Synthesis of Some Benzopyranocyclopentapyridine and Pyranoacridine Derivatives

J. R. Merchant*, Gail Martyres and N. M. Koshti

Department of Organic Chemistry, Institute of Science, Bombay, 400 032, India

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Aminocoumarins react with ethyl cyclopentanone- and ethyl cyclohexanone-2-carboxylates to afford intermediates which on thermal cyclisation yield the title compounds.

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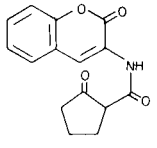
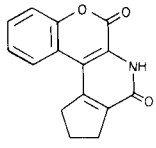
Cyclopentapyridines are reported to possess fungicidal and bactericidal (1,2) as also neuropharmacological (3) properties. It was our intention to combine both the coumarin and cyclopentapyridine ring systems to obtain benzopyranocyclopentapyridines and to study their bactericidal properties. We therefore first investigated the reactions of 3- and 6-aminocoumarins with ethyl cyclopentanone-2-carboxylate. The two aminocoumarins reacted differently with the ester under identical experimental conditions, but with ethyl cyclohexanone-2-carboxylate identical results were obtained in both cases.

3-Aminocoumarins (4) was condensed with ethyl cyclopentanone-2-carboxylate to afford a yellow crystalline compound which could be an amide or an anil. Spectral and analytical data (Table) indicated that the compound had the amide structure (M^+ 271) (I). Thermal cyclisation of the latter afforded 2,3-dihydro-1*H*,5*H*-[1]benzopyrano-[3,4-*b*]cyclopenta[*d*]pyridine-4,6-dione (II).

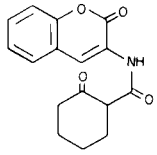


I

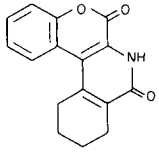


II

The reaction of 3-aminocoumarin with ethyl cyclohexanone-2-carboxylate gave the amide III which was cyclised to 2,3-dihydro-1*H*,4*H*,6*H*[1]benzopyrano[3,4-*c*]isoquinoline-5,7-dione (IV). Both the structures were fully consistent with the spectral evidence (Table).



III

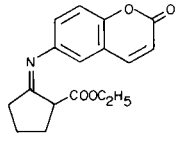


IV

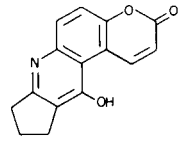
When 6-aminocoumarin (5) was condensed with ethyl cyclopentanone-2-carboxylate, the compound obtained was found to be V as seen from its mass spectrum (M^+ 299) and other data (Table).

On thermal cyclisation V afforded 11-hydroxy-2,3-dihydro-1*H*-[1]benzopyrano[5,6-*e*]cyclopenta[*b*]pyridin-8-one (VI). The appearance of protons at C_5 and C_6 in the form of an AB pattern at δ 7.3 and δ 7.6 in its nmr (deuterated dimethyl sulphoxide) spectrum showed that cyclisation of the anil had occurred at position 5 of the coumarin nucleus.

6-Aminocoumarin on condensation with ethyl cycloxanone-2-carboxylate gave VII (M^+ 313), as indicated by its spectral and analytical data (Table). the latter on cyclisation gave 8,9,10,11-tetrahydro-7*H*-pyrano[3,2-*a*]acridine-3,12-dione. Compounds V to VIII have been reported previously (6) but their structures were assigned on the basis of nitrogen analyses alone and hence needed further structural confirmation.

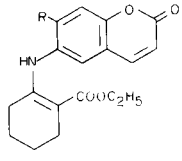


V



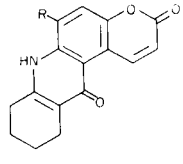
VI

It therefore appears that although 3-aminocoumarins react with β-ketoesters *via* a Knorr reaction, the 6-aminocoumarins undergo a Conrad-Limpach reaction giving anils as intermediates. This was confirmed by reacting 6-amino-7-methylcoumarin (7) with ethyl cyclopentanone- and ethyl cyclohexanone-2-carboxylates to yield the anils IX and X, respectively. Compound IX on thermal cyclisation afforded 5-methyl-1,2,3,4,-tetrahydro[1]benzopyrano[5,6-*e*]cyclopenta[*b*]pyridine-8,11-dione (XI), while with the anil *X*, (XII) was obtained.



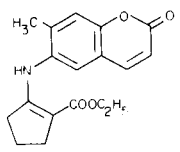
VII, R = H

X, R = CH_3

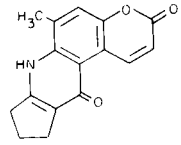


VIII, R = H

XII, R = CH_3



IX



XI

The cyclised compounds were tested for antibacterial activity using the agar diffusion method. Bacteria used were *Eschericha coli, Aerobacter aerogenes, Pseudomonas aeruginosa* and *Staphylococcus aureus.* All the compounds were found inactive against the gram negative species while against the gram positive species they exhibited weak activity insufficient to justify further testing.

Table

Physical, Analytical and Spectral Data

Compound	MP °C	Yield mg	Molecular formula	Analysis % Calcd./Found C	H	N	Spectral data
I	128-130	150	$C_{15}H_{13}NO_4$	66.42 66.00	4.79 5.12	5.16 5.32	ir (nujol): ν 3270 (NH), 1720 (C=O of lactone), 1680 (cyclic ketone), 1630 (C=O of amide) cm^{-1}. nmr (deuteriochloroform): δ 2.0-2.83 (m, three CH_2 of cyclopentane, 6H), 7.3-7.6 (m, aromatic and C_4H of coumarin, 5H).
II	310-312	75	$C_{15}H_{11}NO_3$	71.14 71.40	4.34 4.62	5.53 5.35	uv (dioxane): λ max 330 (log ϵ = 4.45), 240 (log ϵ = 4.07). ir (potassium bromide): ν 3220 (NH), 1720 (C=O) of lactone), 1665 (C=O of lactam) cm^{-1}.
III	125-127	150	$C_{16}H_{15}NO_4$	67.36 67.48	5.26 5.39	4.91 4.52	ir (nujol): ν 3380 (NH), 1700 (C=O of lactone), 1640 (C=O of amide). nmr (deuteriochloroform): δ 1.7-2.7 (m, four CH_2 of cyclohexane ring, 8H), 7.2-7.8 (m, aromatic and C_4H of coumarin, 5H), 12.5 (s, NH, 1H).
IV	323-325	60	$C_{16}H_{13}NO_3$	71.91 71.69	4.86 4.97	5.24 5.40	ir (nujol): ν 3310 (NH), 1720 (C=O of lactone), 1665 (C=O of lactam) cm^{-1}
V	136-137	200	$C_{17}H_{17}NO_4$	68.22 68.48	5.68 5.73	4.68 5.25	ir (potassium bromide): ν 1720 (C=O), 1640 (C=N) cm^{-1}. nmr (deuteriochloroform): δ 1.3 (t, $-CH_3$, 3H), 1.83-2.25 (m, CH_2, 2H), 2.5-3.0 (m, two CH_2 and CH, 5H), 4.3 (q, $-COOCH_2CH_3$, 2H), 6.5 (d, C_3H of coumarin, 1H), 7.18-7.74 (m, aromatic, 3H), 7.72 (d, C_4H of coumarin, 1H).
VI	348-350	100	$C_{15}H_{11}NO_3$	71.14 70.63	4.34 4.72	5.53 5.18	ir (potassium bromide): ν 3540 (OH), 1700 (C=O) cm^{-1}. nmr (80 MHz DMSO-d_6 at 350°): δ 0.6-1.73 (m, three CH_2, 6H): 6.4 (d, C_7H, 1H, J = 9 Hz), 7.3 (d, aromatic, 1H, J = 9 Hz), 7.6 (d, aromatic, 1H, J = 9 Hz), 9.4 (d, C_6H, 1H, J = 9 Hz).
VII	115-117	140	$C_{18}H_{19}NO_4$	69.00 69.12	6.07 5.74	4.47 4.58	ir (potassium bromide): ν 3410 (NH), 1710 (C=O) cm^{-1}. nmr (deuteriochloroform): δ 1.3 (t, CH_3, 3H), 1.33-1.66 (m, two CH_2, 4H), 3.9-4.33 (q, $-COOCH_2CH_3$, 2H), 6.33 (d, C_3H of coumarin ring, 1H), 6.66-7.33 (m, aromatic, 3H), 7.66 (d, C_4H of coumarin ring, 1H), 10.7 (s, NH, 1H).

VIII	345-347	90	$C_{16}H_{13}NO_3$	71.71 71.62	4.86 4.90	5.24 5.38	ir	(potassium bromide): ν 3410 (NH), 1720 (C=O of lactone), 1635 (C=O of pyridone ring) cm^{-1}.
							nmr	(80 MHz DMSO-d_6 at 350°C): δ 0.5-0.7 (m, two CH_2, 4H), 1.5-2.0 (m, two CH_2, 4H), 6.5 (d, C_8H, 1H, J = 9 Hz), 7.5 (d, aromatic, 1H, J = 9 Hz), 7.75 (d, aromatic 1H, J = 9 Hz), 9.4 (d, C_4H, 1H, J = 9 Hz).
IX	194-196	120	$C_{18}H_{19}NO_4$	69.00 69.38	6.07 5.81	4.47 4.30	ir	(nujol): ν 3400, 3340 (NH), 1700 (C=O) cm^{-1}.
X	159-161	140	$C_{19}H_{21}NO_4$	69.72 69.60	6.42 6.54	4.28 4.30	ir	(potassium bromide): ν 3400 (NH), 1700 (C=O) cm^{-1}
XI	348-350	90	$C_{16}H_{13}NO_3$	71.91 72.38	4.86 4.64	5.24 5.50	ir	(potassium bromide): ν 3400 (NH), 1720 (C=O of lactone), 1635 (C=O of pyridone ring) cm^{-1}.
XII	333-335	90	$C_{17}H_{15}NO_3$	72.59 72.12	5.33 5.68	4.98 4.52	ir	(potassium bromide): ν 3410 (NH), 1710 (C=O of lactone) 1640 (C=O of pyridone ring) cm^{-1}.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer spectrophotometer and the nmr spectra were determined on a 60 MHz Varian instrument except where otherwise mentioned. Tetramethylsilane was used as internal standard. The homogeneity of the compounds were ascertained by tlc on silica gel-G plates.

Condensation of Aminocoumarins With β-Ketoester.

The aminocoumarin (250 mg) and the β-ketoester (0.25 ml) were dissloved in dry xylene and refluxed for 4 hours. The solvent was distilled under vacuum and the residue crystallised from petroleum ether (100-120°) to afford the intermediates as yellow needles.

Thermal Cyclisation of the Intermediates.

The intermediates (200 mg) in diphenyl ether (10 ml) was refluxed for 2 hours. The solvent was removed under vacuum and petroleum-ether (40-60°) was added when a solid separated which was crystallised from boiling alcohol.

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REFERENCES AND NOTES

(1) R. Ichizawa, Japanese, Kokai, 76,121,517; *Chem. Abstr.*, **86**, 116062 (1977).

(2) S. H. Ruetman, U. S., 3,853,885 (1973); *Chem. Abstr.*, **82**, 111950 (1975).

(3) A. Upadysheva, *Khim.-Farm. Zh.*, **11**, 40 (1977); *Chem. Abstr.*, **86**, 189676 (1977).

(4) F. W. Linch, *J. Chem. Soc.*, 1759 (1912).

(5) T. Morgan and F. M. C. Micklethwait, *ibid.*, **85**, 1230 (1904).

(6) D. P. Ahuja, K. K. Chakravarti, and S. Siddiqui, *J. Sci. Ind. Res.*, **9B**, 165 (1950).

(7) A. Clayton, *J. Chem. Soc.*, **97**, 1352, 1397 (1910).