Preparation of Uracil by Cycloreversion. Structure of Cycloalkane/ene- and Norbornane/ene-fused Dihydrouracils [1]

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The reactions of the 2-amino-1-cycloalkane-, cycloalkene-, norbornane- and norbornenecarboxylates **1-9** with potassium cyanate gave urea esters, which were cyclized to cycloalkane-, cycloalkene-, norbornane- and norbornene-fused 5,6-dihydrouracils **10-17**. On cyclization, the urea ester formed from *trans*-4-cyclohexene-1-carboxylate, furnished the *cis*-fused 5,6-dihydropyrimidine-2,4(1*H*,3*H*)-dione. On heating, the norbornene-*diexo*-fused dihydrouracil **16** yielded 2,4-pyrimidinedione through the splitting-off of cyclopentadiene. The structures of the compounds were proved by ^1H and ^{13}C nmr spectroscopy.

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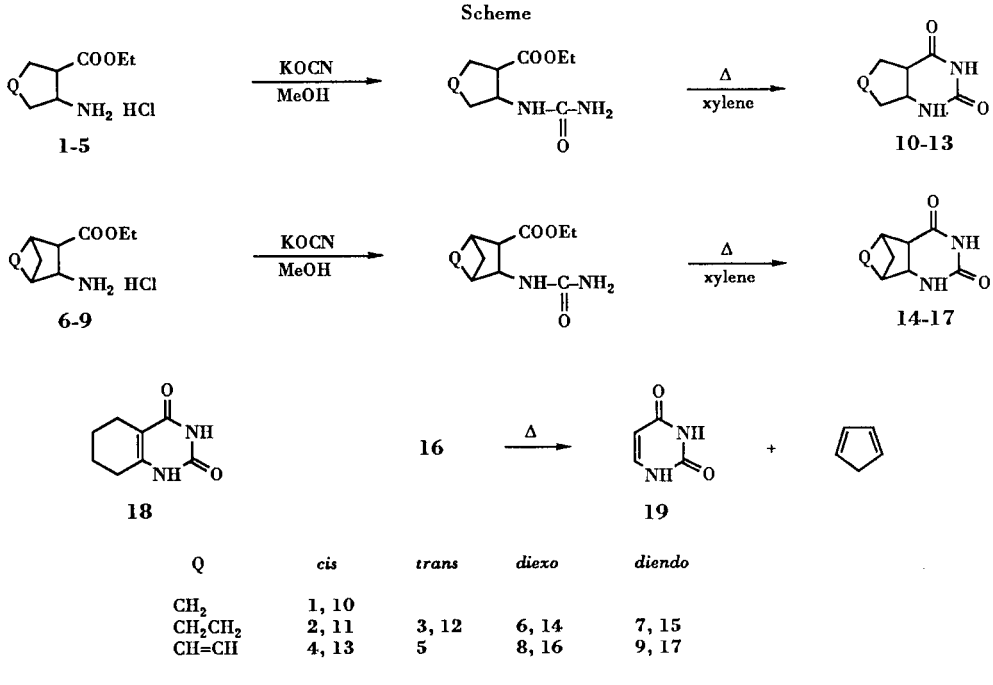
Earlier, norbornane and norbornene *diexo*-condensed azetidinones were isomerized with polyphosphoric acid to methylene-bridged quinazolinediones, while 3-substituted uracils were prepared from the derivatives containing a double bond in the bicycle under very mild conditions by thermal cycloreversion [2,3].

The present paper describes the synthesis of the unsubstituted derivatives, which are potential drug compounds. Derivative **16** provides a new example of the retro Diels-Alder reaction suitable for preparative purposes.

Results.

The reactions of ethyl *cis*-2-amino-1-cyclopentanecarboxylate hydrochloride **1** [4], *cis*- and *trans*-1-cyclohexanecarboxylate **2** and **3**, *cis*- and *trans*-4-cyclohexene-1-carboxylate hydrochloride **4** and **5**, *exo*- and *endo*-3-aminobicyclo[2.2.1]heptane-2-*exo*- and -2-*endo*-carboxylate **6** and **7**, and *exo*- and *endo*-3-aminobicyclo[2.2.1]hept-5-ene-2-*exo*- and -2-*endo*-carboxylate hydrochloride **8** and **9** [5] with potassium cyanate yielded urea esters, which were transformed to the cyclic products **10-17** without purification, on boiling in xylene. After evaporation of the mixture, fused 5,6-dihydropyrimidine-2,4(1*H*,3*H*)-diones were obtained in good yields. *cis*-5,6-Trimethylene-5,6-dihydropyrimidin-2,4(1*H*,3*H*)-dione **10**, the known *cis*-5,6-tetramethylene-5,6-dihydropyrimidine-2,4(1*H*,3*H*)-dione **11** [6], the *cis*-cyclohexene analogue **13**, the *diexo*- and *diendo*-norbornene-condensed dihydrouracils **14** and **15** and the

Scheme



Q	*cis*	*trans*	*diexo*	*diendo*
CH_2	1, 10			
CH_2CH_2	2, 11	3, 12	6, 14	7, 15
CH=CH	4, 13	5	8, 16	9, 17

corresponding norbornenepyrimidinediones **16** and **17** were obtained (Scheme).

The *cis*-**4** and *trans*-**5** aminoesters furnished the same *cis*-annelated derivatives, *i.e.* a *trans* → *cis* isomerization took place during the transformation **5** → **13**. We experienced the opposite, *cis* → *trans* isomerization in the intramolecular transacylation of the condensed cyclohexane-azetidinone [3]. The *cis* → *trans* epimerization and equilibrium of the dihydrouracil and its tetramethylene derivative were investigated earlier [7,8]. Our results show that, depending on the structures and reaction conditions, not only the common *cis* → *trans*, but in some cases, the much more infrequent *trans* → *cis* epimerization can also take place.

For completeness of the spectral data, the 2,3,5,6,7,8-hexahydro-4(1*H*)-pyrimidine-2,4-dione **18** was also prepared by a known method [10].

For cyclohexane-fused six-membered heterocycles, the *trans* structure is more favourable than the *cis*. In the present case, however, in the cyclohexene-fused six-membered heterocycle the *cis* fusion of the carbo- and heterocycle will be most advantageous, with a resulting change in the configuration. We observed a similar phenomenon for the cyclopentane-condensed six-membered systems containing two heteroatoms, where the *cis*-annelation was much more stable and the *trans*-condensed bicycle could be prepared only in exceptional cases [9].

On heating to its melting point, the 5,8-methano-4a*r*,5*c*,-8*c*,8a*c*-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione (**16**) decomposes to the 2,4(1*H*,3*H*)-pyrimidinedione **19** by splitting off cyclopentadiene. An analogous retro Diels-Alder reaction was earlier applied to prepare the 3-substituted pyrimidinedione derivatives [2]. Thus, our method involving the retro Diels-Alder reaction is also a new pathway for the synthesis of the unsubstituted uracils.

Structure.

The ir and nmr data important for structure elucidation are listed in Tables 1 and 2.

The spectral data for the pairs **11-12** reveal that the C-1 and C-2 configurations of the starting compounds remain unchanged, *i.e.* the *cis*-**11** and *trans*-annelated **12** structures of the quinazolinediones are obvious. For **11**, this is proved by the upfield shifts of all of the cyclohexane carbon lines relative to those for the *trans* isomer **12** [11a]. The ^{1}H nmr data show the preferred conformation for **11**, in which the 4-carbonyl is *axial*, so N-1 is attached *equatorially* to the alicyclic ring in the chair form. This follows on the one hand from the 5.8 Hz quartet splitting of the H-4a signal, in accordance with the ~60° dihedral angles of the bonds between C-H-4a—C-H-8a, C-H-4a—C-H-5*ax* and C-H-4a—C-H-5*eq*, respectively [12], in the presumed conformation, and on the other from the high (~30 Hz) half-bandwidth value and the ~0.32 ppm downfield shift of the H-8a signal consists of coalesced lines compared with those for the isomer **12**.

The steric structure is supported by the downfield separation of the signal of one of the methylene hydrogens: H-5*eq* is approximately coplanar with the 4-carbonyl group and the anisotropic effect of the latter decreases the shielding [11b]. The other relative stable conformation, in which the 4-carbonyl is attached *equatorially* to the alicycle, contains no methylene hydrogen coplanar with the carbonyl.

Earlier nmr investigations demonstrated that **11** has no preferred conformation in THF, and a mixture of the two

Table 1

Characteristic IR-frequencies and ^{1}H NMR Chemical Shifts on Compounds 10-18 [a]

Compound	vC=O	vNH	5-5,6,7,8,9 m's (6/8H) [b]	H-4a (1H) [c]	H-8a (1H) [d]	NH(1) s (1H)	NH(3) s (1H)
10	1717	3300-2800	1.5 - 2.1 [e]	2.68	3.79	7.42	9.90
11	~1700	~3230	1.2 - 1.7 [f], ~1.95 [g]	2.60	3.42	7.53	9.86
12	1715, 1668	3400-2800	1.0 - 1.3 [h], ~1.7 [i], ~1.95 [g], ~2.1 [i]		3.10	7.60	10.00
13	1713, 1670	3400-2800	~2.0 [i], ~2.4 [j], 5.65 [i]		3.40 [k]	7.69	9.90
14	1724, 1680	3400-2800	1.1 - 1.6 [e], 2.17 [l], ~2.5 [i,m]		3.37	7.47	9.98
15	1713, 1675	3400-2800	1.1 - 1.5 [e], 2.26 [l], ~2.5 [g,m]	2.80	3.65	7.41	9.98
16	1725, 1675	3400-2800	1.37 [n], 2.83 [l], 3.10 [o], 6.12 [p], 6.32 [p]	2.39	3.27	7.68	10.10
17	1722	3400-2800	1.35 [n], 3.03 [r], 3.23 [o], 6.15 [p]		3.92	7.50	9.73
18	1703, 1642	3300-2500	~1.6 [h], 2.14 [i], 2.30 [i]			10.57	10.85

[a] Infrared (potassium bromide), cm^{-1}; chemical shifts in ppm, δ_{TMS} = 0 ppm, in DMSO-d_6 solution, at 250.14 MHz. [b] Total intensity: 6H (**10**, **13**, **16**, **17**), 8H (**11**, **12**, **14**, **15**, **18**). [c] Multiplicity and spittings: ~qa, J: 9.3 Hz (**10**), 5.8 Hz (**11**); dd, J: 12.0 and 4.9 Hz (**15**), 9.7 and 4.0 Hz (**17**); d, J: 8.5 Hz (**16**). [d] Multiplicity and splittings: qa, J: 4.2 Hz (**10**); d, J: 9.0 Hz (**14**), 8.5 Hz (**16**); dt, J: 12, ~4 and ~4 Hz (**15**), ddd, J: 9.7, 3.5 and 2,2 Hz (**17**, the further splitting of dd to dt and to ddd, respectively, due to H-8a, NH-interaction); half signal-width for coalesced m: 12 Hz (**11**), 30 Hz (**12**), ~20 Hz (**13**). [e-j] 6H/7H/1H/4H/2H/3H. [k,m] Overlapped by the water/light isotope signal of the solvent. [l] H-5, s (1H). [n] H-9, s (2H). [o] H-8, s (1H). [p] H-6,7, 2 x dd (2 x 1H), J: 5.6 and 3.0 Hz (**16**), ~s (2H) for **17**. [r] Coalesced signals of H-4a and H-5 (s + dd, 2H).

Table 2

^{13}C NMR Data on Compounds 10-18 [a]

Compound	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9
10	154.5	174.9	44.6	29.5	23.5		34.8	51.1	–
11	155.1	174.3	42.2	24.1 [b]	25.4	23.7 [b]	31.0	49.1	–
12	155.3	174.3	46.0	26.3	25.5 [b]	25.2 [b]	32.7	53.1	–
13	154.9	174.1	41.8	26.3	125.7	127.4	32.8	49.5	–
14	153.4	173.1	46.8	43.9	26.3	30.3	47.3	56.6	34.8
15 [c]	154.2	173.4	44.5	42.5 [b]	26.3	22.0	42.7 [b]	53.1	37.7
16 [c]	153.7	172.5	52.6	42.9	140.1	136.9	49.3	53.4	45.1
17	153.7	172.9	50.4	43.2	137.8	136.9	49.2	53.2	47.5
18	152.8	166.3	107.6	23.3 [b]	22.4 [b]	22.9 [b]	27.6	150.7	–

[a] Solvent: DMSO-d_6, δ_{TMS} = 0 ppm, measuring frequency: 62.89 MHz, 20.14 for compound **13**. [b] Interchangeable assignments. [c] Assignments were proved by DEPT measurement.

Table 3

Physical and Analytical data on Compounds 10-18

Compound	Mp °C	Yield %	Molecular Formula	Analysis % Calcd./Found C	H	N
10	222-225 [a]	56	$C_7H_{10}N_2O_2$	54.54/54.14	6.54/6.30	18.17/18.27
11	263-265 [b,c]	61	$C_8H_{12}N_2O_2$			
12	276-278 [b,d]	60	$C_8H_{12}N_2O_2$			
13	315-317 [b]	58	$C_8H_{10}N_2O_2$	57.82/57.79	6.07/6.22	16.86/16.52
14	289-290 [a]	55	$C_9H_{12}N_2O_2$	60.54/60.42	6.71/6.92	15.55/15.50
15	284-287 [a]	50	$C_9H_{12}N_2O_2$	60.54/60.50	6.71/6.81	15.55/15.58
16	325-328 [a]	54	$C_9H_{10}N_2O_2$	60.67/60.72	5.66/5.88	15.72/15.60
17	334-338 [a]	52	$C_9H_{10}N_2O_2$	60.67/60.74	5.66/5.89	15.72/15.83
18	321-323 [e-f]	65	$C_8H_{10}N_2O_2$			

[a] From methanol. [b] From DMSO. [c] Lit mp 242--244° [6]. [d] Lit mp 255-258° [6]. [e] From ethanol. [f] Lit mp 295-297° [8].

possible half-chair conformers is present, whereas only one conformer is possible for the *trans* derivative **12** [8].

The H-4a and H-8a signals for the *cis*-condensed cyclopentane derivative **10** are downfield shifted by ~0.10 and 0.45 ppm, respectively, relative to those for the cyclohexane homologue **11**, and the former signal is broader ($\Delta\nu$ = 28 Hz for **10** and 18 Hz for **11**), while the latter is sharper ($\Delta\nu$ = 12 Hz instead of 15 Hz). This shows that the conformational equilibrium is shifted towards the less abundant form of **11**.

Because of the strained condensed heteroring, these compounds are flexible and in solution a conformational equilibrium exists also for the cyclohexane compounds. In agreement, we earlier found the 3-substituted analogues to be flexible molecules existing in the *N-in* and *N-out* conformers in roughly 1:1 ratio [3].

For the *cis*-cyclohexene derivative **13**, the ^1H nmr chemical shifts of H-4a,8a and the ^{13}C nmr shifts of C-4a,8a are not essentially different from those for the saturated compound **11**, *i.e.* the conformational relations are similar. This also indicates the flexibility of the molecule **11**, which is obvious for **13**.

For the carbobicyclic-condensed derivatives **14-17**, the heteroring has no influence on the original configurations, *i.e.* **14** and **16** are *diexo*- while **15** and **17** are *diendo*-annelated, which follows from the multiplicity of the H-4a,8a signals. In earlier investigations, these signals appeared as doublets for the *diexo* and double doublets for the *diendo* analogues [13]. The mutual interactions of H-4a and H-8 result in a doublet, while the further splitting to double doublets originates from the coupling of these hydrogens and their neighbours H-5 and H-8. The latter interaction does not cause a significant splitting in the case of *diexo*-annelated compounds because the corresponding dihedral angle is ~90° [12].

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were determined in potassium bromide discs on a Bruker IFS 113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer. The ^1H and ^{13}C nmr spectra were recorded in DMSO-d_6 solution in 5 or 10 mm tubes, at room temperature, on a Bruker WM 250 (^1H, ^{13}C) or WP 80-SY (^{13}C) FT-spectrometer controlled by an Aspect 2000 computer at 250.13 (^1H) and 62.89 or 20.14 (^{13}C)

MHz, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: spectrum width 5 and 15 or 5 kHz, pulse width 1 and 7 or 3.5 μs (35° flip angle), acquisition time 1.64 and 1.02 or 1.64 s, number of scans 4-16 and 0.5-15 K, computer memory 16 and 32 or 16 K. Complete proton noise decoupling (~3 or ~1.5 W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width 0.7 and 1.0 or 2.0 Hz).

The DEPT [14] spectra were run in a standard way [15], using only the $\theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively. Typical acquisition data were: number of scans 128-512, relaxation delay for protons 3 s, 90° pulse widths 17.5 and 43 μs for ^{13}C and ^{1}H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

Preparation of *cis*-5,6-Trimethylene-5,6-dihydro-2,4(1*H*,3*H*)-pyrimidinedione **10**, 4a*r*,5,6,7,8,8a*c*-Hexahydro- **11**, 4a*r*,5,8,8a*c*-Tetrahydro- **13**, 5,8-Methano-4a*r*,5,6,7,8,8a*c*-hexahydro- **14**, 4a*r*,5,6,7,8,8a*t*-Hexahydro- **15**, 4a*r*,5,8,8a*c*-Tetrahydro- **16** and 4a*r*,5,8,8a*t*-Tetrahydro-2,4(1*H*,3*H*)-quinazolidinedione **17**.

A mixture of the ester hydrochloride (**1**: 19.4 g, **2** and **3**: 20.8 g, **4** and **5**: 20.6 g, **6** and **7**: 22.0 g, **8** and **9**: 21.8 g, 0.01 mole) and powdered potassium cyanate (9.72 g, 0.12 mole) in methanol (300 ml) was refluxed for 3 hours. After filtration of the hot suspension, the filtrate was evaporated and xylene (50 ml) was added to the residue. The mixture was refluxed for 5 hours and the solid was filtered off. Data on compounds **10-17** are listed in Table 3.

Thermal Decomposition of 5,8-Methano-4a*r*,5*c*,8*c*,8a*c*-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione **16** to Pyrimidine-2,4(1*H*,3*H*)-dione **19**.

Compound **16** (1 g) was heated for 15 minutes at 350° in a metal bath. After cooling, the residue was crystallized from hot water, colourless crystals **19**, mp 352-354° (gas evolution), lit mp 335° [16]. Compound **19** was identified by mp and ir on comparison with an authentic sample (Aldrich 13,078-8).

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