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SELECTIVE QUATERNERIZATION IN THE MORPHINE SERIES.

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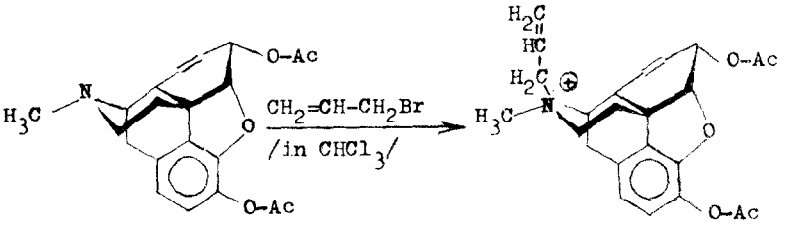
The stereoselectivity of the quaternerization of certain tertiary amines of the tropane series /1/ was found leading to N-epimeric quaternary salts depending on the sequence of introducing the two different groups onto the ring nitrogen /2,3/. The absolute configurations of a number of quaternary tropanium salts have been determined and an empirical rule concerning the equatorial position of the group which entered last was outlined /4/. The same phenomenon was recorded later for codeine /5/ and tetrahydroisoquinoline derivatives /6/. The reason for this stereoselectivity has been discussed and is still under consideration /7/.

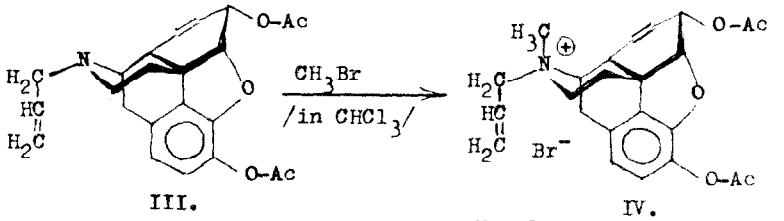
In our laboratory the behaviour of diacetyl-morphine derivatives in quaternerization reactions has been investigated. O_3,O_6-diacetyl-morphine /I/ in chloroform solution afforded with allyl bromide at room temperature diacetyl-morphine allylobromide /II/. However, when O_3,O_6-diacetyl-N-allyl-normorphine /III/ - the acetylated derivative of the well-known morphine antagonist - was

quaternerized with methyl bromide, the N-epimeric O_3,O_6-diacetyl-N-allyl-normorphine methobromide /IV/ was formed. The N-epimers /II/ and /IV/ proved quite different as to m.p., $/\alpha/_D$ values and also in crystal form.



I. II.

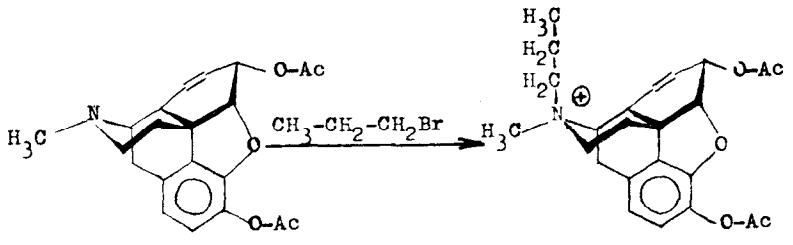
Prisms with 1 mol water of cryst. /from aqueous methanol/,
M.p. : 229 - 229.5°C.
$/\alpha/_D^{23°}$ = -112.6° ± 0.2°
/c=1.0; H_2O/



III. IV.

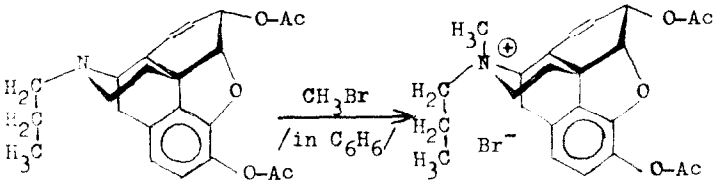
Needles with 2 mols water of cryst./from water+acetone/,
M.p. : 126 - 130°, then after hardening: 230°C.
$/\alpha/_D^{23°}$ = -152.9° ± 0.2°
/c=1.0; H_2O/

The same discrepancy was observed by preparing in an analogous manner the corresponding saturated epimers, i.e. N-propyl-diacetyl-morphinium salts. Diacetyl-morphine propylobromide /V/ showed different properties from those of diacetyl-N-propyl-normorphine methobromide /VII/, prepared from diacetyl-N-propyl-normorphine /VI/ in a benzene solution. Although the melting points are close, the mixed melting point gave a depression of 10°. Comparison of the difference in $/\alpha/_D$ values between the N-epimeric morphinium salts showed the same value /40.2°-40.3°/ within the limits of experimental error, which means that the contribution of the ring nitrogen to the whole molecular asymmetry is the half of this value, 20.1°- 20.15°. Furthermore, in considering the already known absolute configuration of morphine based upon the rule of optical additivity, an absolute configuration may tentatively be assigned to the ring nitrogen in the individual quaternary salts.



I. V.

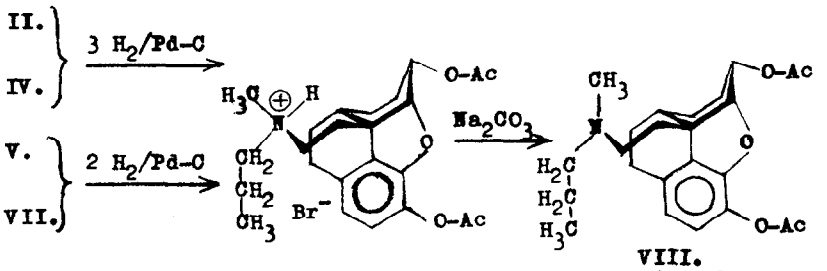
Needles /from methanol/,
M.p. : 251 - 251.5°C.
$/\alpha/_D^{23°}$ = -120.2° ± 0.2°
/c=1.0; H_2O/



VI.

VII.
Plates with 0.5 mol acetone of cryst./from acetone/
M.p. : 249.5 -250°C.
$/\alpha/_D^{23^\circ} = -160.4^\circ \pm 0.2^\circ$
/c=1.0; H_2O/

Catalytic hydrogenation of the two epimeric pairs gave unexpected result. In addition to the two double bonds in the allyl derivatives /II/ and /IV/, a third molecule of hydrogen was taken up. Similarly, the two N-propyl-diacetyl-morphinium salt epimers /V/ and /VII/ showed the absorption of a second mole of hydrogen after saturation of the double bond in ring C. All four compounds produced the same tertiary base /VIII/, m.p. 165 - 165.5°C, $/\alpha/_D = -105.4^\circ$/c=2.5; acetone/. This fact is hardly to be reconciled with other facts except than by considering hydrogenolytic ring cleavage between carbon no. 9 and ring nitrogen, leading to a dihydromorphimethine derivative. This type of reductive opening of the morphine skeleton was hitherto unknown and awaits a more profound investigation.



VIII.
Needles from benzene + petrolether,
M.p. : 165 - 165.5°C.,
$[\alpha]_D$ = -105.4° ± 0.2°
/c=0.5; acetone/

Methiodide:
M.p. : 250°C.,
$[\alpha]_D$ = -47.5° ± 0.2°
/c=0.5; H_2O/.

Our perspectivic formulae are based upon an analogy with other derivatives of these series having the N-methyl group in an equatorial position, as determined by X-ray investigations /8/; so the group we are introducing in the last step is presumed to be axial.

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