1348. *Chromeno-oxazines*

By J. Hill and G. R. Ramage

Routes to derivatives of the tricyclic system 6-oxo-2*H*,6*H*-chromeno[7,6-*b*]-[1,4]-oxazine (III) are described. 3-Methyldihydrochromeno-oxazines (I) and 3-oxodihydrochromeno-oxazines (VII) were synthesised from the 3-methylbenzoxazine (IV) and the 3-oxobenzoxazine (V; R = H) respectively. Reduction of the chromone (VI; R = CH_2Ac) led to both dihydrochromeno-oxazines (I) and tetrahydrochromeno-oxazines (IX), as well as the hydroxychromeno-oxazine (X).

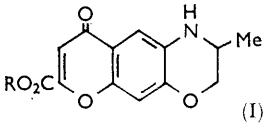
Many chromone derivatives which possess spasmolytic properties have been described recently.[1-3] Emphasis has been laid on the introduction into chromones of basic groups, leading to enhanced solubility through salt formation and, in certain cases, marked pharmacological activity.[4,5] We attempted to synthesise basic chromones (*e.g.*, I; R = Et) which are aza-analogues of the spasmolytically active, but sparingly soluble, pyranochromones (II; R = H, Me, CO_2H, or CO_2Et).[2] Such basic chromones are derivatives of the novel tricyclic system 6-oxo-2*H*,6*H*-chromeno[7,6-*b*]-[1,4]-oxazine (III).

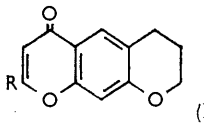
Chromeno-oxazines were synthesised from the benzoxazines (IV) and (V; R = H) or, alternatively, from the chromone (VI; R = H).

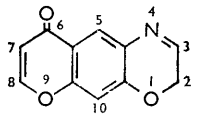
6-Acetyl-3,4-dihydro-7-hydroxy-3-methyl-2*H*-1,4-benzoxazine (IV)[6] was condensed with diethyl oxalate and the product cyclised to 8-ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2*H*,6*H*-chromeno[7,6-*b*]-[1,4]-oxazine (I; R = Et) which afforded the corresponding acid (I; R = H) on hydrolysis. The chromeno-oxazine (I; R = Et) was not appreciably basic and was sparingly soluble in 5N-hydrochloric acid. No trace of hydrochloride formation could be detected when the compound was treated with ethanolic hydrogen chloride.

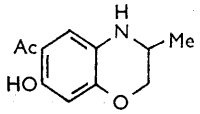
[1] C. Mentzer and H. Pacheco, Fr. P. 1,288,710/1962.
[2] P. Naylor and G. R. Ramage, *J.*, 1960, 1956.
[3] P. da Re, *et al.*, *Farmaco* (*Pavia*) *Ed. sci.*, 1958, **13**, 561 (*Chem. Abs.*, 1960, **54**, 517).
[4] B. Reichert, *Arch. Pharm.*, 1960, **293**, 111.
[5] P. da Re, *et al.*, *Boll. Chim. farm.*, 1960, **99**, 3 (*Chem. Abs.*, 1960, **54**, 11,009).
[6] J. Hill and G. R. Ramage, *J.*, 1964, 3709.

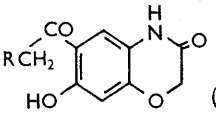
3-Oxochromeno-oxazines (VII) were prepared in a similar manner. 6-Acetyl-3,4-dihydro-7-hydroxy-3-oxo-2*H*-1,4-benzoxazine (V; R = H) [6] was condensed with diethyl oxalate and the resulting diketone (V; R = CO·CO_2Et) was cyclised in ethanolic hydrogen chloride to 8-ethoxycarbonyl-3,4-dihydro-3,6-dioxo-2*H*,6*H*-chromeno[7,6-*b*]-[1,4]-oxazine

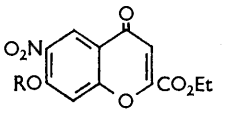

(I)


(II)


(III)


(IV)

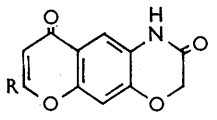

(V)

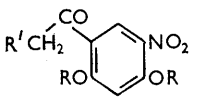

(VI)

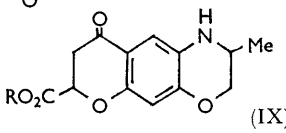
(VII; R = CO_2Et). Cyclisation of the diketone under aqueous conditions yielded the corresponding acid (VII; R = CO_2H) which on decarboxylation gave the 3-oxochromeno-oxazine (VII; R = H).

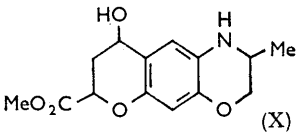
Condensation of 5-nitroresacetophenone diacetate (VIII; R = Ac, R′ = H) with diethyl oxalate followed by cyclisation gave the chromone (VI; R = H) which was used in the alternative approach to the chromeno-oxazine system. Its acetonyl ether (VI; R = CH_2Ac) was expected to undergo reductive cyclisation to form the chromeno-oxazine (I; R = Et). However, catalytic reduction (Raney nickel) of a suspension of the chromone ether (VI; R = CH_2Ac) in ethanol led only to the tetrahydrochromeno-oxazine (IX; R = Et). Unlike the corresponding dihydrochromeno-oxazine (I; R = Et), the tetrahydro-derivative was appreciably basic, being soluble in dilute hydrochloric acid.

With methanol as solvent, reduction of the chromone ether proceeded smoothly to the dihydrochromeno-oxazine methyl ester (I; R = Me), and on adsorption of a further equivalent of hydrogen the tetrahydrochromeno-oxazine methyl ester (IX; R = Me) was formed. Reduction to completion gave the 6-hydroxychromeno-oxazine (X) which was also prepared by reduction of a solution of the dihydrochromeno-oxazine (I; R = Et) in methanol.


(VII)


(VIII)


(IX)


(X)

The ease of the trans-esterification (catalysed presumably by traces of alkali in the Raney nickel), which occurs during reduction in methanol, was demonstrated by the quantitative conversion of the ethyl ester (I; R = Et) into the methyl ester (I; R = Me) when a solution of the former in methanol, with Raney nickel or a trace of sodium methoxide as catalyst, was set aside for several hours at room temperature. Attempts to reduce the chromone ether (VI; R = CH_2Ac) in non-hydroxylic solvents were unsuccessful.

Some details of the infrared and ultraviolet absorption spectra of the 3-methylchromeno-oxazines are tabulated below. The dihydrochromeno-oxazines (I) can be readily distinguished from the tetrahydrochromeno-oxazines (IX) by inspection of their infrared spectra, the absorption band of the ring-carbonyl group occurring at 6·10 μ in the former case and at 5·99 μ in the latter. In the ultraviolet, the spectra of the dihydrochromeno-oxazines differ in the long-wavelength region (above 350 mμ) from those of the tetrahydrochromeno-oxazines, whose absorption patterns are similar to that of the benzoxazine (IV). As

expected, the 6-hydroxychromeno-oxazine (X) which lacks the ring-carbonyl chromophore, exhibits no absorption above 350 mμ.

Infrared absorption spectra in Nujol mulls

Substance	Wavelength of absorption in μ: NH stretching	Ester carbonyl	Ring-carbonyl
Chromone (VI; R = H)		5·77	6·06
Dihydrochromeno-oxazine (I; R = Et)	2·96 (m)	5·77	6·10
Dihydrochromeno-oxazine (I; R = Me)	2·97 (m)	5·78	6·10
Tetrahydrochromeno-oxazine (IX; R = Et)	3·00 (m)	5·75	5·99
Tetrahydrochromeno-oxazine (IX; R = Me)	2·95 (m)	5·70	5·99
Hydroxychromeno-oxazine (X)	2·95 (3·12) [a]	5·71	

[a] OH stretching.

(m): Medium strength absorption (40—50% of the strongest absorption band). All other bands given are strong (over 60% of the strongest absorption band).

Ultraviolet absorption spectra in methanol solution

Substance	Absorption maxima: in mμ ($\log_{10}\varepsilon$)
Dihydrochromeno-oxazine (I; R = Et)	256 (4·3), 294 (3·8), 404 (3·8)
Dihydrochromeno-oxazine (I; R = Me)	256 (4·4), 293 (3·9), 403 (3·9)
Tetrahydrochromeno-oxazine (IX; R = Et)	255 (4·2), *ca.* 284,[b] 377 (3·5)
Tetrahydrochromeno-oxazine (IX; R = Me)	256 (4·2), 284 (3·8), 378 (3·4)
Benzoxazine (IV)	253 (4·3), 283 (3·9), 378 (3·6)
Hydroxychromeno-oxazine (X)	241 (3·6), 304 (3·4)

[b] Shoulder.

Experimental

8-*Ethoxycarbonyl*-3,4-*dihydro*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (I; R = Et).—A mixture of 6-acetyl-3,4-dihydro-7-hydroxy-3-methyl-2*H*-1,4-benzoxazine [6] (0·5 g.), diethyl oxalate (5 ml.), and sodium ethoxide (0·25 g. of sodium in the minimum of ethanol), was heated during 60 min. on the water-bath. Ether was added to the cooled solution and the solid obtained on filtration was washed with ether and stirred into 10% hydrochloric acid. The mixture was extracted with ether, the dried ethereal extract evaporated, and the residue heated under reflux with saturated ethanolic hydrogen chloride (5 ml.) for 1 hr. Evaporation, and trituration of the residue with aqueous sodium carbonate, yielded a yellow solid which was crystallised from ethanol to give 8-*ethoxycarbonyl*-3,4-*dihydro*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*-[7,6-*b*]-[1,4]-oxazine (0·4 g.) as golden blades, m. p. 191—192° (Found: C, 62·2; H, 5·3; N, 4·8. $C_{15}H_{15}NO_5$ requires C, 62·3; H, 5·2; N, 4·8%).

8-*Carboxy*-3,4-*dihydro*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (I; R = H).—The 8-ethoxycarbonylchromeno-oxazine (I; R = Et) (0·3 g.) was heated under reflux during 2 hr. with glacial acetic acid (2 ml.) and sulphuric acid (2 ml. of 4N). On cooling, 8-*carboxy*-3,4-*dihydro*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* separated as its *monohydrate* (0·24 g.), brown plates (from aqueous dioxan), m. p. 286—287° (decomp.) (Found: C, 56·2; H, 4·4. $C_{13}H_{13}NO_6$ requires C, 55·9; H, 4·7%). Drying for 4 hr. at 135°/5 mm. converted the monohydrate into the *anhydrous acid*, m. p. 290—292° (decomp.) (Found: C, 59·5; H, 4·6. $C_{13}H_{11}NO_5$ requires C, 59·8; H, 4·2%).

6-(3-*Ethoxycarbonyl*-3-*oxopropionyl*)-3,4-*dihydro*-7-*hydroxy*-3-*oxo*-2H-1,4-*benzoxazine* (V; R = $CO{\cdot}CO_2Et$).—A solution of 6-acetyl-3,4-dihydro-7-hydroxy-3-oxo-2*H*-1,4-benzoxazine [6] (0·75 g.) in diethyl oxalate (20 ml.) was heated during 30 min. on the water-bath with a solution of sodium ethoxide (0·45 g. of sodium in 10 ml. of ethanol). The resulting mixture was kept for 30 min. at room temperature, cooled and stirred with ether, filtered, the solid washed with ether and then stirred well with hydrochloric acid (15 ml. of 2N). 6-(3-*Ethoxycarbonyl*-3-*oxopropionyl*)-3,4-*dihydro*-7-*hydroxy*-3-*oxo*-2H-1,4-*benzoxazine* (0·88 g.) was obtained and crystallised from methanol as yellow cubes, m. p. 215—216° (block preheated to 160°) (Found: C, 54·6; H, 4·0. $C_{14}H_{13}NO_7$ requires C, 54·7; H, 4·3%).

8-*Ethoxycarbonyl*-3,4-*dihydro*-3,6-*dioxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (VII; R = CO_2Et).—The diketone (V; R = $CO{\cdot}CO_2Et$) (0·2 g.) was heated under reflux with saturated

ethanolic hydrogen chloride (8 ml.) during 15 min. On cooling, *8-ethoxycarbonyl-3,4-dihydro-3,6-dioxo-2H,6H-chromeno*[7,6-b]-[1,4]-*oxazine* (0·16 g.) separated, and crystallised from dioxan as yellow needles, m. p. 295—297° (Found: C, 58·0; H, 3·7; N, 5·0. $C_{14}H_{11}NO_6$ requires C, 58·1; H, 3·8; N, 4·8%).

8-Carboxy-3,4-dihydro-3,6-dioxo-2H,6H-chromeno[7,6-b]-[1,4]-*oxazine* (VII; R = CO_2H).—The diketone (V; R = $CO{\cdot}CO_2Et$) (3·7 g.) was heated under reflux with glacial acetic acid (30 ml.) and concentrated hydrochloric acid (6 ml.) during 2 hr. On cooling, *8-carboxy-3,4-dihydro-3,6-dioxo-2H,6H-chromeno*[7,6-b]-[1,4]-*oxazine monohydrate* (2·85 g.) separated, and crystallised from methanol as needles, m. p. 310° (decomp.) (Found: C, 51·6; H, 3·4. $C_{12}H_9NO_7$ requires C, 51·6; H, 3·2%). Drying for 2 hr. at 135°/4 mm. converted the monohydrate into the *anhydrous acid*, m. p. 305° (decomp.) (Found: C, 55·3; H, 3·1; N, 5·3. $C_{12}H_7NO_6$ requires C, 55·2; H, 2·7; N, 5·4%).

3,4-Dihydro-3,6-dioxo-2H,6H-chromeno[7,6-b]-[1,4]-*oxazine* (VII; R = H).—The acid (VII; R = CO_2H) (0·7 g.) was heated at 280—305°/1 mm. to give, on sublimation, *3,4-dihydro-3,6-dioxo-2H,6H-chromeno*[7,6-b]-[1,4]-*oxazine* (0·5 g.), purified by resublimation, m. p. 330—333° (decomp.) (Found: C, 60·6; H, 3·6; N, 6·5. $C_{11}H_7NO_4$ requires C, 60·8; H, 3·2; N, 6·5%).

5-Nitroresacetophenone Diacetate (VIII; R = Ac, R′ = H).—5-Nitroresacetophenone [7] (80 g.) was shaken during 10 min. with acetic anhydride (200 ml.) and pyridine (5 ml.) and the resulting solution then warmed at 35—40° during 15 min. The solution was kept at room temp. during 30 min., poured into water (1500 ml.), and the mixture stirred well for 30 min. The mixture was filtered and the solid was crystallised twice from ethanol to yield *5-nitroresacetophenone diacetate* (93 g.), cream plates (from ethanol), m. p. 90° (Found: C, 51·3; H, 4·0; N, 5·2. $C_{12}H_{11}NO_7$ requires C, 51·2; H, 3·9; N, 5·0%).

4-(3-Ethoxycarbonyl-3-oxopropionyl)-6-nitroresorcinol (VIII; R = H, R′ = $CO{\cdot}CO_2Et$).—Ethanolic sodium ethoxide (3·24 g. of sodium in 80 ml. of ethanol) was added, in two equal portions, to a stirred solution of 5-nitroresacetophenone diacetate (10 g.) in diethyl oxalate (25 ml.) and diethylene glycol dimethyl ether (50 ml.). The first portion was added during 15 min. and the second during 2 min., the temperature being maintained below 5°. The mixture was heated slowly, during 15 min., to a temperature of 75°, and then stirred for a further 15 min. with the source of heat removed. On slurrying the mixture with ether, a solid was obtained which was stirred into 10% hydrochloric acid and the resulting mixture was extracted with ether. Evaporation of the dried ether extract, and crystallisation of the residue from carbon tetrachloride, gave *4-(3-ethoxycarbonyl-3-oxopropionyl)-6-nitroresorcinol* (2·45 g.), yellow needles (from carbon tetrachloride), m. p. 130° (Found: C, 48·5; H, 3·9. $C_{12}H_{11}NO_8$ requires C, 48·5; H, 3·7%).

2-Ethoxycarbonyl-7-hydroxy-6-nitrochromone (VI; R = H).—4-(3-Ethoxycarbonyl-3-oxopropionyl)-6-nitroresorcinol (2·4 g.) was heated under reflux with saturated ethanolic hydrogen chloride (15 ml.) during 40 min. The mixture was cooled and filtered to give *2-ethoxycarbonyl-7-hydroxy-6-nitrochromone* (2·1 g.), fawn prisms (from ethanol), m. p. 199° (Found: C, 51·8; H, 3·3; N, 5·3. $C_{12}H_9NO_7$ requires C, 51·6; H, 3·2; N, 5·0%).

2-Carboxy-7-hydroxy-6-nitrochromone.—The ester (VI; R = H) (0·5 g.) was heated under reflux with glacial acetic acid (5 ml.) and concentrated hydrochloric acid (1 ml.) during 1 hr. On cooling, *2-carboxy-7-hydroxy-6-nitrochromone* (0·25 g.) separated as needles, m. p. 280—281° (Found: C, 47·9; H, 2·2. $C_{10}H_5NO_7$ requires C, 47·8; H, 2·0%).

7-Acetonyloxy-2-ethoxycarbonyl-6-nitrochromone (VI; R = CH_2Ac).—2-Ethoxycarbonyl-7-hydroxy-6-nitrochromone (3·95 g.), anhydrous potassium carbonate (2·06 g.), potassium iodide (0·5 g.), chloroacetone (1·45 ml.), and acetone (100 ml.), were heated under reflux, with stirring, during 6 hr. The mixture was filtered, the filtrate concentrated by evaporation to a volume of 25 ml. and stirred with ethanol (10 ml.) to give *7-acetonyloxy-2-ethoxycarbonyl-6-nitrochromone* (3·3 g.), needles (from acetone), m. p. 186° (Found: C, 53·4; H, 3·5. $C_{15}H_{13}NO_8$ requires C, 53·7; H, 3·9%).

8-Ethoxycarbonyl-3,4,7,8-tetrahydro-3-methyl-6-oxo-2H,6H-chromeno[7,6-b]-[1,4]-*oxazine* (IX; R = Et).—A suspension of 7-acetonyloxy-2-ethoxycarbonyl-6-nitrochromone (0·96 g.) in ethanol (60 ml.) was shaken under hydrogen, with Raney nickel prepared by Nishimura's method,[8] until the volume of hydrogen adsorbed was 286 ml. measured at 25° and 734 mm. The mixture was filtered, the filtrate evaporated, and the residue was crystallised from ethanol to

[7] R. E. Omer and C. S. Hamilton, *J. Amer. Chem. Soc.*, 1937, **59**, 642.
[8] S. Nishimura, *Bull. Chem. Soc. Japan*, 1959, **32**, 61.

yield 8-*ethoxycarbonyl*-3,4,7,8-*tetrahydro*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (0·61 g.), fawn prisms (from ethanol), m. p. 164—165° (Found: C, 61·8; H, 5·7. $C_{15}H_{17}NO_5$ requires C, 61·8; H, 5·9%).

3,4-*Dihydro*-8-*methoxycarbonyl*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (I; R = Me).—(i) 7-Acetonyloxy-2-ethoxycarbonyl-6-nitrochromone (0·87 g.) was shaken with methanol (50 ml.) and Raney nickel, under hydrogen, until the volume of hydrogen adsorbed was 258 ml. (4 moles of hydrogen per mole of chromone, measured at 25°/745 mm.). The mixture was filtered, the filtrate evaporated, and the residue crystallised from methanol to give 3,4-*dihydro*-8-*methoxycarbonyl*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (0·3 g.), yellow blades (from methanol), m. p. 229—230° (Found: C, 61·4; H, 5·0; N, 5·3. $C_{14}H_{13}NO_5$ requires C, 61·1; H, 4·8; N, 5·1%).

(ii) A solution of the chromeno-oxazine ethyl ester (I; R = Et) (50 mg.) in methanol (20 ml.) was kept for 6 hr. at room temperature with sodium methoxide (from 10 mg. of sodium). Glacial acetic acid (0·1 ml.) was added and the solution was evaporated to give the chromeno-oxazine methyl ester (I; R = Me), m. p. 229—230° (from methanol), identical to the material prepared by method (i).

A similar result was obtained when the experiment was repeated using Raney nickel as catalyst in place of sodium methoxide.

3,4,7,8-*Tetrahydro*-8-*methoxycarbonyl*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (IX; R = Me).—7-Acetonyloxy-2-ethoxycarbonyl-6-nitrochromone (0·5 g.) was shaken under hydrogen with methanol (40 ml.) and Raney nickel, until the uptake of hydrogen was 185 ml. (5 moles of hydrogen per mole of chromone, measured at 25°/753 mm.). The mixture was filtered, the filtrate evaporated, and the residue crystallised from methanol to give 3,4,7,8-*tetrahydro*-8-*methoxycarbonyl*-3-*methyl*-6-*oxo*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (0·12 g.), yellow prisms (from methanol), m. p. 158—159° (Found: C, 60·1; H, 5·7. $C_{14}H_{15}NO_5$ requires C, 60·6; H, 5·5%).

Treatment with 2,4-dinitrophenylhydrazine yielded a 2,4-*dinitrophenylhydrazone*, red needles (from ethanol), m. p. 260° (decomp.) (Found: C, 52·5; H, 4·3. $C_{20}H_{19}N_5O_8$ requires C, 52·5; H, 4·2%).

3,4,7,8-*Tetrahydro*-6-*hydroxy*-8-*methoxycarbonyl*-3-*methyl*-2H,6H-*chromeno*[7,6-b]-[1,4]-*oxazine* (X).—(*a*) 7-Acetonyloxy-2-ethoxycarbonyl-6-nitrochromone (1 g.) was shaken under hydrogen with methanol (50 ml.) and Raney nickel, until no further uptake of hydrogen was observed. The mixture was filtered, the filtrate evaporated, and the residue crystallised from ethanol to yield 3,4,7,8-*tetrahydro*-6-*hydroxy*-8-*methoxycarbonyl*-3-*methyl*-2H,6H-*chromeno*[7,6-b]-1,4-*oxazine* (0·35 g.), cream blades (from ethanol), m. p. 170—171° (Found: C, 60·3; H, 6·1. $C_{14}H_{17}NO_5$ requires C, 60·2; H, 6·1%).

(*b*) 8-Ethoxycarbonyl-3,4-dihydro-3-methyl-6-oxo-2H,6H-chromeno[7,6-b]-[1,4]-oxazine (0·65 g.) was reduced in methanol solution, as under method (*a*), to give the 6-hydroxychromeno-oxazine (X) (0·32 g.), cream blades (from ethanol), m. p. 170—171°, identical to the sample prepared by method (*a*).

The authors are indebted to the D.S.I.R. for a Studentship (to J. H.).

THE ROYAL COLLEGE OF ADVANCED TECHNOLOGY,
SALFORD, LANCS.

[*Received, June 11th,* 1965.]