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BRIDGEHEAD NITROGEN HETEROCYCLICS VIA IMIDE REDUCTION.

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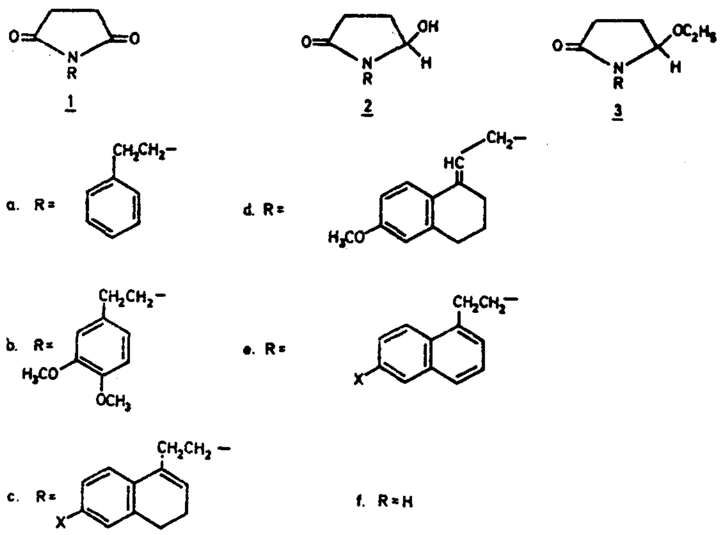
Incorporation of imides in condensed heterocyclics via a Bischler-Napieralski type of ring closure often leads to low yields of cyclization products[1]. On the other hand the continuing interest[2] in the chemistry of the indole and isoquinoline alkaloids emphasizes the potential value which a general method of synthesis for these types of compound might have. As reported recently the acid-catalyzed cyclization[3] of 5-hydroxy-2-pyrrolidinones and 5-alkoxy-2-pyrrolidinones offers an attractive method to circumvent the difficulties in working with concentrated inorganic acids or phosphorus oxychloride[4].



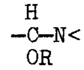
The hydroxy compounds 2a-2e were prepared via $p_H$controlled $NaBH_4$ reduction of the corresponding cyclic imides 1a-1e and "base work-up". The corresponding ethoxy derivatives 3a-3e, generally obtained as slightly unstable oils in quantitative yield, could be synthesized following an analogous procedure except that work-up of the compounds was carried out at $p_H<7$("acid work-up"). Pertinent analytical data on both types of compound are listed in the table.

Cyclization of $2b^3$, 2e, 3b, 3c, 3d and 3e, in which the aryl nucleus is activated by a methoxy substituent, was carried out in refluxing benzene/TsOH and proceeded under mild conditions and in high yields to the corresponding ring closed products.

TABLE

Compound	mp[a]	IR[b]	NMR[c]	yield
2a	120-125°	1660/cm	4.9 - 5.05	75%
2b	107-110°	1640	4.9 - 5.1	70
2c (X=H)	80-82°	1660	5.0 - 5.15	80
2d (X=OMe)	104-110°	1650	5.1 - 5.25	93
2e (X=H)	113-115°	1660	4.75 - 4.95	89
3a	-	1685/cm	4.5 - 4.75	
3b	-	1685	4.6 - 4.85	
3c (X=H)	-	1675	4.78 - 4.91	
3c (X=OMe)	-	1675	4.75 - 4.95	
3d (X=OMe)	-	1680	4.85 - 5.05	
3e (X=H)	-	1680	4.4 - 4,6	

a) the sometimes relatively large melting range is due to thermal instability. b) Solids determined in KBr; oils in $CHCl_3$.

c) $\delta(CDCl_3)$ 

$$\overset{H}{\underset{OR}{-C-}}N<$$

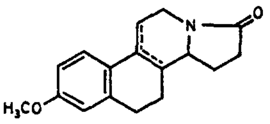
Thus the Δ9,11-13-azasteroid 4a could be prepared directly via the cyclization of either 2d, 3d or a mixture of 2d and 3d in a yield of 46%, mp. 150-152°, NMR ($CDCl_3$) δ 6.14 (H_{11}, X part of ABX). From the mother liquor the known[1h] Δ8,9-steroid 4b was obtained in 33% yield after HCl-MeOH isomerisation of the remaining traces of the Δ9,11-isomer 4a into 4b.

The reduction of 1c (X=OMe) ("base work-up") led directly (21% yield) to the 9-hydroxy-13-azasteroid 5, mp. ± 180° decomp.; IR (KBr) 3280(OH), 1655

(C=O)cm^{-1}; NMR ($CDCl_3$) δ 3.0-3.4 (double t, $\underline{H}_{14}$) 3.5-3.9 (1H m, $\underline{H}_{12}$) 3.76 (s, $C\underline{H}_3O$) 4.0-4.25 (1H m, $\underline{H}_{12}$) 6.55-6.85 ($\underline{H}_2$ and $\underline{H}_4$) 7.35-7.5($\underline{H}_1$); thus illustrating the high nucleophilicity of the Δ8,9 bond in this system. Mild treatment of 5 with acid gave a 1:1 mixture of 4a and 4b. On the contrary, in the reduction of 1c (X=H) no trace of a 9-hydroxy-compound could be detected. Cyclization of a mixture of 3e (X=OMe) and 2e (X=OMe) gave the known[1e,f] 15-aza-equilenin methyl ether in 76% yield, mp. 184-188°.

Acid treatment of compounds 2a, 3a, 2e (X=H) and 3e (X=H) afforded mainly the corresponding cyclization products as estimated via GLC-analysis and IR and NMR-spectroscopical data. In these reactions, however, considerable amounts of side-products were formed presumably as a consequence of the instability of the intermediate cyclic imminium form 6 and the relative inertness of the unactivated aromatic ring towards electrophilic substitution under the reaction circumstances[5].

To examine the applicability of the imide reductive cyclization method in a different field, experiments were carried out in the tryptamine series. Tryptamine is known to condense with 2-pyrrolinones to the 11H-indolo-[3,2-g]-indolizine derivative 7 (n=1)[6]. When 5-ethoxy-2-pyrrolidinone[7] was reacted with tryptamine in acetic acid the 11H-indolo-[3,2-g]-indolizine 7 (n=1) was obtained in 67% yield. The corresponding 6-ethoxy-2-piperidone[7] afforded in a similar reaction 12H-indolo-[2,3-a]-quinolizine 7 (n=2)[8] in 81% yield.



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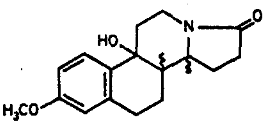
a. Δ 9,11
b. Δ 8,9



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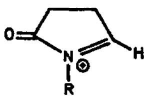

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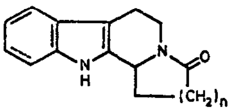

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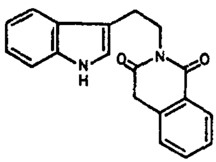

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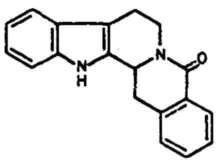

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The latter reaction most probably proceeds via 3,4-dihydro-2(1H)-pyridinone[7]; 7 (n=2) being also obtained in comparable yield from the condensation of the enamide with tryptamine. This method of preparing 7 (n=2) circumvents the use of the difficultly prepared α-ketoadipic acid[9].

Finally the reductive cyclization was applied to the homophthalimide[10] 8. The corresponding iso-carbostyril derivative smoothly cyclized to 9 by refluxing in HCl-methanol in 86% yield; mp.[11] 250-260° (dec.).

Various other ring closure reactions of compounds containing the structural elements of the types $-\overset{\text{H}}{\text{C}}\text{OH}-\text{NR}-\text{CO}-$ and $-\overset{\text{H}}{\text{C}}\text{OEt}-\text{NR}-\text{CO}-$ in the synthesis of alkaloidal systems are being currently explored.

REFERENCES:

1) a. T. Kametani, S. Tabaro and E. Karibe, Yakugaku Zasshi 83 1039 (1963), cf. CA.60 132236 (1964);
   b. E. Wenkert, S. Garratt and K.E. Dave, Can.J.Chem. 42 489 (1964);
   c. G.C. Morrison, W. Cetenko and J. Shavel Jr., J.Org.Chem. 29 2771 (1964)
   d. W.E. Schleigh, A. Catala and F.D. Popp, J.Heterocycl.Chem. 2 379 (1965)
   e. S.V. Kessar, M. Singh and A. Kumar, Tetrahedron Letters (1965) 3245;
   f. A.J. Birch and G.S.R. Subba Rao, J.Chem.Soc.(C) 1965 3007;
   g. T. Kametani, R. Yanase and S. Takano, Yakugatu Kenkyu 37 23 (1966), cf. CA.65 153206 (1966);
   h. J.C. Hubert, W.N. Speckamp and H.O. Huisman, Tetrahedron Letters (1969) 1553.

2) a. F.V. Brutcher Jr., W.D. Vanderwerff and B. Dreikorn, J.Org.Chem. 37 297-302 (1972);
   b. Atta-Ur-Rahman, J.C.S. Perkin I 1972 731-5, 736-8;
   c. T. Kametani, K. Fukumoto, T. Terui, K. Yamaki and E. Taeuchi, J.Chem.Soc.(C) 1971 2709-11;
   d. G.C. Morrison, W.A. Cetenko and J. Shavel Jr., J.Org.Chem. 36 3624-7 (1971);

3) J.C. Hubert, W. Steege, W.N. Speckamp and H.O. Huisman, Synth.Comm. 1 103 (1971).

4) M. Winn and H.E. Zaugg, J.Org.Chem. 33 3779 (1968).

5) The corresponding phtalimide derivatives of 2a and 2e (X=H) give nearly quantitative yields of cyclization product (as will be published elsewhere see also ref.3); in that case the intermediate is presumably a relatively stable immonium ion.

6) V. Bocchi, G. Casnati and G.P. Gardini, Tetrahedron Letters (1971) 683.

7) The synthesis of this compound will be published in our full paper.

8) S. Corsano and S. Algieri, Ann.Chim.(Roma) 50 75 (1960).

9) a. G. Hahn and A. Hansel, Chem.Ber. 71 2163 (1938);
   b. W. Mayer, R. Bachmann and F. Krauss, Chem.Ber. 88 316 (1955).

10) G.R. Clemo and G.A. Swan, J.Chem.Soc. (1946) 617.

11) C. Ribbens, Scient.Comm.Research Dept. N.V. Koninkl.Pharm.Fabrieken v/h Brocades-Stheeman & Pharmacia 10 9 (1960-1), cf. CA.56 7379 g (1962).