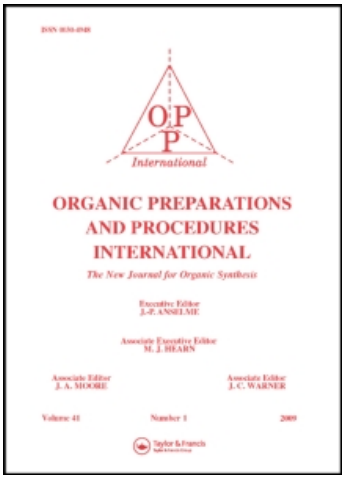

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SYNTHESIS OF NEW HETEROCYCLOCOUMARINS FROM 3,4-DIAMINO- AND 4-CHLORO-3-NITROCOUMARINS

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SYNTHESIS OF NEW HETEROCYCLOCOUMARINS FROM 3,4-DIAMINO- AND 4-CHLORO-3-NITROCOUMARINS

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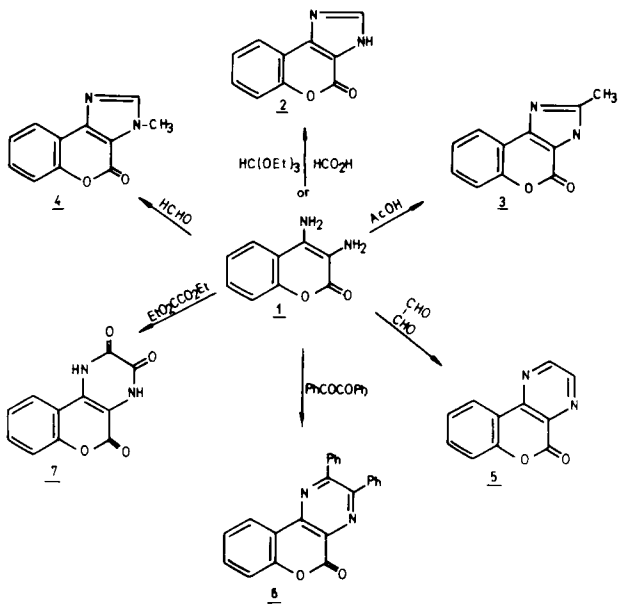
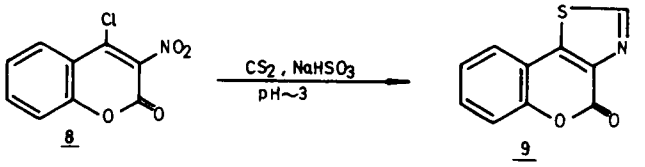
Coumarin derivatives still receive attention as possible leading compounds in drug design;[1] coumarin itself seems to inhibit the onset and growth of induced mammary cancer.[2] We have prepared several condensed ring-systems containing nitrogen and sulfur. Although the methods used for the preparation were not novel, they provided relatively good yields of pure products. The starting 3,4-diaminocoumarin obtained earlier[3] by catalytic hydrogenation of 4-amino-3-nitrocoumarin,[4] was prepared by



electrochemical reduction of the same compound. Condensation at the 3,4-positions was achieved as shown in the Scheme. Imidazolo[3,4-b]benzo[a]-2H-2-oxopyrans (2-4) and the related pyrazine derivatives (5-7) were prepared from 1. The condensed system 5 is unknown and as yet not listed in condensed-ring indexes. Another new ring system 9 was obtained by condensation of 4-chloro-3-nitrocoumarin 8 with carbon disulfide.



8 9

EXPERIMENTAL SECTION

Mixtures of starting compound with other components (including 0.5 ml of conc. HCl when necessary) were refluxed with magnetic stirring, and allowed to cool without interruption of stirring. Solvents and other volatile components of reaction mixtures were removed by evaporation under reduced pressure. Residues were taken up in water, acidic components (if still present) were neutralized with satd. aq. $NaHCO_3$, and the solid fractions were collected. Washing was carried out with water, sometimes followed by organic solvent(s). The crude products were air-dried, then purified by crystallisation. All mps (uncorr.) were determined on a hot-stage microscope. Nmr spectra were recorded (DMSO d-6) with a Perkin-Elmer R-12B instrument. The mass spectrum of 7 was recorded with a Hitachi Perkin-Elmer RMU-6L spectrometer.

3,4-Diaminocoumarin (1).- The procedure was based on a general method for electrochemical reduction.[5] Four hundred and fifty ml of 96% ethanol and 150 ml of 1 M HCl were placed into a 2 L beaker, over a 150 cm^2 mercury cathode. 4-Amino-3-nitrocoumarin[5] (5.6 g, 20 mmol) was added with stirring (magnetic stirrer). A narrow cylindrical porous-wall vessel was lowered into the beaker and 1 M HCl poured in, to reach the height of liquid outside. A piece of Pt-wire (anode) was dipped to 1 cm below the inner liquid surface and direct current maintained at 1.6 A, was passed across the cell. During its passage, the starting material gradually went into solution while a yellow solid separated. The progress of reduction was monitored (TLC) and found to be complete after 5 hrs of electrolysis.

The current was then discontinued and the content of the cathode compartment worked up (collection of the product, followed by washing with H_2O, MeOH and Et_2O). Crystallization from MeOH yielded 0.59 g (73%) of 1, mp. 202-204°, lit.[4] mp. 202-204°, whose identity was confirmed by spectral data identical to those previously reported.[4]

Imidazolo[3,4-b]benzo[a]-2H-2-oxopyran (2).- A mixture of 1 (1 g, 5.6 mmol), formic acid (50 ml) and conc. HCl was heated for 12 hrs, then worked up to yield 0.92 g (87%) of crude product. Crystallization, either from 1:1 aqueous AcOH or 1:1 aqueous EtOH, gave colorless needles of the same mp. 299-301°.

An alternate synthesis involved heating 1 (1 g, 5.6 mmol), EtOH (50 ml), triethyl orthoformate (1.5 g, 10 mmol) and conc. HCl for 2 hrs followed by evaporation to dryness. Crystallization of the residue from 1:1 aq. AcOH yielded 0.72 g (68%) of colorless needles, mp. 299-301°, which had the same spectral characteristics as the product above.

Nmr: δ 8.38 (s, NH), 8.05 (t, CH), 7.23-7.65 (m, 4H, ArH).

Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.47; H, 3.23; N, 14.99

Found: C, 64.55; H, 3.51, N, 14.96

2'-Methylimidazolo[3,4-b]benzo[a]-2H-2-oxopyran (3).- A mixture of 1 (1 g, 5.6 mmol), glac. AcOH (50 ml) and conc. HCl was heated at reflux for 12 hrs then worked up to yield 1 g (92%) of crude product. Cyrstallization from EtOH gave colorless needles mp. 334-336°.

Nmr: δ 8.3-8.7 (broad s, NH), 7.1-8.1 (m, 4H, ArH), 1.90 (t, CH_3).

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99

Found: C, 66.19; H, 3.92; N, 13.76

N-Methylimidazolo[3,4-b]benzo[a]-2H-2-oxopyran (4).- A mixture of 1 (1 g, 5.5 mmol), 35% aq. formaldehyde (1.58 ml), EtOH (25 ml) and conc. HCl was heated at reflux for 12 hrs then worked up. Crystallization of the crude

product from 96% EtOH yielded 0.9 g (82%) of purified material, mp. 328-331°.

Nmr: δ 8.0 (t, CH), 7.2-7.7 (m, 4H, ArH), 1.56 (t, CH_3).

Anal. Calcd. for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99

Found: C, 66.10; H, 3.92; N, 14.13

In an alternative synthesis, 0.5 g (2.7 mmol) of 2 in MeOH (25 ml) was left overnight with excess ethereal diazomethane. Evaporation left 0.54 g of a residue which, on crystallization from EtOH, gave a product having the same mp. and spectral characteristics as the one obtained above.

2'H-3'H-2',3'-Dioxopyrazino[3,4-b]benzo[a]-2H-2-oxopyran (7).- A mixture of 1 (1 g, 5.6 mmol), EtOH (25 ml), diethyl oxalate (0.8 ml, 5.5 mmol) and conc. HCl was heated 4 hrs. The usual work-up yielded 0.56 g (46%) of crude product. Crystallization from dimethylformamide (DMF) gave colorless cubic crystals, mp. >300° (dec.).

Nmr. δ 8.1-8.4 (q, 2H, NH), 7.2-7.6 (m, 4H arH). Ms: 230 (M^+)

Anal. Calcd. for $C_{11}H_6N_2O_4$: C, 57.40; H, 2.63; N, 12.17

Found: C, 57.50; H, 2.46; N, 12.30

Alternatively, a mixture of 1 (1 g, 5.6 mmol) and diethyl oxalate (0.8 ml, 5.5 mmol) was heated at reflux for 2 hrs then evaporated to dryness (red. pressure). Crystallization of the residue from DMF yielded 0.92 g (72%) of colorless cubic crystals with the same melting and spectral characteristics as the above material.

Pyrazino[3,4-b]benzo[a]-2H-2-oxopyran (5).- A mixture of 1 (1 g, 5.6 mmol), EtOH (50 ml), glyoxal (40% aq., 0.82 ml) and conc. HCl was heated at reflux for 4 hrs. The collected solid product was washed with satd. aq. $NaHCO_3$ then with water. Crystallization from 96% EtOH yielded 1 g (96%) of colorless needles, mp. 172-174°.

Nmr. δ 8.05-8.15 (m, 2H, 2CH), 7.10-7.65 (m, 4H, ArH)

Anal. Calcd. for $C_{11}H_6N_2O_2$: C, 66.67; H, 3.05; N, 14.14

Found: C, 66.28; H, 3.30; N, 13.98

2',3'-Diphenylpyrazino[3,4-b]benzo[a]-2H-2-oxopyran (6).- A mixture of 1 (1 g, 5.6 mmol), EtOH (50 ml), benzil (1.2 g, 7.8 mmol) and conc. HCl was heated 2 hrs and yielded 0.9 g (90%) of crude product. Crystallization from 96% EtOH gave short thick white crystals, mp. 206-208°.

Nmr: δ 7.1-8.7 (m, 4H, ArH)

Anal. Calcd. for $C_{23}H_{14}N_2O_2$: C, 78.84; H, 4.03; N, 7.99

Found: C, 78.60; H, 4.28; N, 7.86

Thiazolo[3,4-b]benzo[a]-2H-2-oxopyran (9).- A mixture of 4-chloro-3-nitrocoumarin[4] (1 g, 4.4 mmol), EtOH (50 ml), carbon disulfide (0.3 ml, 3.0 mmol) and $NaHSO_3$ (0.4 g, 3.8 mmol) was adjusted to pH about 3 with aq. HCl, then heated at reflux for 3 hrs. Complete evaporation (red. pressure) left a residue which, on crystallization from EtOH, yielded 0.7 g (78%) of yellow needles, mp. 311-312°.

Nmr. δ 7.1-7.8 (m, 4H, ArH), 6.75 (s, CH)

Anal. Calcd. for $C_{10}H_5NO_2S$: C, 59.11; H, 2.47; N, 6.87

Found: C, 59.32; H, 2.50; N, 6.74

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α,α-DIBROMODESOXYBENZOIN FROM THE REACTION OF THIONYL BROMIDE WITH BENZOIN

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Thionyl bromide reacts with aromatic aldehydes to yield either the acid bromides, the benzal bromides or the corresponding acid with 2-anisaldehyde.[1] We now report that thionyl bromide converts benzoin(1) to α,α-dibromodesoxybenzoin(2) as the major product (66%) along with small amounts of benzil and elemental sulfur. This method is superior to the one used by Limpricht and Schwanert[2] involving the bromination of the molten desoxybenzoin.

$$\underset{\underline{1}}{PhCOCHOHPh} + SOBr_2 \longrightarrow \underset{\underline{2}}{PhCOBr_2Ph} + PhCOCOPh + S$$

While the formation of benzil may be rationalized via either the intramolecular fragmentation of an intermediate bromosulfinate ester or the enediol sulfite, the formation of 2 probably proceeds via a radical