HETEROCYCLES, Vol 14, No 6, 1980

# CONDENSATION WITH TETRAHYDROPYRANYLUREA: SYNTHESIS OF 3-TETRAHYDROPYRANYL URACILS.

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Abstract – The 3-tetrahydropyranyl uracil derivatives 1 and 2 have been obtained by reaction of tetrahydropyranylurea (THPU) with diethyl ethoxymethylenemalonate. The sodium salt (monohydrate) of 1 was also isolated in the same reaction. In a similar way, THPU has been condensed with ethyl ethoxymethylenecyanoacetate to give the open chain compound 3, which was identified as a mixture of the E (3a) and Z (3b) isomers. Heating of THPU with triethyl orthoformate and ethyl cyanoacetate afforded an identical mixture of isomers. By using this last procedure, the ureidoethylene derivatives of diethyl malonate, malononitrile and malonic acid (4, 5 and 6, respectively) have also been isolated and identified.

During the last few years, some papers[1-3] have pointed out the biological interest of uracil derivatives substituted by a cyclic ether at the N-3 position. In connection with this matter, we are now studying the synthesis of 3-tetrahydropyranylpyrimidines. By using similar reaction conditions to those described by Whitehead[4] for the preparation of 3-methyl substituted pyrimidines, we have attempted some condensation reactions of tetrahydropyranyl urea. Treatment of THPU with diethyl ethoxymethylenemalonate in the presence of sodium ethoxide (25° C , 7 days), afforded a solid, which was identified as the sodium salt (monohydrate) of the ester 1 on the basis of its spectroscopic data and analysis ($C_{12}H_{15}N_2O_5Na.1H_2O$; mp 208-210°C; uv, $\lambda_{max}^{EtOH}$, nm ($\varepsilon$), 224 (1900), 242 (2900), 301 (4300); ir (nujol) $\bar{\nu}$, 3530, 3300, 1705, 1650, 1580 cm$^{-1}$). This compound was dissolved in water and treated with HCl 6N until pH = 7. Work up on this solution led to the isolation of tetrahydropyranyl-5-ethoxycarbonyluracil, 1 ($C_{12}H_{16}N_2O_5$; mp 127-8° C, 40% yield, uv $\lambda_{max}^{EtOH}$, nm ($\varepsilon$), 222 (8000), 276 (10000), ir (nujol), $\bar{\nu}$ , 3100, 1750, 1710, 1655, 1620, 1505 cm$^{-1}$).

When the same reaction was performed at 40° C partial hydrolysis at the ester group took place and, in addition to compound 1, the carboxylic acid 2 was obtained ($C_{10}H_{12}N_2O_5$; mp 123-5° C; uv, $\lambda_{max}^{EtOH}$, nm ($\varepsilon$), 220 (8500), 280 (9600), ir (nujol) $\bar{\nu}$, 3300-2500, 1750, 1630, 1525 cm$^{-1}$). If the reaction is carried out in refluxing ethanol, the hydrolysis is total, and only compound 2 is obtained, (Figure 1).

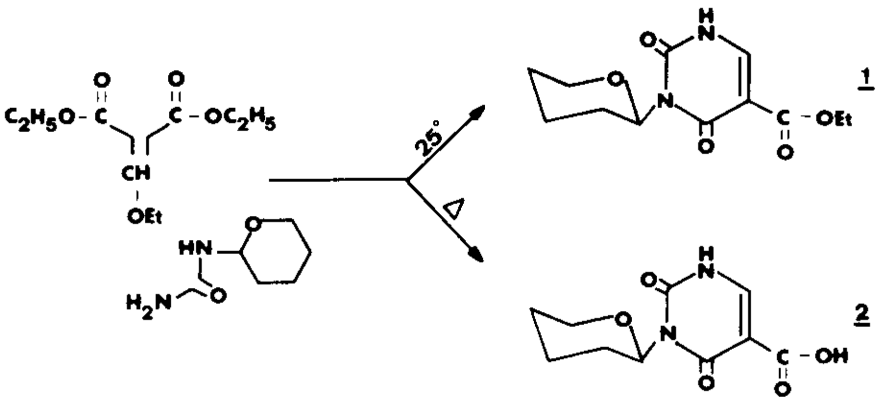
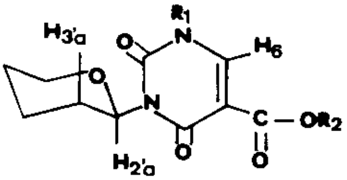


Fig. 1

The $^1$Hnmr data for these compounds are summarized in Table 1. When the spectra are recorded in $CCl_3D$, it can be seen that the H-6 signals appear as doublets (collapsing to singlets by $D_2O$ treatment) both in 1 and 2 at $\delta = 8.35$ and $\delta = 8.65$ ppm, respectively. However, this coupling with the neighbouring NH cannot be observed in DMSO-$d_6$, and this fact could be indicative of a change from the amidic to the imidic form, which should be favoured by the greater polarity of this last solvent.

Table I. $^1$Hnmr data of compounds 1 and 2. Shifts are given in ppm. Coupling constants in Hz.

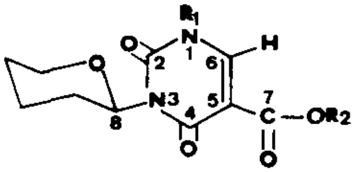


| Compound No. | Solvent | $R_1$ | $R_2$ | $\delta H_6$ | $\delta$H2'a | $\delta H_1$ | JH6H1 | JH2'aH3'a |
|---|---|---|---|---|---|---|---|---|
| Sodium salt of 1.1 $H_2O$ | DMSO-$d_6$ | Na | $C_2H_5$ | 8.46<br>s | 5.95<br>dd | - | - | 11.5 |
| 1 | DMSO-$d_6$ | H | $C_2H_5$ | 8.14<br>s | 5.80<br>dd | 11.75<br>m | - | 8.0 |
| 1 | $Cl_3CD$ | H | $C_2H_5$ | 8.35<br>d | 6.05<br>dd | 10.20<br>m | 6.0 | 10.6 |
| 2 | DMSO-$d_6$ | H | H | 8.23<br>s | 5.80<br>dd | 12.25<br>m, broad | - | 8.0 |
| 2 | $Cl_3CD$ | H | H | 8.65<br>d | 6.02<br>dd | 10.40<br>m, broad | 2.0 | 10.6 |

The H-2' proton at the tetrahydropyran ring, which is close to the N-3 atom, is strongly deshielded (δ = 6 ppm) and appears as a double doublet. One of its coupling constants has a value of about 11Hz, corresponding to an axial axial arrangement. Therefore, the uracil ring must be in an equatorial orientation, with respect to the tetrahydropyran chair form [5].

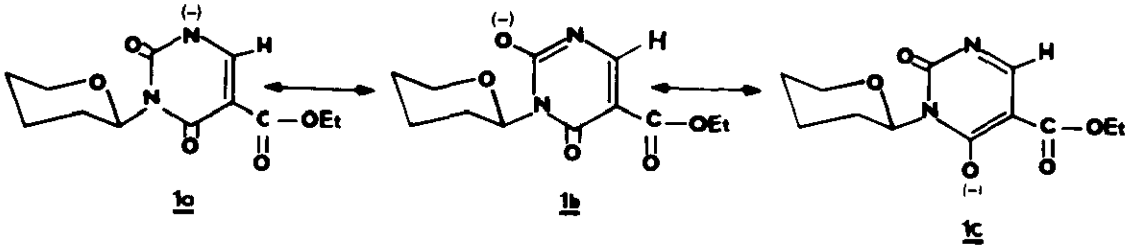
The most significative $^{13}$Cnmr features for these compounds (measured in DMSO-$d_6$ solution) are shown in Table II. The signal corresponding to $C_6$ is readily differentiated because it appear as a doublet in the "off resonance" spectrum. $C_2$, $C_6$ and $C_4$ carbons exhibit chemical shifts analogous to those described for the same carbon atoms in uridine [6] and related compounds (very close to those of the 5-bromouridine). The $C_7$ signal is shielded about 5 ppm in compound 1 (both in the free form and the sodium salt, 158.2 and 158.3 ppm, respectively) with respect to 2 (163.0 ppm). The $^{13}$Cnmr data supply some information about the electronic structure of the sodium salt. Although $C_2$, $C_4$ and $C_6$ are clearly deshielded in it regarding to the free ester, atoms $C_2$ and $C_6$ are much more affected than $C_4$. This is consistent with a situation in which the $Na^+$ is closer to $C_2$ and $C_6$ and therefore, among the three cannonical structures shown in figure 2, the forms 1a and 1b appear as the most significative.

Table II. $^{13}$Cnmr data of compounds 1 and 2



| Compound No. | $R_1$ | $R_2$ | $C_2$ | $C_4$ | $C_5$ | $C_6$ | $C_7$ | $C_8$ |
|---|---|---|---|---|---|---|---|---|
| 2 | H | H | 149.1<br>s | 162.8<br>s | 101.1<br>s | 148.8<br>d | 163.0<br>s | 81.2<br>d |
| 1 | H | $C_2H_5$ | 149.5<br>s | 162.1<br>s | 102.7<br>s | 147.6<br>d | 158.3<br>t | 80.8<br>d |
| Sodium salt of 1. $1H_2O$ | $Na^+$ | $C_2H_5$ | 162.9*<br>s | 165.4*<br>s | 96.4<br>s | 162.2<br>d | 158.2<br>t | 80.6<br>d |

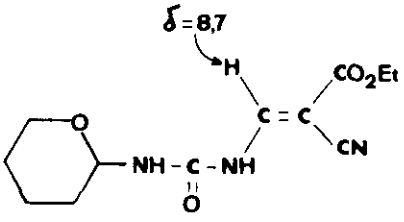
* The two marked signals may be considered interchange.



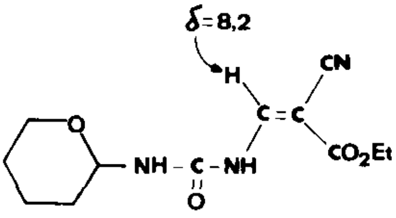
1a 1b 1c

Figure 2.

Reaction of THPU with ethyl ethoxymethylene-cyanoacetate in basic medium (25° C, 5 days) led to a mixture of isomers which have been identified from their $^1$Hnmr spectrum as 3a and 3b formed in a 45/55 ratio. Isomer Z (3b) could be isolated from the mixture by crystallisation

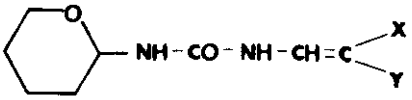


3a (E)



3b (Z)

from benzene (mp 139-40°C, $C_{12}H_{17}N_3O_4$, ir (KBr) $\bar{\nu}$, 3320, 3250, 3060, 2240, 1750, 1695, 1630, 1610, 1560 cm$^{-1}$). An identical result was obtained by reaction of THPU with triethyl orthoformate and ethyl cyanoacetate (85° C, 7 days). By using this last procedure, treatment of THPU with diethyl malonate, malononitrile or malonic acid afforded compounds 4, 5 or 6, respectively (4, $C_{14}H_{22}O_6N_2$, mp 108° C, crystallised from benzene/cyclohexane, ir (KBr) $\bar{\nu}$, 3340, 3250, 3080, 1745, 1700, 1615, 1555 cm$^{-1}$. 5, $C_{10}H_{12}N_4O_6$, mp 186-7° C, crystallised from ethyl acetate/petroleum ether, ir (KBr) $\bar{\nu}$, 3370, 3280, 3070, 2240, 2230, 1745, 1695, 1635, 1550 cm$^{-1}$. 6, $C_{10}H_{14}N_2O_6$, mp 176-7° C, ir (nujol) $\bar{\nu}$, 3600-2300, 3330, 3270, 1740, 1710, 1625, 1610, 1540 cm$^{-1}$).



**4** X = Y = $CO_2Et$

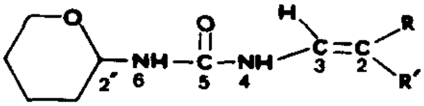
**5** X = Y = CN

**6** X = Y = $CO_2H$

The most significative $^1$Hnmr data among those obtained for isomers 3a and 3b and also for 4, 5 and 6, are gathered in Table III. In all these compounds, the signals corresponding to H-4 and H-6 are readily differentiated. The ethylenic protons exhibit a coupling constant $JH_3H_4$ = 12 Hz in 3, 4 and 6.

Two doublets centered at 8.70 and 8.25 ppm can be seen in the mixture of isomers 3a and 3b. These chemical shifts are consistent with those calculated from the Matter equation[7] for the ethylenic protons at 3a and 3b respectively (Table IV). It must be noted that the D/H

Table III. $^1$Hnmr data of compounds 3 - 6



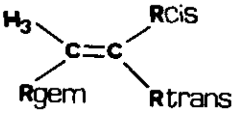
| Compound No. | Solvent | R | R' | $\delta H_3$ | $\delta H_4$ | $\delta H_6$ | $\delta H_{2'}$ | $JH_3H_4$ | $JH_6H_{2'}$ |
|---|---|---|---|---|---|---|---|---|---|
| 3a * | $Cl_3CD$ | $CO_2Et$ | CN | 8.70<br>d | 9.20<br>d | 7.02<br>m(a) | 5.00<br>m(c) | 12.0*** | (a) |
| 3b * | $Cl_3CD$ | CN | $CO_2Et$ | 8.25<br>d | 10.75<br>m(b) | 7.02<br>m(a) | 5.00<br>m(c) | 12.0 | (a) |
| 3b ** | $Cl_3CD$ | CN | $CO_2Et$ | 8.25<br>d | 10.75<br>m(b) | 7.04<br>d | 5.00<br>m(c) | 12.0 | 8.0 |
| 4 | $Cl_3CD$ | $CO_2Et$ | $CO_2Et$ | 8.64<br>d | 10.95<br>m(b) | 6.98<br>d | 5.05<br>m(c) | 12.2 | 8.0 |
| 5 | DMSO-$d_6$ | CN | CN | 8.42<br>s | 10.60<br>s | 7.78<br>d | 4.96<br>m(c) | - | 8.5 |
| 6 | DMSO-$d_6$ | $CO_2H$ | $CO_2H$ | 8.74<br>d | 11.0<br>d | 9.04<br>d | 4.98<br>m(c) | 12.6 | 8.6 |

* Data obtained from the mixture of 3a and 3b (crude reaction product).

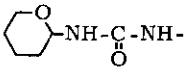
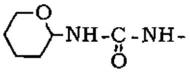
** Data obtained from pure simple of 3b crystallised from benzene.

*** This coupling constant seems to depend on the concentration. a) The signals corresponding to H-6 in both isomers overlap and $JH_6H_{2'}$ cannot be measured in this spectrum. b) broad. c) Appearing as a triplet.

Table IV. Estimation of the chemical shifts of the olefinic proton H-3 of the 3a (E) and 3b (Z) isomers using additive increments



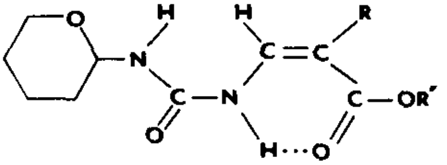
$$\delta_{C=C\diagdown H} = 5.25 + Z_{gem} + Z_{cis} + Z_{trans}$$

| Compound No. | $R_{gem}$ | $R_{cis}$ | $R_{trans}$ | $Z_{gem}$ | $Z_{cis}$ | $Z_{trans}$ | $\delta H_3$ calc. | $\delta H_3$ exp. |
|---|---|---|---|---|---|---|---|---|
| 3 a |  | $CO_2Et$ | CN | 1.89* | 1.01 | 0.55 | 8.70 | 8.70 |
| 3 b |  | CN | $CO_2Et$ | 1.89* | 0.75 | 0.46 | 8.35 | 8.25 |

* Average of the $Z_{gem}$ values calculated from the experimental chemical shifts of H-3 in compound 4 and 5.

exchange rate in the presence of $D_2O$ is clearly different in both signals.

Thus, the doublet assigned to the E isomer 3a ($\delta$ = 8.70 ppm) readily collapses to a singlet after deuteration, whereas that one corresponding to the Z isomer 3b ($\delta$ = 8.25 ppm), requires a slow stirring with $D_2O$ for a long time in order to achieve the complete collapse of the intermediate signal to a singlet. A similar behaviour regarding to the exchange rate of H-4 has also been found in compounds 4 and 6. These facts could be explained by supposing that the spacial orientation of the carbonyl groups in 3b (and also in 4 and 6) *must favour the formation* of hydrogen bonding with the $N\text{-}H_4$ group[8]. (Figure 3).



**3b**, $R = CN$, $R' = Et$

**4**, $R = CO_2Et$, $R' = Et$

**6**, $R = CO_2H$, $R' = H$

Figure 3

Such hypothesis is supported by great *deshielding found for* H-4 in 3a with respect to the same proton in 3b (1.5 ppm) and also by the fact that the ir bands corresponding to the NH groups of 3a display *higher wave numbers* than those of 3b.

Acknowledgments. We thank Professor Dr. J. Elguero for hepful comment on this work specially on the $^{13}$Cnmr spectra.

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Received, 13th March, 1980