Pechmann Reaction of 4-Hydroxycoumarins and Thiocoumarins with Cyclohexanone and Ethyl Cyclopentanone-2-carboxylates

J. R. Merchant, N. M. Koshti and K. M. Bakre*

Department of Chemistry, Institute of Science,
Bombay-400032, India

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The Pechmann reaction of 4-hydroxycoumarins with cyclohexanone and ethyl cyclopentanone-2-carboxylates affords 1,2,3,4-tetrahydro[2]benzopyrano[4,3-*c*][1]benzopyran-5,12-diones and cyclopenta[3',4']pyrano-[3,2-*c*][1]benzopyran-4,11-diones. Dehydrogenation of the former yields [2]benzopyrano[4,3-*c*][1]benzopyran-5,12-diones. Alkaline hydrolysis of a typical compound Va affords 2-hydroxy-2'-carboxydeoxybenzoin which on boiling with acetic anhydride gives an isocoumarin derivative.

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The marked anticoagulant activity of 2*H*,5*H*-pyrano-[3,2-*c*][1]benzopyrans (1-3) prompted us to investigate the synthesis of compounds having the above heterocyclic system by the application of well-known Pechmann reaction.

For this purpose, 4-hydroxycoumarin derivatives were condensed with ethyl cyclohexanone-2-carboxylate in the presence of anhydrous potassium carbonate to obtain single crystalline substances in good yields (Table I).

Based on the mechanism given below (Scheme I), four structures are possible for the condensation product of 4-hydroxycoumarin with ethyl cyclohexanone-2-carboxylate. In the structures III and IV, the 4-hydroxycoumarin can react with the above ester in the tautomeric, that is, the 2-hydroxychromone form.

The uv spectrum (methanol) of a typical compound Ia (Table I) showed maxima at λ max nm (log ε): 220 (4.16), 275 (4.12), 345 (4.29).

The ir spectrum (potassium bromide) showed ν max cm^{-1} 1700 and 1750 (>C=O of α-pyrones). In the alternate structures (II, III, IV) the chromone carbonyl band would have appeared around 1660 cm^{-1}.

Its ^1H nmr spectrum (deuteriochloroform) showed signals at 1.8 (m, 4H, at C_2 and C_3), 2.5 (m, 2H, at C_1), 3.2 (m, 2H, at C_4), 7.2-8.2 (m, 4H, phenyl).

The compounds (Table I) were dehydrogenated with palladium on charcoal in diphenyl ether to yield crystalline solids which were assigned structures as [2]benzopyrano[4,3-*c*][1]benzopyran-5,12-diones (Table II).

The uv spectrum (dioxane) of Va (Table II) showed maxima at λ max nm (log ε): 240 (4.5), 340 (4.34).

Its ir (potassium bromide) showed absorption bands at 1720 cm^{-1}, 1745 cm^{-1} (>C=O of α-pyrones).

In order to confirm the assigned structures, compound Va was hydrolysed with aqueous sodium hydroxide to give a crystalline compound in about 50% yield. It had the

Scheme I

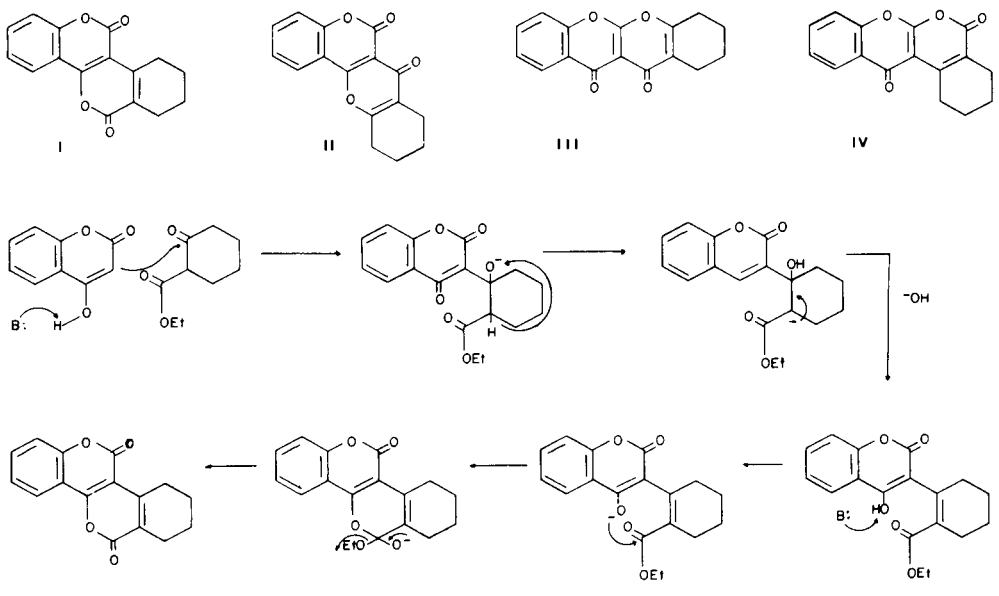
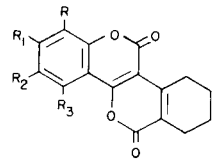


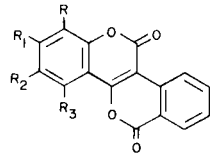
Table I



I

Compound	R	R_1	R_2	R_3	Mp °C	Molecular Formula	Analysis % Calculated C	Calculated H	Found C	Found H
Ia	H	H	H	H	210-211	$C_{16}H_{12}O_4$	71.63	4.77	71.42	4.51
Ib	H	H	CH_3	H	170-172	$C_{17}H_{14}O_4$	72.35	4.96	72.43	4.8
Ic	CH_3	H	H	H	216-217	$C_{17}H_{14}O_4$	72.35	4.96	72.41	4.82
Id	CH_3	H	CH_3	H	182-183	$C_{18}H_{16}O_4$	72.24	5.35	72.14	5.43
Ie	H	CH_3	H	CH_3	240-241	$C_{18}H_{16}O_4$	72.24	5.35	72.13	5.51
If	H	CH_3	H	H	175-176	$C_{17}H_{14}O_4$	72.35	4.96	72.25	5.04

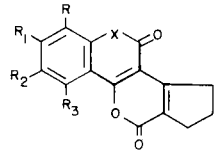
Table II



V

Compound	R	R_1	R_2	R_3	Mp °C	Molecular Formula	Analysis % Calculated C	Calculated H	Found C	Found H
Va	H	H	H	H	286-287	$C_{16}H_8O_4$	72.73	3.03	72.62	3.03
Vb	H	H	CH_3	H	223-225	$C_{17}H_{10}O_4$	71.71	3.59	71.84	3.71
Vc	CH_3	H	CH_3	H	225-227	$C_{18}H_{12}O_4$	73.98	4.11	74.16	4.06
Vd	H	CH_3	H	H	284-285	$C_{17}H_{10}O_4$	71.71	3.59	71.68	3.47
Ve	CH_3	H	H	H	225-226	$C_{17}H_{10}O_4$	71.71	3.59	71.85	3.49

Table III



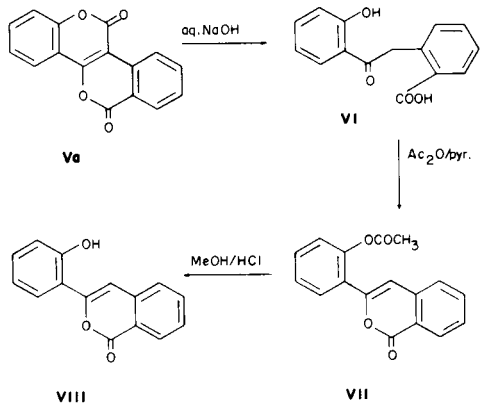
IX

Compound	R	R_1	R_2	R_3	X	Mp °C	Molecular Formula	Analysis % Calculated C	Calculated H	Found C	Found H
IXa	H	H	H	H	O	207-208	$C_{15}H_{10}O_4$	70.87	3.93	70.79	3.82
IXb	H	H	CH_3	H	O	201-202	$C_{16}H_{12}O_4$	71.64	4.47	71.63	4.56
IXc	CH_3	H	H	H	O	221-222	$C_{16}H_{12}O_4$	71.64	4.47	71.61	4.61
IXd	H	CH_3	H	CH_3	O	200-201	$C_{17}H_{14}O_4$	72.35	4.96	72.25	4.94
IXe	CH_3	H	H	CH_3	O	186-187	$C_{17}H_{14}O_4$	72.35	4.96	72.46	5.01
IXf	H	CH_3	H	H	O	177-178	$C_{16}H_{12}O_4$	71.64	4.47	71.59	4.65
IXg	H	H	H	H	S	204-205	$C_{15}H_{10}O_3S$	66.67	3.70	66.73	3.87
IXh	CH_3	H	H	H	S	206-207	$C_{16}H_{12}O_3S$	67.61	4.22	67.82	4.48
IXi	H	CH_3	H	H	S	240-241	$C_{16}H_{12}O_3S$	67.61	4.22	67.51	4.15

molecular composition $C_{15}H_{12}O_4$ (M^+ 256). It gave a red coloration with alcoholic ferric chloride and effervescence with aqueous sodium bicarbonate in which it dissolved and was reprecipitated on acidification. The ir spectrum (potassium bromide) showed ν max cm^{-1} at 2900 (OH of COOH), 3500 (free -OH) and 1670 (>C=O of COOH). Its ^1H nmr spectrum (acetone) showed signals at 4.5 (s, 2H, methylene), 5.8 (s, 1H, hydroxy), 6.4-7.9 (m, 8H, phenyl), 11.6 (s, 1H, carboxy).

Based on the above evidence, the hydrolysis product

Scheme II



was assigned structure as 2-hydroxy-2'-carboxydeoxybenzoin (VI). The latter on boiling with acetic acid anhydride and pyridine afforded a colourless crystalline compound VII identified as 3-(*o*-acetoxyphenyl)isocoumarin. This structure was fully consistent with the spectral and analytical data. The ir spectrum (nujol) did not show any hydroxyl band but bands at 1725 cm^{-1} and 1750 cm^{-1} (>C=O of ester and >C=O of lactone) were obtained. ^1H nmr (dueteriochloroform) showed signals at 1.4 (s, 3H, acetoxy), 6.0 (s, 1H, olefinic) and 6.3-7.0 (m, 8H, phenyl).

Further, VII could be deacetylated by refluxing with methanolic hydrochloric acid to give 3-(*o*-hydroxyphenyl)-isocoumarin (VIII). It did not give any coloration with alcoholic ferric chloride. Its ir spectrum (nujol) revealed absorption bands at 3270 cm^{-1} (-OH) and 1700 cm^{-1} (>C=O of lactone).

Similarly, 4-hydroxycoumarin and thiocoumarin derivatives were condensed with ethyl cyclopentanone-2-carboxylate to yield cyclopenta[3',4']pyrano[3,2-*c*][1]-benzopyran-4,11-diones and cyclopenta[3',4']pyrano-[3,2-*c*][1]benzothiopyran-4,11-diones respectively. (Table III). However, all attempts to dehydrogenate these compounds proved futile. Also, 4-hydroxythiocoumarins failed to condense with cyclohexanone-2-ethyl carboxylate.

Results.

The compounds in Table I (Ia-If) and in Table III (IXa-IXf) were tested by whole blood capillary method (4) in rats of Haffkine Strain (5) (either sex weighing 180-200 g) at the dose levels of 5 and 10 mg per kg adminstered intraperitonially daily.

Warfarin sodium (1 mg/kg ip) was used as positive control while 5% carboxymethyl cellulose (0.4 ml ip) was used as negative control. The clotting time of the animals was tested every 24 hours. Warfarin sodium produced 23, 30, 145 per cent increase in the clotting time 24, 48, 72 hours whereas the above compounds did not produce any increase over the control values.

The above compounds were also tested in rabbits (albino, weighing 1.2-1.4 kg) at the same dose levels employing the same route of administration and the blood was withdrawn from the marginal ear vein every half an hour to determine the clotting time by capillary method. However, no increase over the control values was observed in any case.

EXPERIMENTAL

All melting points were recorded in open capillaries and are uncorrected. The uv spectra were measured with a Hilger H-700 spectrophotometer. The ir spectra were recorded on a Perkin Elmer 127 spectrophotometer. The nmr spectra were recorded on a Varian 60 MHz spectrometer using TMS as the internal standard and chemical shifts are expressed as δ, parts per million. The homogeneity of the compounds was ascertained by tlc on silica gel G plates.

General Procedure for 1,2,3,4-Tetrahydro[2]benzopyrano[4,3-*c*][1]-benzopyran-5,12-diones (Table I).

A mixture of the appropriate 4-hydroxycoumarin (0.0006 mole), ethyl cyclohexanone-2-carboxylate (0.016 mole) and potassium carbonate (5 mg) was heated on a water bath for 6 hours. On cooling, the reaction mixture deposited the dione as colourless needles. These were filtered, washed with aqueous sodium bicarbonate and water and then crystallized from methanol.

General Procedure for Cyclopenta[3',4']pyrano[3,2-*c*][1]benzopyran-4,11-diones and cyclopenta-3',4'-pyrano[3,2-*c*][1]benzothiopyran-4,11-diones (Table III).

A mixture of the appropriate 4-hydroxycoumarin or 4-hydroxythiocoumarin (0.0006 mole), ethyl cyclopentanone-2-carboxylate (0.016 mole) and potassium carbonate (5 mg) was heated on a water bath for 6 hours. On cooling the reaction mixture deposited the dione. It was filtered, washed with aqueous sodium bicarbonate and then with water, and crystallised from methanol.

General Procedure for [2]Benzopyrano[4,3-*c*][1]benzopyran-5,12-diones (Table II).

The appropriate 1,2,3,4-tetrahydro[2]benzopyrano[1]benzopyran-5,12-dione (0.0004 mole) and palladium charcoal (10%) (10 mg) were taken in 10 ml of diphenyl ether and refluxed for 6 hours. The reaction mixture was filtered hot. On cooling, a crystalline solid separated which was subsequently washed with diethyl ether and crystallised from benzene.

2-Hydroxy-2'-carboxydeoxybenzoin (VI).

The dione Va (0.0013 mole) was refluxed with aqueous sodium hydroxide (30%, 6 ml) for 6 hours. On cooling the reaction mixture was neutralized by concentrated hydrochloric acid. The solid which separated was filtered, washed with water and crystallised from benzene, mp 160-161°.

Anal. Calcd. for $C_{15}H_{12}O_4$: C, 70.6; H, 4.3. Found: C, 70.8; H, 4.4.

3-(*o*-Acetoxyphenyl)isocoumarin (VII).

A mixture of 2-hydroxy-2'-carboxydeoxybenzoin (VI) (0.00058 mole), acetic anhydride (2 ml) and a few drops of pyridine was refluxed for 4 hours. On cooling, the reaction mixture was decomposed on ice-hydrochloric acid and allowed to stand overnight. The solid which separated was filtered and crystallised from petroleum ether (40-60°) as white needles, mp 93-94°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.52; H, 4.30. Found: C, 72.55; H, 4.51.

3-(*o*-Hydroxyphenyl)isocoumarin (VIII).

3-(*o*-Acetoxyphenyl)isocoumarin (0.0003 mole) and methanolic hydrochloric acid (1:2, 5 ml) was refluxed on water bath for 6 hours. The reaction mixture was cooled and the solid that separated was filtered, washed with water and crystallised from benzene as colourless needles, mp 180-181°.

Anal. Calcd. for $C_{15}H_{10}O_4$: C, 75.6; H, 4.2. Found: C, 75.3; H, 4.51.

REFERENCES AND NOTES

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