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An approach to the synthesis of the benzo[f]quinazoline ring system using a preformed pyrimidine is described. A facile cyclization of a ketone function into the 5-position of uracil is the key step in this sequence.

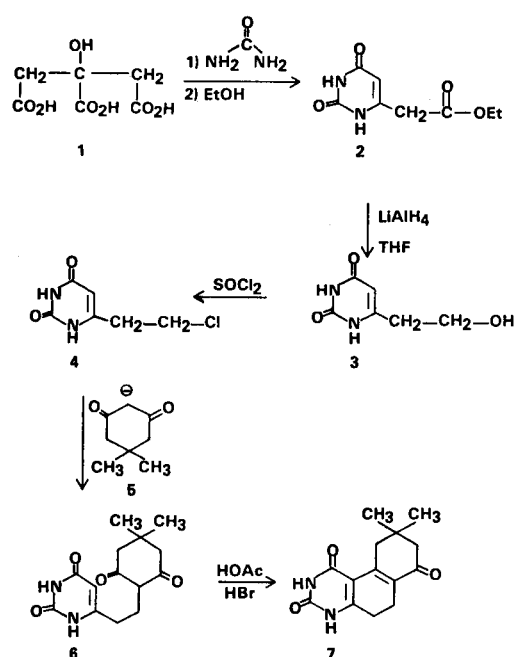
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Many examples of the benzo[f]quinazoline ring system have appeared in the literature wherein both differently substituted derivatives (1,2) and systems with varying degrees of saturation have been reported. To date, however, the synthesis of benzo[f]quinazolines has usually relied on the condensation of an appropriate substrate, such as a substituted naphthyl or tetralone derivative, with some small nitrogen containing compound such as guanidine, urea, or formamide (1-3). We now wish to report on a novel synthesis of a partially saturated benzo[f]quinazoline.

As outlined in Scheme I, citric acid (1) was condensed with urea, then treated with ethanol to yield the ethyl ester of uracil-6-acetic acid (2) (4). This ester was reduced (5) with lithium aluminum hydride to the corresponding alcohol (3) which, upon treatment with thionyl chloride, give 6-(2-chloroethyl)uracil (4) (5). The chloro group of 4 was displaced by the anion of dimedone (5) (generated by aqueous potassium hydroxide) with the formation of 6-[2-(4,4-dimethyl-2,6-dioxocyclohexyl)ethyl]uracil (6) in 60% yield. The structure of compound 6 was confirmed by uv, ir, pmr, mass spectrum and elemental analysis. The infrared carbonyl absorption seen at 1740 cm^{-1} and 1650 cm^{-1} corresponds to the amide portion of the uracil structure and the diketone moiety, respectively. In addition, the presence of two peaks centered at 1380 cm^{-1} is consistent with the geminal dimethyl functionality of the dimedone portion of the molecule. The pmr spectrum obtained in trifluoroacetic acid consists of a singlet at δ 1.21 which corresponds to the six protons of the geminal dimethyl group, a broad multiplet centered at δ 2.85 corresponding to eight protons (four from the dimedone ring and four from the connecting side chain), and a singlet at δ 6.09 corresponding to the one proton at the C-5 position of the uracil ring. The proton α to both carbonyls of the dimedone moiety would not be expected to show in this spectrum since it would most likely be present in the enolic form and hence absorb far enough downfield to be obscured by the trifluoroacetic acid (solvent) absorption. Likewise, N-H protons frequently don't appear when trifluoroacetic acid is used as the solvent. The ultraviolet spectrum of this compound, recorded in methanol, consists of a single peak at 265 nm ($\log \epsilon = 4.3$) which corresponds well with observed values for uracil (260 nm

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Scheme I



$\log \epsilon = 3.9$, 205 nm $\log \epsilon = 3.9$; water, pH 7.2) (6) and dimedone (257 nm $\log \epsilon = 4.22$) (7). Hence, the single peak most probably results from the overlapping of the two above mentioned peaks. Compound 6 could not be obtained without the presence of solvent of recrystallization. Consequently a mass spectrum was obtained which indicated a molecular weight of 278. Elemental analysis of the compound incorporating one mole of water was obtained.

Upon treatment with a solution of hydrobromic acid-acetic acid, (6) gave the cyclized product (7) in 75% yield. The structure of 7 was confirmed by uv, ir, pmr, and elemental analysis. The infrared spectrum of compound 7 shows complex carbonyl absorption in the $1750\text{--}1600\text{ cm}^{-1}$ range and the geminal dimethyl absorption centered at 1380 cm^{-1} . The pmr spectrum of compound 7 shows a singlet at δ 1.17 corresponding to the six protons of the geminal dimethyl group, and a broad multiplet centered at δ 2.84 representing the remaining eight protons (again N-H protons do not appear under these conditions). Also of

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diagnostic value is the disappearance of the C-5 proton of uracil seen in the spectrum of the starting material (**6**). The ultraviolet spectrum of **7** recorded in methanol, consists of three absorptions, 340 nm ($\log \epsilon = 4.1$), 275 nm ($\log \epsilon = 4.0$), and 230 nm ($\log \epsilon = 3.7$), which are consistent with the proposed structure. The peak at 340 nm corresponds to the highly conjugated dienone portion of the molecule which has been shifted bathochromically from the base value of 245 nm for an unsubstituted dienone. This is quite reasonable when one considers the high degree of substitution of the basic dienone structure. Both remaining peaks are characteristic of uracil absorption which has also been shifted bathochromically. The peak at 230 nm did not appear in compound **6** because it occurs below the solvent absorption prior to its red shift.

EXPERIMENTAL

Melting points were taken on a Hoover-Thomas melting point apparatus and are uncorrected. The spectra cited were obtained using a Perkin-Elmer 257 grating infrared spectrophotometer (as potassium bromide discs), a Varian T-60 nmr spectrometer (with TMS as internal standard) and a Cary 14 ultraviolet spectrophotometer. Compounds were analyzed by the Galbraith Laboratories, Knoxville, TN.

6-Chloroethyluracil (**4**).

6-Hydroxyethyluracil (**3**) (3.0 g., 0.19 mole) was allowed to stir in 40 ml. thionyl chloride for 24 hours and was then refluxed for 6 hours. At the end of this time, the thionyl chloride was removed *in vacuo* and the residue crystallized from 300 ml. water (Norit) to yield 0.90 g. Concentration of the mother liquor to 125 ml. yielded another 0.85 g. to bring the total yield to 1.78 g. (52%), m.p. 207-208°; ir (potassium bromide): 670, 765, 840, 1430, 1510, 1650, 1730, 2820, 2860, 2980, 3420 cm^{-1} ; pmr (DMSO- d_6): 1.8 (t, 2H), 3.9 (t, 2H), 5.5 (s, 1H), 11.0 (bs, 2H).

6-[2-(4,4-Dimethyl-2,6-dioxocyclohexyl)ethyl]uracil (**6**).

Dimedone (1.22 g., 8.7 mmoles) was suspended in 55 ml. of water, and to this was added potassium hydroxide (0.49 g., 8.7 mmoles) while maintaining stirring. 6-Chloroethyluracil (1.5 g., 8.6 mmoles) was then added dropwise, and the resulting mixture refluxed for 7 hours. At the end of this time, the mixture was allowed to cool to room temperature and then cooled to ice bath

temperature. The precipitated material was filtered and the filtrate acidified to about pH 3 and extracted twice with equal volumes of chloroform. The aqueous layer was separated and the volume reduced *in vacuo* to about 5 or 10 ml. and the precipitated material filtered and combined with the original precipitate. Crystallization from about 150 ml. water yielded 1.10 g. of product. Concentration of the mother liquor to about 40 ml. yielded a second crop of 0.25 g., to bring the total yield to 1.35 g. (57%), m.p. 242-244°; uv (methanol): 265 nm ($\log \epsilon = 4.3$); ir (potassium bromide): 1170, 1380, 1590, 1650, 1740, 2950, 3150, 3440 cm^{-1} ; pmr (trifluoroacetic acid): 1.2 (s, 6H), 2.8 (m, 8H), 6.1 (s, 1H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C, 56.75; H, 6.76; N, 9.46. Found: C, 56.51; H, 6.77; N, 9.46.

6,8,9,10-Tetrahydro-9,9-dimethylbenzo[*l*]quinazoline-1,3,7 (2*H*, 4*H*,5*H*)trione (**7**).

Compound **5** (1.0 g., 3.6 mmoles) was suspended in 20 ml. of glacial acetic acid and to this was added 10 ml. of 48% hydrobromic acid while maintaining stirring. Upon addition of the hydrobromic acid, all the undissolved material went into solution and was then heated to reflux for ten minutes. The solution was then cooled to room temperature and evaporated to dryness, leaving a yellowish solid. Crystallization (Norit) from about 300 ml. water yielded 0.66 g. of product (70%), m.p. 309-310°; uv (methanol): 340 nm ($\log \epsilon = 4.1$), 275 nm ($\log \epsilon = 4.0$), 230 nm ($\log \epsilon = 3.7$); ir (potassium bromide): 1030, 1220, 1310, 1380, 1420, 1570, 1650, 1720, 2950, 3180, 3450 cm^{-1} ; pmr (trifluoroacetic acid): 1.2 (s, 6H), 2.84 (m, 8H).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_3$: C, 64.60; H, 6.20; N, 10.72. Found: C, 64.44; H, 6.12; N, 10.64.

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