THE CONFIGURATION OF RETRONECINE AND OF RELATED COMPOUNDS (STEREOCHEMISTRY OF PYRROLIZIDINE ALKALOIDS. PART II[1])

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N-ethoxycarbonylmethyl O-acetyl retronecanol and the corresponding N-acetic acid and betaine have been prepared. The failure of the cyclisation of these compounds permits to assign 7α-position to the hydroxyl group at C_7 in these compounds and to the genuine alkaloids retronecine and platynecine. ADAMS and DUUREN reached the same conclusions by a different approach to the problem.

In the course of a program designed by one of us (G. F.) to study the stereochemistry of the ring nitrogen in heterocyclic systems, particularly in tropanes [1], it seemed worthy to deal with the pyrrolizidine field since the configurations of these alkaloids of high interest have not yet been determined at that time.

As a first item an approach by deduction has been recorded by one of us [1], [2] suggesting an *anti* orientation of the C_7—OH group with respect to the nitrogen in retronecine (I), platynecine and their esters, resp., based merely upon an interpretation of the stereochemical course of the formation of anhydroplatynecine from platynecine [3]. Experimental confirmation of this inference by the response of platynecine and dihydroxy heliotridane to lactone salt formation with ethyl iodoacetate has been aforeshadowed [2].

Unfortunately, a previous article of LEONARD and FELLEY [4] had been overlooked, in which they drew correct conclusions as to the formation of anhydroplatynecine concerning the *trans* position of methylol group at C_1 with respect to the ring nitrogen but keeping any statement impending as to the configuration of the hydroxyl-bearing carbon no. 7. They wrote: »*it cannot be readily ascertained, whether retention or inversion of configuration at C—7 occurs in ether*« (i. e. anhydroplatynecine) »*formation as effected by a variety of reagents*«.

Similar conclusions have been reached by ADAMS [5], MENSHIKOV [6] and TROJÁNEK [7] when reviewing the *Senecio* field.

The first set of our experiments involved the quaternisation of acetyl retronecanol (II) with ethyl iodoacetate to furnish an ester salt (IIIa). Acetyl retronecanol obtained on hydrogenolysis of retronecine esters seemed more suited than retronecine and platynecine [2] since it does not contain any group at C_1 capable of interfering with the hydroxyl at C_7.

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[1] Part I. G. FODOR: Chem. and. Ind., 1424 (1954).

Both N-ethoxycarbonylmethyl-O-acetyl retronecanolium iodide (III a) and tetraphenyloborate (III b) proved to be well defined products. The former one furnished the *betaine* (III e) when treated with wet silver oxide due to the hydrolysis of the N-acetic-ester group but leaving the O_7-acetyl-ester linkage intact. Refluxing with hydriodic acid even for several hours afforded no trace of a lactone salt but only the carboxylic acid salt, identified both as *iodide* (III c) and *tetraphenyloborate* (III d), respectively.

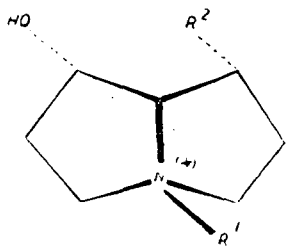

Fig. 1. IIIa: $R_1 = CH_2COO\,Et$, $R_2 = CH_3$; IIIe: $R_1 = CH_2COO-$, $R_2 = CH_3$; I $R_2 = -CH_2OAc$, OAc instead of OH; II $R_2 = CH_3$, OAc instead of OH

N-carboxymethyl derivatives of 3α . 6β-dihydroxy-tropane, oscine [8] and teloidine [9] bearing OH group (s) in the same (1.2) relationship so the nitrogen on their pyrrolidine ring as it occurs with retronecanol — with the difference, however, of being in *syn*-position, — all without exception readily form lactones (even N-ethoxycarbonylmethyl-O-acetyl-oscine iodide underwent immediate transesterification [1]). This failure of the N-carboxymethyl retronecanol ester to be cyclised may be considered as the first experimental evidence in favour of the prediction of one of us [2] as to the *anti*-position of the C_7—OH group in retronecine, platynecine, retronecanol and their derivatives. In addition, this property of the ester group at C_7 to withstand hydrolysis clearly points to its being hindered which can only hold true if this group is enclosed by the two rings, *i. e.* in an *anti*-position. While carrying out the experiments recorded, a simultaneous paper of ADAMS and VAN DUUREN [11] appeared, presenting a detailed picture of the reaction between platynecine and thionyl chloride. In the cold, a cyclic sulphite ester could be isolated, supplying unequivocal evidence of the neighbourhood of the oxygen functions at C_1 and C_7 in this alkaloid. This success can be reconciled quite completely with the experimental facts described above.

Accordingly, the working hypothesis outlined originally [2] proved correct. Lactone salt formation with ethyl iodoacetate in the case of hydroxy-heliotridane, the C_7-epimer of retronecanol might furnish nevertheless a piece of additional evidence as to the steric relationship of nitrogen to the oxygen function at C_7, and hence to the framework of the *Senecio* alkaloids. We wish to introduce the α . β-convention used for steroids and tropanes [10] recently in describing stereoisomers of the pyrrolizidine field.

Experimental

Senecio alkaloids have been isolated from *Senecio cineraria* D. C. grown in this country, adopting essentially the method of G. BARGER and J. J. BLACKIE [12]. The crude alkaloid mixture could be separated by paper chromatography according to R. MUNIER and M. MACHEBOEUF [13] furnishing the *R* values 0,63; 0,52 and 0,064 resp., pure jacobine showing *R* 0,52. Hydrolysis

to retronecine has been performed following the data of R. ADAMS and E. F. ROGERS [14] given for the cleavage of monocrotaline.

Extraction of Senecio cineraria

55 kg humid leaves were cut into pieces, dried at 70° by dry-steam and milled thoroughly to yield 12 kg dry powder. 3 kg of this was extracted according to the *Soxhlet principle* under 10 fold suction with 20 l warm ethanol, prior to which the powder had been treated with lime hydrate (150 g slaked lime and 300 ml water). The deep green extract as concentrated to a sirup, then treated mechanically with 500 ml 5% hydrochloric acid for 4 hours, cooled in ice and filtered. The filtered precipitate was subsequently shaken for further 4 hours with 250 ml 5% hydrochloric acid, filtered and the filtrate thus obtained combined with the former acidic one, extracted with 10×50 ml ether, alkalified by ammonium hydroxide and extracted again with 8×50 ml chloroform. The chloroform layer was, in turn, shaken with 50 ml water, dried and evaporated *in vacuo* to afford 2,8 g brown crystalline residue. The chloroform extract of the ammonia solution gave an additional crop of 0,85 g oily substance. The crystalline product recrystallised from ethanol, weighed 1 g, m. p.: 176°—184°.

Hydrolysis of jacobine

1,95 g product obtained from the previous experiment was mixed with 4 g/25 ml barium hydroxide and refluxed in an oil-bath for 1.5 hours. Subsequently the mixture was filtered, barium removed by carbon dioxide, the precipitate filtered and the mother liquor adjusted to pH 3 with dilute HCl. The solution was then submitted to ether-extraction in a percolator for 16 hours. The pale brown acidic aqueous layer was filtered and the filtrate evaporated *in vacuo*. The dark grey resideu thus obtained was 3 times repeatedly evaporated with ether to dryness, the residue, in turn, extracted with 3×15 ml ether and filtered. On standing in ice-water, crystals (columns and rosettes) begin to separate, weighing 0,7 g which decomposed at 152°—156°. (MANSKE—HOLMES' monograph: »*The Alkaloids*« records m. p. 161°, 162°—163°, 164° for retronecine hydrochloride.)

Diacetyl-retronecine [15] *(Diacetyl-I.)*

Retronecine hydrochloride (0,685 g) was refluxed for 2,5 hours with acetic anhydride 3 ml) and sodium acetate (10,423 g). The solution was evaporated to dryness *in vacuo* to give a black residue which, in turn, was treated with potassium carbonate (0,3 g) in water (3 ml), extracted with chloroform and filtered. Evaporation *in vacuo* afforded a pale brown oil (0,8163 g; 95%).

Acetyl retronecanol (II)

Retronecine diacetate (0,5 g) in 5 ml dry ethanol was hydrogenated for 14 hours over 0,0586 g ADAMS platinum oxide catalyst at 20°; 97 ml (2 mole) of hydrogen were taken up. The solution was evaporated *in vacuo* to give a sirup which was purified by vacuum distillation.

N-ethoxycarbonylmethyl-1α-methyl-7α-acetoxy-pyrrolizidinium iodide (IIIa)

Ethyl iodoacetate (0,5 ml, 2 m mole) was added to a solution of 0,364 g (0,002 mole) acetyl retronecanol (II) in 2 ml ethanol. After allowing to stand for 1 day, on addition of few ml ether pale brown crystals were deposited. The quaternary salt (44,5%) thus obtained had m. p. 196°. (Found: C 42,48; H 6,08; J^- 31,95. $C_{14}H_{24}O_4NJ$ requires: C 42,81; H 6,29; J^- 32,78%.)

N-carboxymethyl-1α-methyl-7α-acetoxy-pyrrolizidinium betaine (IIIe)

1α-methyl-7α-acetoxy-N-ethoxycarbonylmethyl-pyrrolizidinium iodide (IIIa) (0,38 g) in 20 ml water was shaken mechanically with 0,27 g silver oxide (prepared from 0,4 g $AgNO_3$ and 0,12 g NaOH) for 2 hours. After both silver oxide and iodide have been removed by centrifuging, the precipitate was washed with a few ml of water. The supernatant liquors have been combined and refluxed in an oil-bath, heated to 140° for 3 hours and finally evaporated *in vacuo*. The oily residue deposited crystals after a short time. (Found: N 5,86; $C_{12}H_{19}O_4N$ requires: N 5,76%.)

N-carboxymethyl-1α-methyl-7α-acetoxy-pyrrolizidinium iodide (IIIc)

Freshly prepared hydriodic acid (10 ml) was poured onto 0,2 g betaine and evaporated *in vacuo* at 50°—60° to give 0,121 g crystalline product, m. p.: 203°—204°. (Found: C 39,56; H 6,17; J 34,65. $C_{12}H_{20}O_4NJ$ requires: C 39,05; H 5.45; J 34.36%.)

Tetraphenyloborate (IIId). 0,1 g *iodide* (IIIc) was refluxed with freshly distilled hydriodic acid (2 ml) in an oil-bath of 180° for 2 hours. The reddish solution was evaporated leaving a residue which was again evaporated with dry acetone twice, than taken up in a few ml of acetone. After the addition of aqueous sodium tetraphenyloborate pale yellow crystals were obtained. M. p.: 103°—104° (Found: C 77,36; 77,05; H 7,76; 8,02. $C_{12}H_{20}O_4N$. $(C_6H_5)_4B$ requires: C 77,00; H 7,18%.)

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Microanalyses have been performed by the staff of the Analytical Laboratory of this Institute (Dr. ÉVA FODOR-VARGA, Misses K. LÁNG and R. MINÁROVICS).

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