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A NEW APPROACH TO THE SYNTHESIS OF STABLE DERIVATIVES OF AZACYCLOLS

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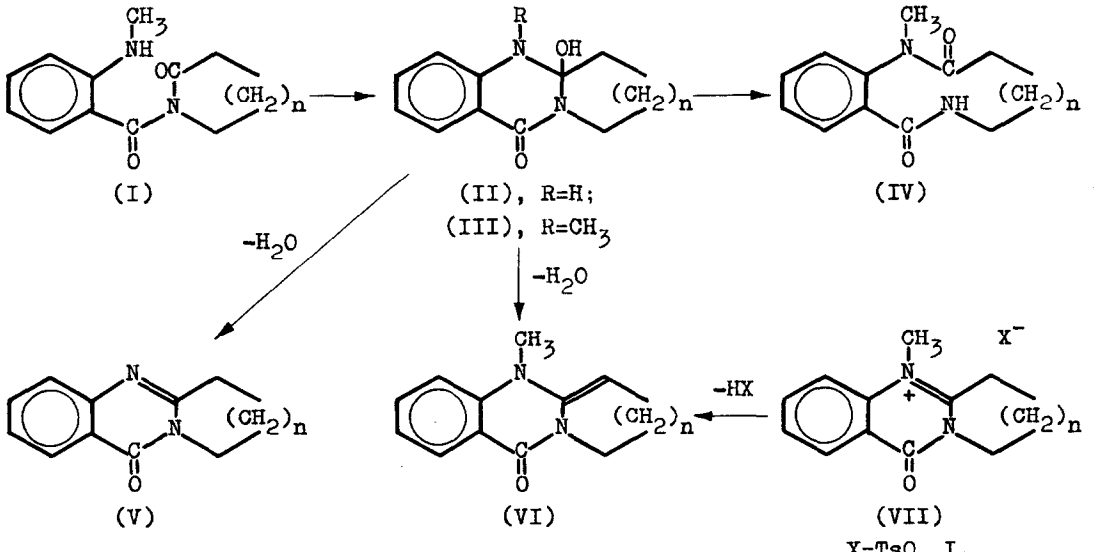
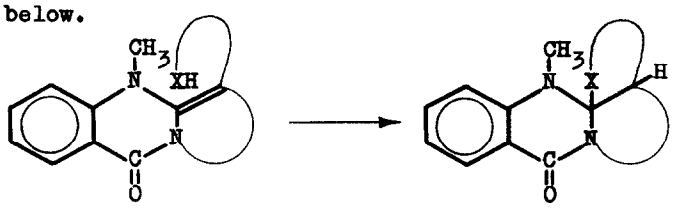
DESPITE an increasing interest in the study of intramolecular conversions of amides and peptides, which proceed via formation of azacyclols, neither the latter nor their stable derivatives have been isolated up to now (1-5). This prompted us to undertake a systematic investigation of the chemical properties of azacyclols aiming at preparation of stable compounds of this type as has been done for oxacyclols (1).

The azacyclols (III) studied in this work differ from those described earlier by the presence of an N-methyl group, thereby eliminating the possibility of conversion to the acylamidines (II⟶V). However attempts to prepare the azacyclols (III) by way of the N-anthranoyllactams (I) or the salts (VII) showed that these cyclols immediately undergo either isomerisation to the cyclodipeptides (IV) or dehydration to the unstable anhydrocompounds (VI) (6-8).



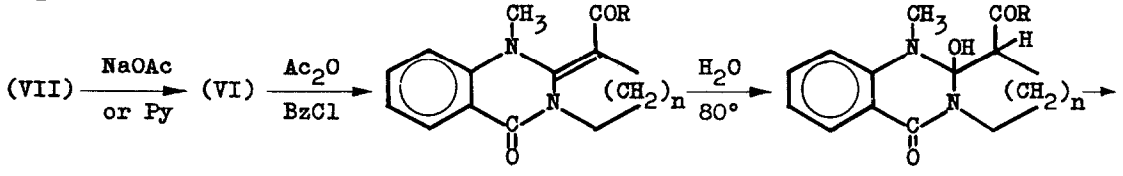
a, n=1; b, n=2; c, n=3.

At the same time we were able to prepare stable derivatives of the azacyclols (III), namely some of the orthoamides of type (IX), by intramolecular addition of nucleophilic residues to the double bond of the anhydrocompounds (VIII) as shown below.



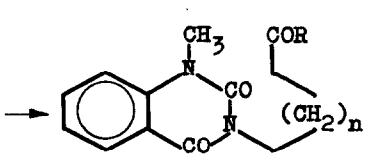
(VIII) X=NR, O. (IX)

Compounds (VIII) can be synthesized by acylation of the anhydroazacyclols (VI). Stable C-acylated anhydrocompounds such as (X) or (XI) are obtained by the action of acylating agents on the salts (VII) in the presence of bases. The properties of these anhydrocompounds are similar to those of compound (XII) prepared by acylation of 3-carbethoxyvalerolactam with N-methylisatoic anhydride (MIA) (8). All of them undergo hydration on heating in aqueous alcohol; but the resultant azacyclols (XIII) are unstable and suffer retro-aldol fission, yielding the quinazolinedione derivatives (XIV) (cf. (9)). If the reaction is carried out in D_2O or $H_2{}^{18}O$, incorporation of deuterium in α-position to the RCO-grouping or of ^{18}O into the ureide carbonyl is observed. The structure of compounds (XIV) follows from their n.m.r. and mass spectra (see e.g. (XV)).

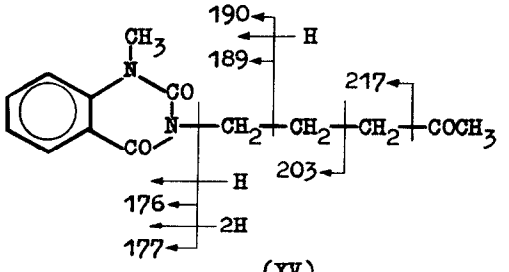


(X), R=CH_3;
(XI), R=C_6H_5;
(XII), R=OC_2H_5.

(XIII)



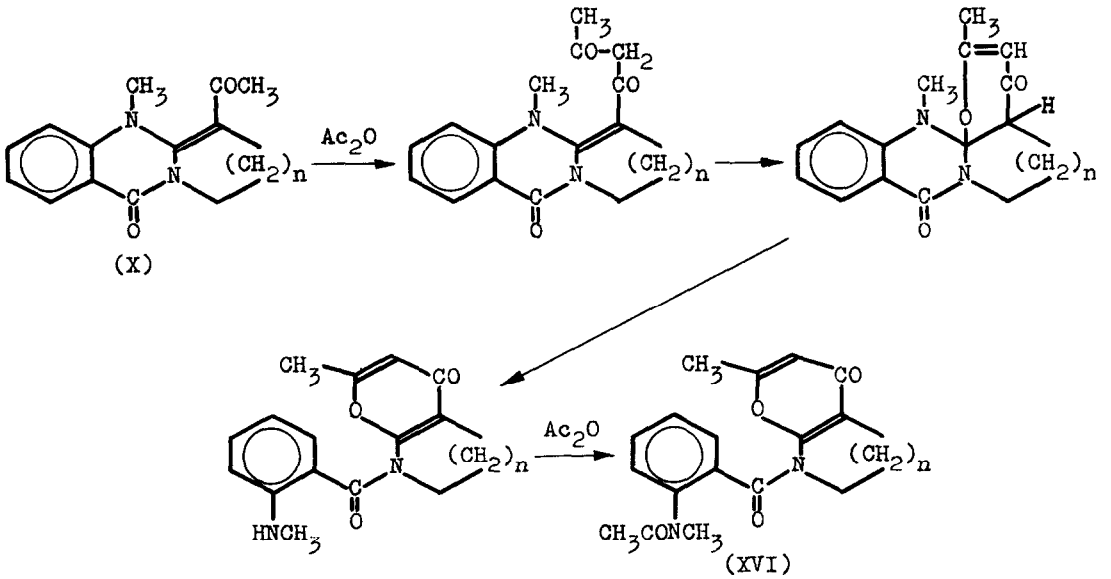
(XIV)



(XV)

a, n=1; b, n=2; c, n=3.

The hydration of compounds (X-XII) provides an example of addition to the double bond in anhydroazacyclols. That such a reaction can also occur intramolecularly was observed by us on refluxing the salts (VII) with excess Ac_2O in the presence of K_2CO_3 or NaOAc. Under such drastic conditions the primarily formed compounds (X) react further to give the pyrone derivatives (XVI), the ease of conversion being in the order (Xa)< (Xb)< (Xc). The reaction mechanism is schematically outlined below; the structure of the end products (XVI) follows from their i.r., n.m.r. and mass spectra.



(X) (XVI)

a, n=1; b, n=2; c, n=3.

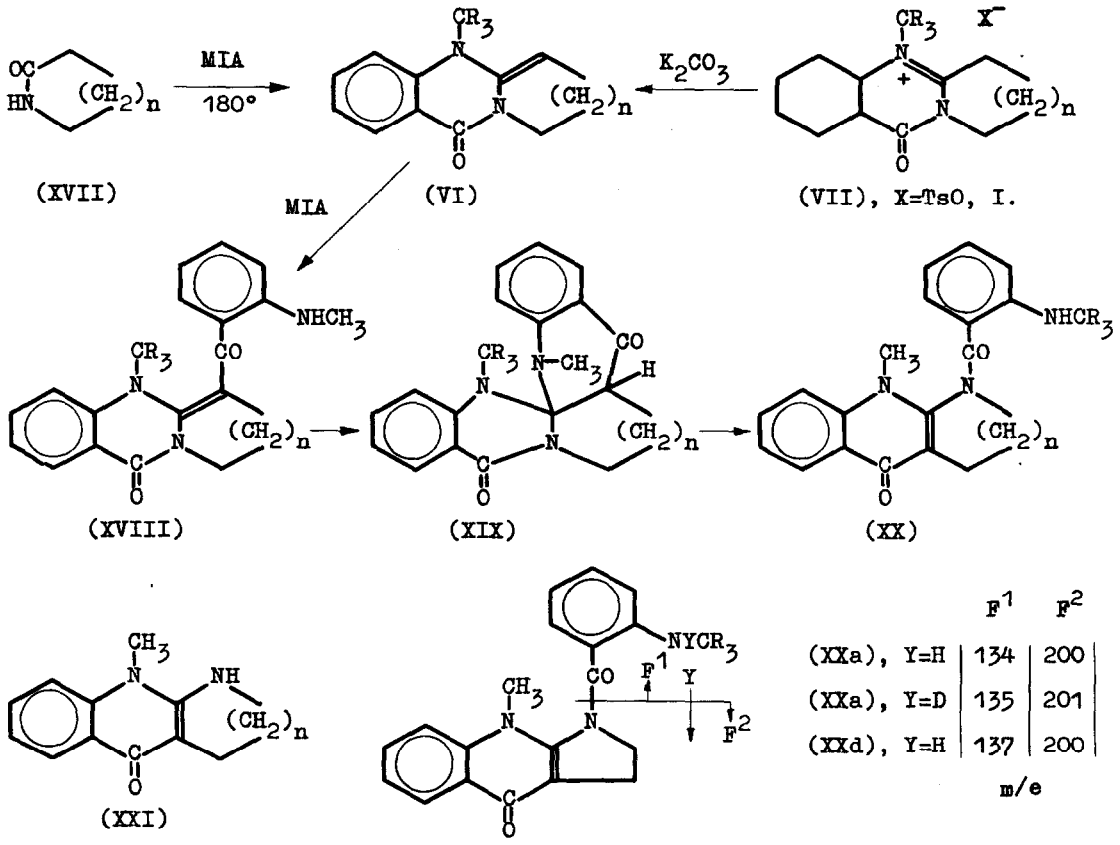
Intramolecular nucleophilic addition occurs on acylation of the anhydrocyclols (VI) with MIA. The MIA reacts with the lactams (XVII) or the salts (VII) in the presence of bases to give the N-anthranoyl compounds (XX), whose structure is supported by i.r. and mass spectra and is confirmed by hydrolysis to compounds (XXI); the acylation of the latter with MIA leads to regeneration of (XX). The labeled compound (XXd), obtained from the salt (VIId, X=I), contains the $N\text{-}CD_3$ group in the anthranoyl moiety which is split off by hydrolysis or on mass spectrometric fragmentation. These data confirm the reaction mechanism shown in the scheme below which include the intermediate formation of the orthoamides (XIX).

TABLE 1

Melting points and i.r. data

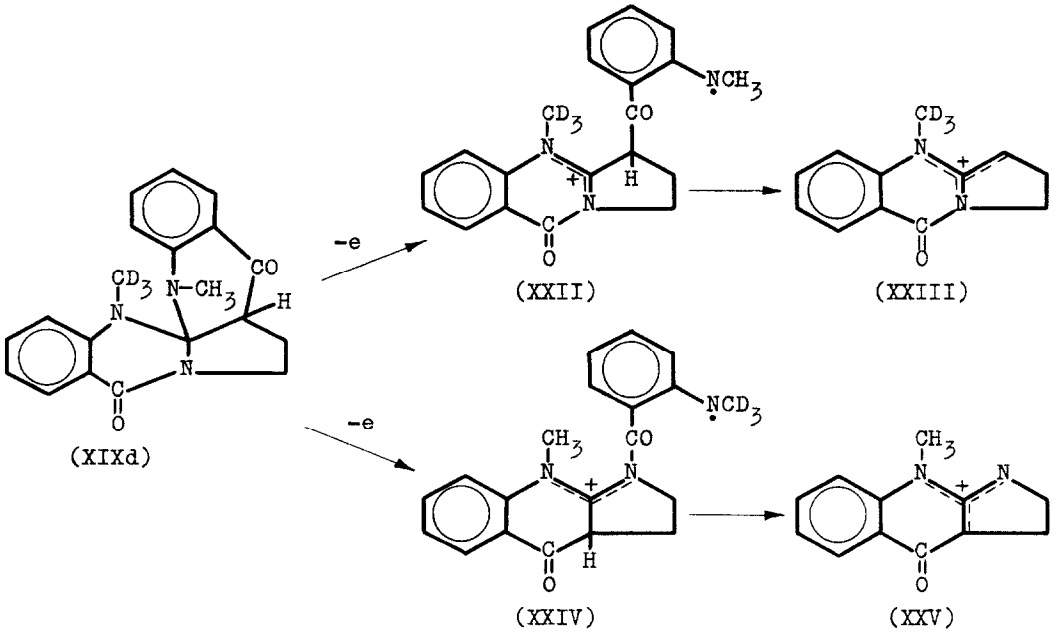
Compounds	M.p. in °C	ν_{max}^{nujol}, in cm^{-1} *
IVc	163-165	1657, 1603, 1585, 3060, 3190
VIIa, X=TsO	177-178	1706, 1649, 1615, 1578, 1522
VIIa, X=I	289-290	1704, 1645, 1612, 1577, 1511
VIIb, X=TsO	185-186	1710, 1620, 1561, 1519
VIIc, X=I	231-233	1700, 1619, 1559, 1506
Xa	163-164	1675, 1633, 1609, 1540_{sh}, 1535, 1500
Xb	162-164	1674, 1625, 1612, 1555_{sh}, 1518, 1502
XIa	223-225	1670, 1620, 1602_{sh}, 1576, 1524, 1496
XIb	191-192	1675, 1615, 1603_{sh}, 1525, 1515_{sh}, 1490
XIIb	131-132	1676, 1618, 1598, 1571, 1565_{sh}, 1492
XIVa, R=CH_3	110-111	1710, 1694, 1659, 1647_{sh}, 1617
XIVa, R=C_6H_5	140-141	1699, 1677, 1659, 1648_{sh}, 1614, 1600_{sh}
XIVb, R=C_6H_5	89-90	1700, 1689, 1656, 1615, 1600_{sh}
XIVb, R=OC_2H_5	78-79	1723, 1693, 1660, 1653_{sh}, 1616, 1600_{sh}
XVIa	243-245	1711, 1661, 1602, 1584, 1555_{sh}, 1500
XVIb	245-247	1706, 1664, 1622, 1601, 1578, 1530, 1499
XVIc	172-174	1715, 1648, 1627, 1604, 1584, 1549, 1502
XIXa	196-198	1667, 1651, 1607, 1570
XXa**	290-293	1647, 1623, 1592, 1580_{sh}, 1552, 3400
XXb**	204-206	1645, 1621, 1603, 1583, 1551, 3420
XXc**	178-180	1643, 1620, 1600, 1583, 1551, 3430
XXIa	278-280	1614, 1600, 1580, 1547, 1538, 3090
XXIb	249-251	1613, 1594, 1566, 1554, 1532, 3200
XXIc	248-249	1611, 1593, 1560, 1540, 1520, 3280

* sh=shoulder; ** The i.r. spectrum is obtained in $CHCl_3$ solution (c=1%).



a, n=1, R=H; b, n=2, R=H; c, n=3, R=H; d, n=1, R=D.

Compounds (XIXa,d) were isolated from the reaction mixture resulting from acylation of the butyrolactam (XVIIa) or the salts (VIIa,d). As far as we know these are the first examples of stable azacyclol derivatives. The structure of these compounds follows from their isomerisation to (XXa,d) on heating above the melting point and the absence of either NH or OH groups (see Table 1) as well as from their n.m.r. spectra which show one proton signal due to an α-CO methine adjacent to a methylene (for details see (8)). The isomerisation of (XIX) to (XX) appears to proceed by thermal syn-1,2-elimination, not being accelerated substantially in the presence of acids or bases. The mass spectrum of (XIXd) shows the presence of fragments (XXIII) and (XXV) with an intensity ratio 10:3. This could be due to a more effective delocalisation of the positive charge in the ion-radical (XXII) as compared with (XXIV).



At present we are applying the intramolecular nucleophilic addition principle to the synthesis of new stable derivatives of azacyclols.

REFERENCES

1. M.M. Shemyakin, V.K. Antonov, A.M. Shkrob, V.I. Shchelokov, Z.E. Agadzhanyan, Tetrahedron, 21, 3537 (1965).
2. G.I. Glover, H. Rapoport, J.Am.Chem.Soc., 87, 2003 (1965).
3. I.J. Pachter, R. Mohrbacher, D. Zacharias, J.Am.Chem.Soc., 83, 635 (1961).
4. D.S. Jones, G.W. Kenner, J. Preston, R.C. Sheppard, Peptides, Proc. 6-th European Symposium, Athens, 1963; p.313, Pergamon Press (1966).
5. K. Poduška, G.S. Katrukha, A.B. Silaev, J. Rudinger, Coll. Czech. Chem.Commun., 30, 2410 (1965).
6. The salts (VII) are prepared by alkylation of acylamidines (V) (see (8)).
7. Transannular cyclolisation of cyclodipeptides (IV) is also accompanied by dehydration to anhydroazacyclols (VI). For example, heating of (IVc) with Ac_2O or MIA yields the compounds (XVIc) and (XXc), respectively.
8. A.M. Shkrob, V.K. Antonov, M.M. Shemyakin, J.Gen.Chem.(USSR), in press.
9. M.M. Shemyakin, L.A. Shchukina, Quart.Rev., 10, 261 (1956).