Cyclisation of Arylcarboxamidouracils. Synthesis of a New 4*H*-3,1-Benzoxazin-4-one. Use of Mass Spectrometry as a Probe

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The action of acetic anhydride on an anthranylcarboxamidouracil led to a new 2-substituted 4*H*-3,1-benzoxazin-4-one with potential analgesic activity. Mass spectrometry has been used as a method for structure confirmation and several fragmentation pathways were proposed. Furthermore, an additional probe was given by opening of the lactonic ring submitted to the action of aliphatic and aromatic primary amines.

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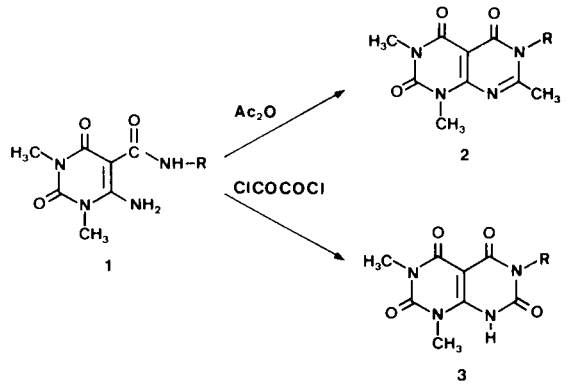
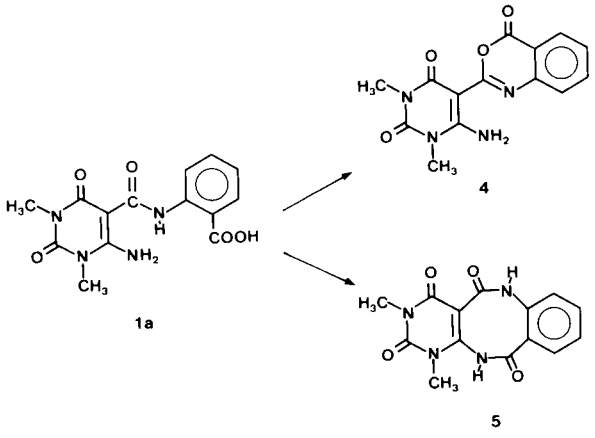
We previously reported (2) the synthesis and the chemical properties of new 1,3-dimethyl-5-carboxamidouracils (**1**). These compounds were useful starting material for prior synthetic work on new polyhydropyrimido[4,5-*d*]pyrimidines (**3**). Their cyclisation using acetic anhydride led to 2,4,5-trioxo-1,2,3,4,5,6-hexahydropyrimido[4,5-*d*]pyrimidines (**2**), but upon treatment with oxalyl chloride, 2,4,5,7-tetraoxo-1,2,3,4,5,6,7,8-octahydropyrimido[4,5-*d*]pyrimidines were obtained (**3**).



Scheme I

These molecules exhibit interesting levels of analgesic activity and antiinflammatory effects. In order to increase such pharmacological properties, we have introduced the anthranilic moiety into the ring structure of **1**, and we report here the peculiar behavior of the corresponding amide **1a** upon treatment with acetic anhydride. Under our reaction conditions, *N*-anthranylcarboxamide **1a** does not lead to a pyrimido[4,5-*d*]pyrimidinetrione



Scheme II

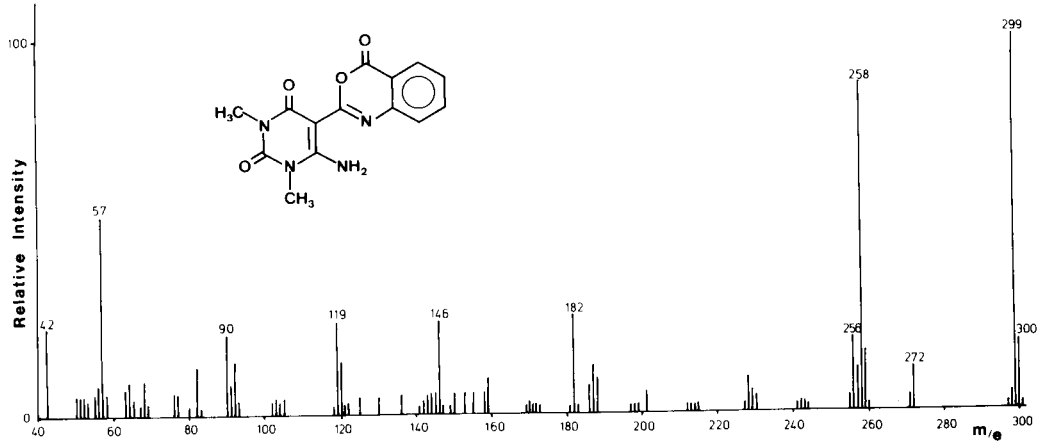


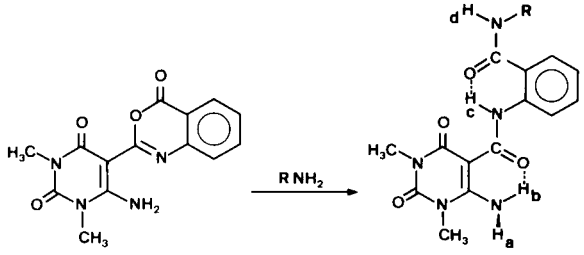
Figure I

as previously described for the aromatic starting amides. Rather, cyclising dehydration involving the free carboxylic acid group occurs to afford a compound $C_{14}H_{12}N_4O_4$, m.p. > 270°, which could be considered to contain the lactonic structure **4** or the tricyclic form **5** (Scheme II).

The reaction does not give a mixture of **4** and **5**. With tlc using a two solvent system, only one spot can be observed. This spot revealed by uv is not stained by iodine, which is incompatible with the presence of CO-NH groups present in compound **5**. The ir absorption spectrum exhibits a strong band at 1755 cm^{-1}, which supports the δ lactone structure **4**. The carbonyl band in six-membered ring lactones fused with other cyclic systems is generally reported as appearing in the 1750-1790 cm^{-1} range (4,5), while the carbonyl band of secondary amides (as in **5**) appears between 1650 and 1700 cm^{-1} (6). Moreover, this structural assignment is substantiated by a mass spectroscopic examination (5) which shows the existence of a 3,1-benzoxazin-4-one fraction (m/e = 146) and its characteristic fragmentation.

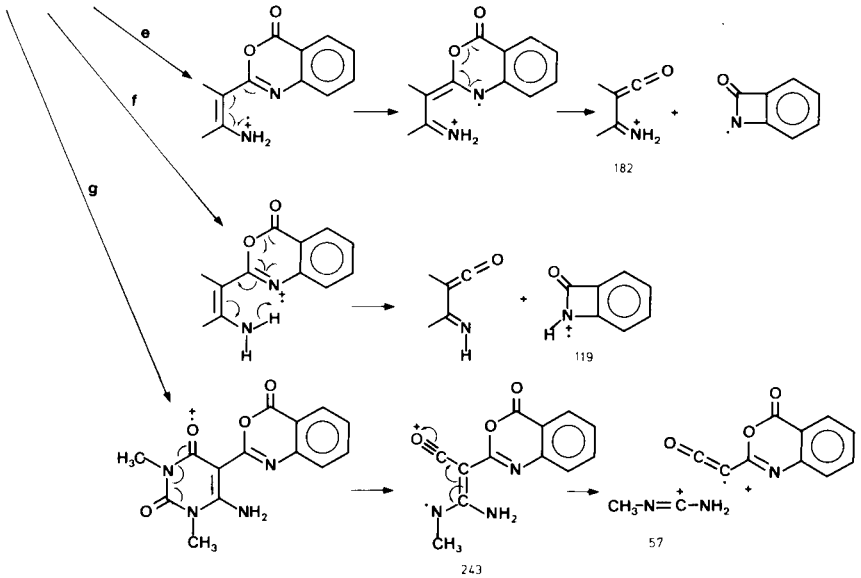
If the parent ion corresponds to M-1, the major fragmentation pathways involve the 4*H*-3,1-benzoxazin-4-one moiety. The loss of small neutral molecules (CO and CO_2) corresponds to a classical mechanism (8-9). For these fragmentation patterns (a, b; Scheme III), a rearrangement into oxaziridine intermediates could occur as previously reported for similar systems (10-11). Fragmentation of the molecular ion and rearrangement account for the appearance of peaks at m/e 258, m/e 182 and m/e 119 (12). Fragmentation pathways of substituted uracils were previously investigated (13-18) and these studies showed that uracils having methyl substituents located in the 1- and 3-positions are characterized by abundant molecular ions. In the case of **4** however, the fragmentation pattern involving the uracil ring is minor. Nevertheless, an abundant ion appearing at m/e 57 corresponding to $CH_3\text{-}N{=}\overset{+}{C}\text{-}NH_2$, with a metastable transition, is specific for the 1,3-dimethyl-4-aminouracil ion fragmentation.

The fragmentation routes described above involving rearrangements to benzaziridine are in accordance with the instability of the oxygen-carbon linkage of the lactone under electron impact. It can be concluded that mass spectral data confirm the structure of the dehydration product of **1a** as 4*H*-3,1-benzoxazin-4-one **4**. Furthermore, the chemical behavior of this compound in the presence of primary amines can be examined for information concerning its structure. Thus, it affords the amides **6** (Scheme IV) by the opening of the lactone ring. The nmr spectra of these amides have been recorded and agree with their proposed structure (19).

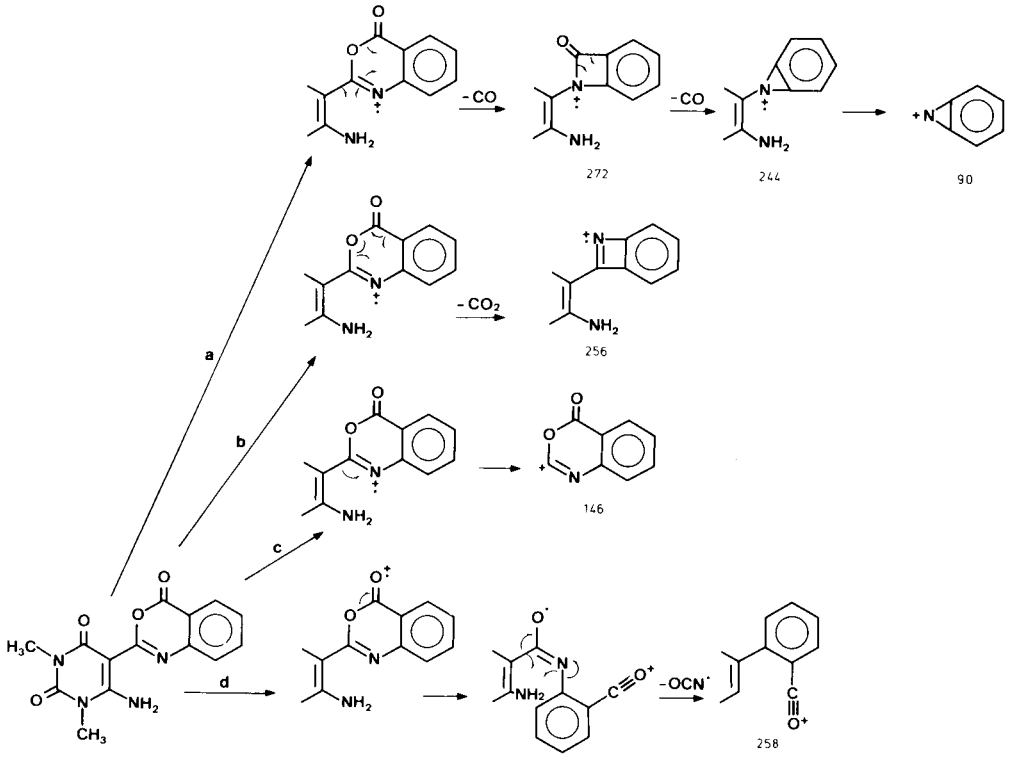


Scheme IV

Thus, the introduction of an anthranilic substituent on a molecule having important analgesic and antiinflammatory activities led, after cyclisation, to a new 2-substituted 4*H*-3,1-benzoxazin-4-one product, a structural



Scheme III



analogue of the known 3*H*-1,3-benzoxazin-2,4-dione or 4*H*-1,3-benzoxazin-4-one, whose pharmalogical properties have been the subject of extensive studies (20-23).

EXPERIMENTAL (24)

1,3-Dimethyl-6-amino-5-(*N*-anthranilylcarboxamido)uracil (**1a**).

This compound was prepared from phenyl 1,3-dimethyl-4-aminouracil-5-carboxylate (27.5 g.; 0.1 mole) and anthranilic acid (13.7 g.; 0.1 mole) heated in pyridine for 6 hours. After cooling, the white product was crystallized twice from pyridine. The yield was 71%, m.p. >270°; ir (potassium bromide): ν 1710 cm^{-1}, 1730 (C=O). The purity of **1a** was determined by a tlc method (22). A single spot could be observed in the E_1 system (Rf_1 = 0.74) and in the E_2 system (Rf_2 = 0). Both spots could be stained by exposure to iodine.

Anal. Calcd. for $C_{14}H_{14}N_4O_5$: C, 52.83; H, 4.43; N, 17.60. Found: C, 52.92; H, 4.44; N, 17.69.

2-(1,3-Dimethyl-2,4-dioxo-6-amino-1,2,3,4-tetrahydropyrimidine-5-yl)4*H*-3,1-benzoxazin-4-one (**4**).

A mixture of 31.8 g. of **1a** and 50 cm^3 of acetic anhydride was heated under reflux for 3 hours. The cooled precipitated material **4** was filtered giving a yield of 66% and crystallised twice from a mixture of pyridine-DMSO (4:1), m.p. > 270°; ir (potassium bromide): ν 1755 cm^{-1} (lactonic C=O); tlc: in both systems (E_1 and E_2) the product **4** did not migrate. The spots could not be seen by iodine exposure, which agrees with the proposed structure **4**.

Anal. Calcd. for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.60. Found: C, 56.13; H, 4.05; N, 18.99.

(1,3-Dimethyl-2,4-dioxo-6-amino-1,2,3,4-tetrahydropyrimidine-5-yl)-2-carbonylamino-*N*-methylbenzamide (**6a**).

Benzoxazinone **4** (3 g.; 0.010 mole) treated by 30% aqueous solution of methylamine (50 cm^3) afforded the corresponding amide **5a**, which crystallized from the reaction medium with a yield of 73%. Another crystallisation was made using pyridine in which white crystals were obtained, m.p. >270°; ir (potassium bromide): ν 1700 cm^{-1} (C=O); nmr (DMSO-d_6): a 8.35 ppm (s), b 10.75 (s), c 12.25 (s), d 10.20 (s); tlc: both chromatograms exhibited a single spot, iodine stained; Rf_1: 0.62 (E_1 system); Rf_2: 0.63 (E_2 system).

Anal. Calcd. for $C_{15}H_{15}N_4O_4$: C, 54.37; H, 5.17; N, 21.14. Found: C, 53.81; H, 5.22; N, 21.33.

(1,3-Dimethyl-2,4-dioxo-6-amino-1,2,3,4-tetrahydropyrimidine-5-yl)-2-carbonylamino-*N*-phenylbenzamide (**6b**).

Under the same conditions as above, **4** (3 g.) treated with 10 cm^3 of aniline afforded **5b** in 80% yield. White crystals were obtained from pyridine, m.p. > 270°; ir (potassium bromide): ν 1700 cm^{-1} (C=O); nmr (DMSO-d_6): a 8.10 ppm (s); b 10.80 (s); c 12.25 (s); d 10.40 (s); tlc: both chromatograms showed a single spot, iodine stained; Rf_1: 0.81 (E_1 system); Rf_2: 0.63 (E_2 system).

Anal. Calcd. for $C_{20}H_{19}N_4O_4$: C, 61.06; H, 4.87; N, 17.80. Found: C, 60.80; H, 4.89; N, 17.83.

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(24) Infrared spectra were recorded with a Perkin-Elmer 177 infrared spectrometer, using a potassium bromide pellet. Nmr spectra were obtained with a Jeol-JNM-MH-60, using tetramethylsilane as the internal standard. Mass spectra were recorded from a AEI MS-30 Spectrometer. Thin layer chromatograms were run on 5 x 10 cm glass plates precoated with silica gel F_{254} (Merck), 0.25 mm. Two solvent systems were used, E_1: butanol-acetic acid-water (4:1:5) and E_2: chloroform-methanol (4:1) in ammonia atmosphere. The spots on the chromatograms were visualized by uv (254 nm; 366 nm) or by exposure to iodine.