CXXXV.—*Researches on Morphine. Part III.*

By Frederic Herbert Lees.

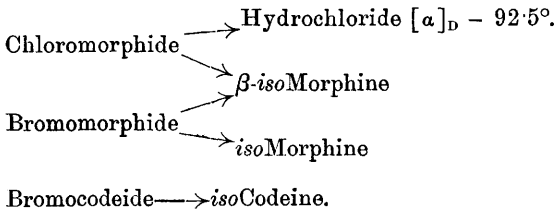
It was shown by Schryver and Lees (Trans., 1900, **77**, 1024, and 1901, **79**, 563) that by the interaction of morphine, and either phosphorus trichloride, phosphorus tribromide or hydrobromic acid, and of codeine and phosphorus tribromide, the alcoholic hydroxyl group of the respective base is replaced by chlorine or bromine. The crystalline bases, chloromorphide, $C_{17}H_{18}O_2NCl$, bromomorphide, $C_{17}H_{18}O_2NBr$, and bromocodeide, $C_{18}H_{20}O_2NBr$, were obtained in this way.

Many years previously, a crystalline base, chlorocodeide, $C_{18}H_{20}O_2NCl$, was described by Vongerichten (*Annalen*, 1881, **210**, 107), who obtained it by the interaction of codeine and phosphorus pentachloride.

More recently it has been shown by Pschorr (*Ber.*, 1906, **39**, 3130) that chloromorphide is also produced by the action of anhydrous liquid hydrogen chloride on morphine.

It was, furthermore, demonstrated by Schryver and Lees (*loc. cit.*) that when chloromorphide, bromomorphide, and bromocodeide are hydrolysed with water, morphine and codeine are not simply regenerated, but in each case at least two bases isomeric, but not identical, with morphine and codeine respectively are produced.

The products isolated by Schryver and Lees from the hydrolysis of these halogen derivatives can be represented as follows:



Of these isomeric bases, *iso*morphine was more fully studied by Schryver and Lees (*loc. cit.*), particularly with respect to its behaviour on exhaustive methylation as compared with that of morphine.

It has since been shown by Vongerichten (*Ber.*, 1903, **36**, 159) and independently by Knorr and Hörlein (*Ber.*, 1906, **39**, 4409) that chlorocodeide on hydrolysis yields an isomeride of codeine melting at 180° and having $[\alpha]_D$ –94° in ethyl alcohol. These investigators found this base to be identical with the so-called "*pseudo*codeine" which was first obtained by Merck (*Arch. Pharm.*, 1891, **229**, 161) by the action of dilute sulphuric acid on codeine.

The further investigation of the halogen derivatives of morphine and codeine and the products of their hydrolysis has been in progress by the author for some considerable time, and the further results obtained form the subject of the present paper.

When chloromorphide is methylated by means of sodium ethoxide and dimethyl sulphate, chlorocodeide, identical with the product of the interaction of phosphorus pentachloride and codeine, is produced. The same substance can also be prepared in good yield by the interaction of phosphorus trichloride and codeine.

When bromomorphide is methylated in a similar manner, bromocodeide is produced.

It is thus proved that chlorocodeide and bromocodeide are simply the codeine analogues or methyl ethers respectively of the corresponding morphides.

It seemed of importance to settle this point in view of the different conditions under which the morphides and codeides have been prepared.

By the hydrolysis of chloromorphide, the author has isolated, besides *β-iso*morphine, an hitherto undescribed isomeride of morphine. On methylation, it yields the codeine analogue which is in all respects identical with the above-mentioned "*pseudo*codeine."

As pointed out by Knorr and Hörlein (*Ber.*, 1906, **39**, 4409), the name "*pseudo*codeine" was not happily chosen by Merck for his base, since it is not the methyl ether of the base known as *pseudo*morphine, which is an oxidation product of the formula $C_{34}H_{36}O_6N_2$. The position becomes more unfortunate, however, now that the morphine analogue of "*pseudo*codeine" has been isolated, inasmuch as the new base cannot, of course, be termed "*pseudo*morphine," which is the name of a well-known base which has been fully characterised by means of a large number of derivatives.

It has therefore been decided to designate the new base from chloromorphide *neo*iso*morphine*, and the author proposes the adoption of *neo*iso*codeine* for the methyl ether to replace "*pseudo*codeine," which is a decided misnomer as applied to this base.

*Neo*iso*morphine*, $C_{17}H_{19}O_3N$, forms brilliant, prismatic needles from ethyl alcohol. These contain one molecule of alcohol of crystallisation and melt at 278°. The *hydrochloride*, $C_{17}H_{19}O_3N,HCl$, has $[\alpha]_D$ −79·1° in aqueous solution; the *methiodide*, $C_{17}H_{19}O_3N,MeI$, melts at 297° and has $[\alpha]_D$ −54·5° in aqueous solution.

*Neo*iso*codeine*, $C_{18}H_{21}O_3N$, obtained by the methylation of neo*iso*morphine, forms large, colourless prisms from ethyl acetate, which melt at 181—182° and have $[\alpha]_D$ −96·6° in ethyl alcohol.

In a preliminary communication (Proc., 1906, **22**, 253), the author in conjunction with F. Tutin has already announced some results

obtained from the hydrolysis of bromocodeide with water. It was shown that by fractional crystallisation of the mixture of bases produced, two definite substances were obtained:

A-Base.—This formed slender, prismatic needles melting at 147—147·5° and had $[\alpha]_D$ −205° in chloroform.

B-Base.—This formed colourless, tabular prisms melting at 171—172° and had $[\alpha]_D$ −155° in chloroform.

The latter was shown to be iso*codeine*, the codeine analogue of *iso*morphine which is the chief product of the hydrolysis of bromomorphide, for when *iso*morphine is methylated, a base identical with the *B*-base is quantitatively produced.

The *A*-base has now been definitely proved to represent a molecular mixture of *iso*codeine and *β-iso*codeine, the codeine analogue of *β-iso*morphine which is formed together with *iso*morphine and neo*iso*morphine respectively by the hydrolysis of bromo- and chloro-morphide.

The composition of the *A*-base was determined by the fact that it was produced by crystallising from ethyl acetate a mixture of equal parts of *iso*codeine and *β-iso*codeine, which were prepared by the methylation of *iso*morphine and *β-iso*morphine respectively, as also by the fact that its methiodide was resolved into *iso*codeine methiodide (m. p. 270°; $[\alpha]_D$ −103·3° in water); methyl *iso*morphimethine (m. p. 168—169°), and *β-iso*codeine methiodide (m. p. 215—216°; $[\alpha]_D$ −140·2° in water).

It must be noted that the *iso*codeine (m. p. 144°; $[\alpha]_D$ −169°) obtained by Schryver and Lees (*loc. cit.*) by the action of water on bromocodeide was not pure and must have contained a small proportion of *β-iso*codeine. The methiodide of this base was, however, purified by recrystallisation, the purified salt being in all respects identical with *iso*codeine methiodide prepared by two independent methods of methylation from pure *iso*morphine (from bromomorphide; m. p. 247°; $[\alpha]_D$ −166·5°). The methiodides produced by the three methods had the same melting point and specific rotatory power, and each specimen afforded methyl *iso*morphimethine (m. p. 167°).

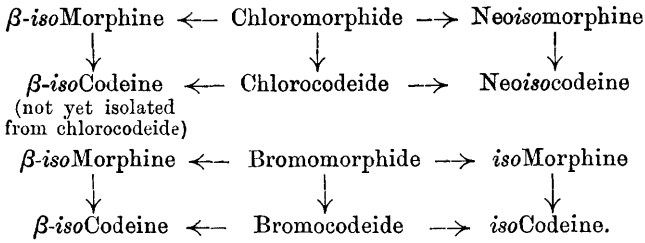
Although the fact that a mixture of bases is the direct result of the hydrolysis of bromocodeide with water was published by Lees and Tutin (*loc. cit.*) in November of last year, Knorr and Hörlein had apparently not seen the publication, for they have recently (*Ber.*, 1907, 40, 2032) based important conclusions respecting the isomerism of codeine, *iso*codeine, and neo*iso*codeine upon the products of the oxidation of these bases when they were obviously unaware that the *iso*codeine of Schryver and Lees (m. p. 144°), which they apparently oxidised, had in the meantime been shown to consist of a mixture of two isomeric bases only one of which is *iso*codeine.*

* See Addendum.

*β-iso*Codeine, $C_{18}H_{21}O_3N$, produced by the methylation of *β-iso*-morphine, is a syrupy base which did not crystallise. Its *methiodide*, $C_{18}H_{21}O_3N,MeI$, however, forms small, glistening, tabular crystals from water (m. p. 215—216°; $[\alpha]_D$ −145·5° in water).

When an aqueous solution of *β-iso*codeine methiodide is boiled with dilute sodium hydroxide, it is converted into a *methine* base which is an almost colourless oil. This methine base forms a *methiodide* which is readily soluble in alcohol or water, and was not further investigated on account of lack of sufficient material.

The relation between the halogen derivative of morphine and codeine and the bases isolated by their hydrolysis can be now represented as follows:



With regard to the relationship of these bases, respectively, to morphine and codeine, the view expressed by Lees and Tutin (*loc. cit.*) that they were optically isomeric with the latter bases was based upon the fact that, besides *iso*codeine and *β-iso*codeine, codeine was also isolated from the hydrolysis of the entire crude product of the interaction of codeine and phosphorus tribromide. Further experiment has shown that this fact does not justify the conclusion arrived at, since the codeine was most probably derived from a codeine ester of phosphorous acid and not from an optically isomeric bromocodeide. Further study of these substances on the lines now being followed by Knorr cannot fail to elucidate the question of the relations of these bases to each other and to morphine and codeine

Experimental.

Methylation of Chloromorphide. Formation of Chlorocodeide.

Chloromorphide was methylated in the usual manner with sodium ethoxide and dimethyl sulphate in alcoholic solution. On cooling, the methylated product separated together with the sodium methyl sulphate formed in the reaction. The crystalline material was collected, washed with water, dried by absorption, and recrystallised from ethyl alcohol. Glistening leaflets were thus obtained melting at 152—153°:

0·3095 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D −9·42°, whence $[\alpha]_D$ −380·4°.

Chlorocodeide, prepared by the interaction of codeine and phosphorus pentachloride according to the conditions given by Vongerichten (*loc. cit.*), melted at 152—153°, and

0·2705 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D −8·25°, whence $[\alpha]_D$ −381·2°.

When the substances prepared by the two methods were intimately mixed, the melting point was not changed.

Action of Phosphorus Trichloride on Codeine. Formation of Chlorocodeide.

The reaction between phosphorus trichloride and codeine in chloroform solution results chiefly in the formation of uncrystallisable codeine esters of phosphorous acid, and very little chlorocodeide is produced, even when the mixture is boiled for several hours. When, however, dry codeine was saturated with excess of phosphorus trichloride, the mixture heated for two hours on a water-bath, the product dissolved in alcohol, poured into water, made alkaline with sodium carbonate, and extracted with chloroform, a good yield of the chloro-base was obtained. After recrystallisation from ethyl alcohol it melted at 152—153°, and

0·3265 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D −9·90°, whence $[\alpha]_D$ −379°.

An intimate mixture of this base and that prepared by other methods showed no change in the melting point.

Methylation of Bromomorphide. Formation of Bromocodeide.

Bromomorphide was methylated in the same manner as was chloromorphide. The methylated base, which crystallised from the alcoholic solution, was freed from sodium methyl sulphate by washing with water, dried on porous earthenware, and recrystallised from ethyl alcohol. It separated as glistening, prismatic crystals, which melted at 161—162°, and this melting point was not affected by admixture with bromocodeide prepared directly from codeine:

0·4890 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D +1·90°, whence $[\alpha]_D$ +48·6°.

A specimen of bromocodeide, prepared by the interaction of phosphorus tribromide and codeine, had the following specific rotatory power:

0·5261 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D +2·00°, whence $[\alpha]_D$ +47·5°.

Hydrolysis of Chloromorphide. Formation of β-iso Morphine and Neoisomorphine, $C_{17}H_{19}O_3N$.

Chloromorphide (39 grams) was suspended in two equal portions in water (150 c.c. in each case). The mixture was then heated on a water-bath, and acetic acid gradually added until solution of the base was effected, when the solutions were then vigorously boiled for three hours in a reflux apparatus. The whole of the pale yellow, aqueous product was then concentrated on a water-bath to a syrup to which alcohol was added repeatedly, followed by continued evaporation. After a time a crystalline salt began to separate from the alcoholic solution, and on standing overnight several grams of this had collected. The crystalline salt was separated from the dark coloured mother-liquor, and on washing with alcohol was obtained quite white. It was found to be only sparingly soluble even in warm water, and was easily purified by recrystallisation from this solvent. The base was isolated from this salt by dissolving in warm water, adding excess of sodium carbonate, and extracting several times with chloroform. The residue from the chloroform solution was a faintly yellow, viscous syrup which was dissolved in warm alcohol. Almost immediately the base separated in the form of beautiful glistening, colourless, prismatic crystals.

This base was readily identified as *β-iso*morphine. It melted at 183—184° and exhibited the characteristic behaviour on heating previously recorded by Schryver and Lees (*loc. cit.*), and also contained one-half a molecule of alcohol of crystallisation:

1·0353 of the air-dried base lost 0·0815 at 110°. $C_2H_6O = 7·87$.

$(C_{17}H_{19}O_3N)_2,C_2H_6O$ requires $C_2H_6O = 7·47$ per cent.

Isolation of Neoisomorphine, $C_{17}H_{19}O_3N$.—The alcoholic mother-liquor from the *β-iso*morphine hydrochloride was further concentrated, and on long standing in a desiccator deposited 13 grams of crystalline salt, which was insoluble in alcohol, and was therefore easily obtained free from the dark coloured mother-liquor by washing. This further fraction of hydrochloride was, unlike the *β-iso*morphine hydrochloride, excessively soluble in water:

0·4898 dissolved in water and made up to 25 c.c. gave in a 2-dcm. tube α_D −3·94°, whence $[\alpha]_D$ −100·5°.

*β-iso*Morphine hydrochloride has the specific rotatory power $[\alpha]_D$ −200·8°.

It was thus apparent that the second fraction of hydrochloride contained a new base.

It was found that the most convenient means of obtaining the base from the hydrochloride is to add, cautiously, dilute ammonia solution to the aqueous solution of the salt, when the base is precipitated and on

stirring becomes crystalline. The crystalline base was collected, washed with water, dried on porous earthenware, and recrystallised from hot ethyl alcohol. It is only very sparingly soluble in this solvent, and a very large amount of the latter was required to effect solution. On concentrating the solution and allowing it to cool undisturbed, the base separated in the form of brilliant, prismatic needles.

*Neo*iso*morphine* melts at 278°, and crystallises from alcohol with one molecule of alcohol of crystallisation:

0·8820 of the air-dried base lost at 110° 0·1180. $C_2H_6O = 13·4$.

0·6700 „ „ „ „ „ 0·0895. $C_2H_6O = 13·4$.

$C_{17}H_{19}O_5N \cdot C_2H_6O$ requires $C_2H_6O = 13·9$ per cent.

0·1672 of the dry base gave 0·4385 CO_2 and 0 1006 H_2O. $C = 71·5$; $H = 6·7$.

$C_{17}H_{19}O_3N$ requires $C = 71·6$; $H = 6·7$ per cent.

It was not possible to determine the specific rotatory power of neo*iso*morphine because of its exceedingly sparing solubility in all organic solvents.

The *hydrochloride* was, however, suitable for the purpose. It was prepared by dissolving the pure base in the theoretical amount of dilute hydrochloric acid and evaporating the solution repeatedly with alcohol. In this way the salt was obtained crystalline and anhydrous, for its weight remained constant on heating at 110°. It did not melt at or below 280°:

0·4600 dissolved in water and made up to 25 c.c. gave in a 2-dcm. tube α_D −2·91°, whence $[\alpha]_D$ −79·1°.

*Neo*iso*morphine hydrochloride* is extremely readily soluble in water, differing markedly in this respect from the hydrochlorides of morphine, *iso*morphine, and *β-iso*morphine.

The *methiodide* separates almost completely from alcohol on gentle warming of the solution of the base with methyl iodide as hard, glistening crystals which melt at 297°:

0·2219 gave 0·4130 CO_2 and 0·1038 H_2O. $C = 50·8$; $H = 5·2$.

$C_{18}H_{22}O_3NI$ requires $C = 50·6$; $H = 5·1$ per cent.

0·3900 dissolved in water and made up to 25 c.c. gave in a 2-dcm. tube α_D −1·70°, whence $[\alpha]_D$ −54·5°.

*Methylation of Neo*iso*morphine. Formation of Neo*iso*codeine*, $C_{18}H_{21}O_3N$.

Neo*iso*morphine (2 grams) was added to a solution of sodium (0·162 gram) in alcohol (20 c.c.), when the base readily passed into solution. A solution of dimethyl sulphate (1 gram) in alcohol was then added and the mixture gently warmed for five minutes. The

solution was then poured into water, a slight excess of sodium hydroxide added, and the methylated base removed by extraction with chloroform. The residue from the chloroform quickly became crystalline. It was recrystallised from ethyl acetate, when it separated in large, colourless prisms, which melted at 181—182°, and this melting point was not altered by further crystallisation:

0·1281 gave 0·3395 CO_2 and 0·0810 H_2O. C = 72·3; H = 7·0.

$C_{18}H_{21}O_3N$ requires C = 72·4; H = 7·0 per cent.

0·3530 dissolved in ethyl alcohol and made up to 10 c.c. gave in a 1-dcm. tube α_D − 3·41°, whence $[\alpha]_D$ − 96·6°.

Methylation of β-iso*Morphine. Formation of* β-iso*Codeine*, $C_{18}H_{21}O_3N$.

*β-iso*Codeine was produced from *β-iso*morphine in the same manner as neo*iso*codeine was prepared from neo*iso*morphine. On removing the chloroform it was obtained as a clear syrup which did not crystallise during the time that could be spared to allow it to stand. It was analysed in the form of the molecular compound which it forms with *iso*codeine (p. 1416).

The *methiodide* was obtained as glistening crystals from alcohol. On recrystallisation from water it formed glistening, tabular prisms which melted at 215—216° without decomposition:

0·0730 gave 0·1365 CO_2 and 0·0390 H_2O. C = 51·0; H = 5·9.

$C_{19}H_{24}O_3NI$ requires C = 51·7; H = 5·4 per cent.

0·1503 dissolved in water and made up to 25 c.c. gave in a 2-dcm. tube α_D − 1·75°, whence $[\alpha]_D$ − 145·5°.

Methylation of iso*Morphine. Formation of* iso*Codeine*, $C_{18}H_{21}O_3N$.

iso*Codeine* was prepared from *iso*morphine in the manner described above. On removing the chloroform, the base formed a hard, crystalline mass, which on recrystallisation from ethyl acetate separated as large, colourless, tabular prisms which melted at 171—172°:

0·1386 gave 0·3670 CO_2 and 0·0865 H_2O. C = 72·2; H = 6·9.

$C_{18}H_{21}O_3N$ requires C = 72·4; H = 7·0 per cent.

0·4690 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D − 5·65°, whence $[\alpha]_D$ − 150·6°.

Hydrolysis of Bromocodeide. Formation of iso*Codeine and* β-iso*Codeine.*

Bromocodeide (m. p. 162°) (20 grams) was suspended in water (150 c.c.) and just sufficient acetic acid added to effect solution of the base. The liquid was then vigorously boiled for four hours in a

reflux apparatus, cooled, treated with excess of sodium carbonate, and the liberated base extracted with chloroform. The chloroform was removed and the syrupy base dissolved in warm ethyl acetate. The crystals which soon separated from the solution were observed to constitute a mixture of substances. By means of a prolonged series of fractional crystallisations from ethyl acetate, two substances were obtained the melting points and specific rotatory powers of which were unchanged by further crystallisation either from ethyl acetate or alcohol. These substances were as follows:

(*a*) A base, $C_{18}H_{21}O_3N$, which formed colourless prisms melting at 171—172°:

0·1935 dissolved in chloroform and made up to 10 c.c. gave in a 1-dcm. tube α_D − 3·0°, whence $[\alpha]_D$ − 155°.

This base was thus identical with *iso*codeine, and, moreover, its melting point remained unchanged on admixture with the base prepared by the methylation of *iso*morphine. It was also further identified by conversion through the methiodide (m. p. 270°; $[\alpha]_D$ − 99°) into methyl *iso*morphimethine which melted at 168—169°.

(*b*) A base, $C_{18}H_{21}O_3N$, which formed slender, glistening, prismatic needles from ethyl acetate and melting at 147—147·5°:

0·1491 gave 0·3957 CO_2 and 0·0953 H_2O. C = 72·4; H = 7·1.

$C_{18}H_{21}O_3N$ requires C = 72·4; H = 7·0 per cent.

0·4712 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D − 7·88°, whence $[\alpha]_D$ − 209·0.

It was shown that this base, which is not resolved by crystallisation, is a molecular mixture of *iso*codeine and *β-iso*codeine in the following way:

(1) *By Crystallisation of its Methiodide.*—Three grams of the base (m. p. 147—147·5°) were dissolved in ethyl alcohol (100 c.c.), excess of methyl iodide added, and the solution boiled for several minutes, when a quantity of glistening, prismatic crystals rapidly separated from the hot liquid. As the latter cooled, it was noticed that a further quantity of a substance different in appearance from that which at first separated was slowly being deposited. On again boiling the liquid, this second substance went into solution, leaving the first fraction undissolved. This beautifully crystalline methiodide was collected and after drying weighed 1·9 grams, which amounts to almost one-half the theoretical amount of salt possible from the 3 grams of base employed. On recrystallisation from water, it formed brilliant, anhydrous, prismatic needles which melted at 270° with slight decomposition:

0·4948 dissolved in water and made up to 25 c.c. gave in a 2-dcm. tube α_D − 4·09°, whence $[\alpha]_D^1$ − 103·3°.

This methiodide was identical in all respects with *iso*codeine methiodide, and on boiling its aqueous solution with sodium hydroxide, readily afforded methyl *iso*morphimethine, which melted at 168—169° (compare Schryver and Lees, Trans., 1901, **79**, 563).

The alcoholic mother-liquor from the above *iso*codeine methiodide on cooling deposited a further crystalline salt in small, glistening, tabular prisms, and this was found to amount to 1·75 grams. On recrystallisation from water, in which it is a trifle more soluble than *iso*codeine methiodide, it formed small, glistening, tabular crystals, which melted at 215—216° without decomposition. It was anhydrous:

0·5010 dissolved in water and made up to 25 c.c. gave in a 2-dcm. tube α_D − 5·62°, whence $[\alpha]_D$ − 140·2°.

Further crystallisation from water caused no change in the properties of this methiodide, and on intimately mixing with *β-iso*codeine methiodide (p. 1415) the mixture melted at 215—216°. This second methiodide was, therefore, definitely identified as *β-iso*codeine methiodide.

(2) *By its Formation by Crystallising together equal amounts of* iso*Codeine and* β-iso*Codeine.*—*iso*Codeine (m. p. 171—172°) (0·343 gram) was dissolved together with an equal weight of *β-iso*codeine (syrupy base) in a small amount of warm ethyl acetate. On standing, slender prismatic needles were obtained identical in appearance with the base (m. p. 147—147·5°) from bromocodeide. 0·5 Gram of crystals was thus obtained. The melting point was also found to be identical, 147—147·5°, and was, moreover, not changed by further crystallisation or by mixing with the base from bromocodeide:

0·0936 gave 0·2495 CO_2 and 0·0592 H_2O. C = 72·7; H = 7·0.

$C_{18}H_{21}O_3N$ requires C = 72·4; H = 7·0 per cent.

0·2673 dissolved in chloroform and made up to 25 c.c. gave in a 2-dcm. tube α_D − 4·48°, whence $[\alpha]_D$ − 209·5°.

Complete identity was thus established between the base (m. p. 147—147·5°; $[\alpha]_D$ − 209·0°) obtained from bromocodeide and the base formed by crystallising together equal amounts of *iso*codeine and *β-iso*codeine.

ADDENDUM.

While this paper was in the Press, a further communication by Knorr and Hörlein has appeared (*Ber.*, 1907, **40**, 3342) in which these authors announce that, since their previous publication (*Ber.*, 1907, **40**, 2032), their attention has been drawn to an abstract (*Chem. Zentr.*, 1907, i, 352) of the communication of Lees and Tutin "according to which the *iso*codeine of Schryver and Lees is a mixture of a base-*A* (m. p. 145°) and a base-*B* (m. p. 170°)." The actual abstract in the

Centralblatt gives the following characters for these two bases: *A-base*, m. p. 145—145·5°; $[\alpha]_D$ −205° in chloroform; *B-base*, m. p. 171—172°; $[\alpha]_D$ −155° in chloroform.

Knorr and Hörlein then state that "Hr. Stud. Grimme has confirmed the results of Lees and Tutin and has proved that the higher melting constituent (*B*-base of Lees and Tutin) is identical with *pseudo*codeine." This identification is stated to have been carried out "by comparison of the bases (m. p. 180—181°), their hydriodides, (m. p. 260—265°; $[\alpha]_D^{15}$ −57°), methiodides (m. p. 270°), and the methine bases prepared from the latter (hydrochloride, m. p. about 150°; $[\alpha]_D$ −154°)."

The statement that the *B*-base of Lees and Tutin is identical with neo*iso*codeine (*pseudo*codeine) is obviously incorrect, for the latter base has been shown by Knorr and Hörlein to have m. p. 180—181° and $[\alpha]_D$ −94°, and these figures are confirmed by the author in the present paper. The statement of Knorr and Hörlein was, moreover, made with the following before them, in the same abstract in the *Centralblatt*: "Da die *B*-Base leicht aus Isomorphin durch methylierung mit Natrium und Dimethyl sulfat entsteht muss sie *Isokodein*, das kodein Analogen des Isomorphins, sein." The identity of the *B*-base (from bromocodeide) and the base produced by the methylation of *iso*morphine (from bromomorphide) was established by Lees and Tutin by the fact that both bases had the same melting point (171—172°) which was not changed when the specimens were mixed, by identity of specific rotatory power, and, furthermore, by the production from each specimen of methyl *iso*morphimethine (m. p. 168—169°; $[\alpha]_D$ +64·6°).

Knorr and Hörlein have themselves shown that neo*iso*codeine (*pseudo*codeine) does not yield methyl *iso*morphimethine.

If further evidence were required to prove that the *B*-base of Lees and Tutin is not identical with neo*iso*codeine (*pseudo*codeine), it is afforded by the fact that an intimate mixture of the two bases was found to melt at 140—145°.

It may be that Hr. Stud. Grimme has isolated neo*iso*codeine (*pseudo*codeine) from among the products of the hydrolysis of bromocodeide, which is not altogether improbable, but it is difficult to understand how Knorr and Hörlein came to the conclusion that it was identical with a base of entirely distinct characters which they had not in hand for comparison.

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