-tolylacrylic acid for two hours with ten parts of hydriodic acid (D 1·7) and one part of red phosphorus. Water was then added to the reaction product, the mixture subsequently filtered, and the filtrate concentrated to a small volume, when colourless crystals of a hydriodide were deposited. These were collected, dissolved in a little water, and the free amino-acid was then precipitated by the addition of the requisite quantity of sodium carbonate. The substance was purified by crystallisation from dilute alcohol, when it was obtained in stellar aggregates of colourless needles, melting at 142—143°:

0·0952 gave 0·2340 CO_2 and 0·0650 H_2O. C=67·0; H=7·6.

$C_{10}H_{13}O_2N$ requires C=67·0; H=7·3 per cent.

β-3-*Amino*-p-*tolylpropionic acid* is readily soluble in alcohol or hot water, but only sparingly so in ether, chloroform, or benzene. Its *diacetyl* derivative, $NAc_2 \cdot C_6H_3Me \cdot CH_2 \cdot CH_2 \cdot CO_2H$, prepared by heating the amino-acid with acetic anhydride for a few hours, and then pouring the mixture into water, crystallises from the latter solvent in glistening leaflets, which sinter at 122° and melt at about 160°:

0·0872 gave 0·2044 CO_2 and 0·0507 H_2O. C=63·9; H=6·5.

$C_{14}H_{17}O_4N$ requires C=63·9; H=6·5 per cent.

The *monoacetyl* derivative, $NHAc \cdot C_6H_3Me \cdot CH_2 \cdot CH_2 \cdot CO_2H$, obtained by dissolving the diacetyl compound in hot dilute ($N/10$) hydrochloric acid, and allowing the solution to cool, crystallises in colourless, slender needles, melting at 200°. It can also be prepared by heating the amino-acid, for a few minutes only, with acetic anhydride:

0·1028 gave 0·2459 CO_2 and 0·0628 H_2O. C=65·2; H=6·8.

$C_{12}H_{15}O_3N$ requires C=65·2; H=6·8 per cent.

The *ethyl* ester of β-3-amino-*p*-tolylpropionic acid,

$NH_2 \cdot C_6H_3Me \cdot CH_2 \cdot CH_2 \cdot CO_2Et$,

prepared from the acid by treatment with hot alcohol in the presence of hydrogen chloride, is a liquid which distils at 208°/ 30 mm., and possesses a pleasant, nut-like odour:

0·1008 gave 0·2564 CO_2 and 0·0758 H_2O. C = 69·4; H = 8·4.
$C_{12}H_{17}O_2N$ requires C = 69·6; H = 8·2 per cent.

The above-described ester yields a *hydrochloride*,

$$CO_2Et{\cdot}CH_2{\cdot}CH_2{\cdot}C_6H_3Me{\cdot}NH_2,HCl,$$

which crystallises from a mixture of ether and alcohol in small, colourless prisms, melting at 115—117°.

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