[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

REACTIONS OF COUMARIN-3-CARBOXYLIC ACID WITH KETONES AND METHYLAMINE[1]

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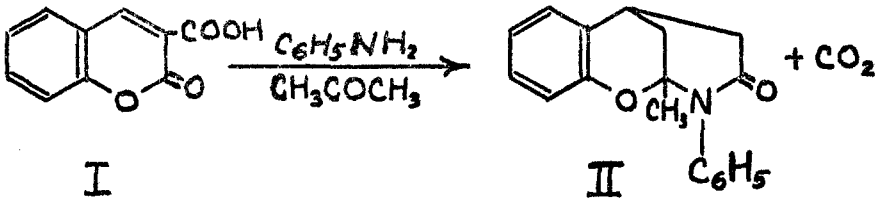
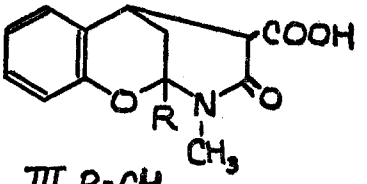
Coumarin-3-carboxylic acid (I) reacts with acetone and aromatic amines to form compounds, for example II, related to 4-(*o*-hydroxyphenyl)piperidine (1). Since such substances were of interest in connection with a projected morphine syntheses (2), some extensions of the reaction by which they are formed were investigated. It was found that methylamine could be used instead of an aromatic amine, and that various ketones could be used instead of acetone.



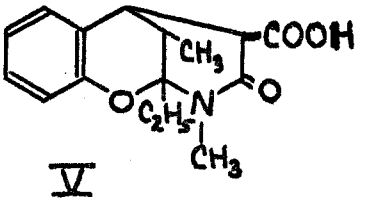
I II

Decarboxylation could not be avoided in reactions involving aromatic amines, but when methylamine was used, carboxylic acids were isolated. The acids produced lost carbon dioxide at about 150°.



III, R = CH_3

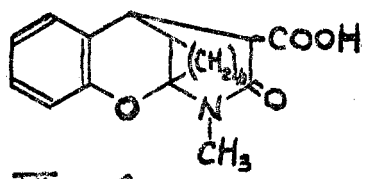
IV, R = C_6H_5



V

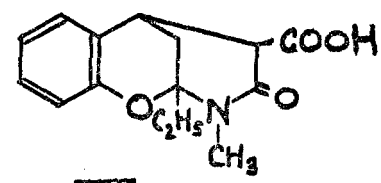
Acetophenone reacted like acetone, giving IV. Diethyl ketone, cyclopentanone, and cyclohexanone yielded disubstituted derivatives V, VI, and VII. Methyl ethyl ketone underwent condensation on its methyl and not on its methylene group; for lactone IX, obtained from the product (VIII) by decarboxylation and hydrolysis, gave no iodoform with alkaline hypoiodite. The analogous lactone (X) from III gave a positive iodoform test.

[1] From the Ph.D. thesis of Marshall C. Freerks, July, 1949.

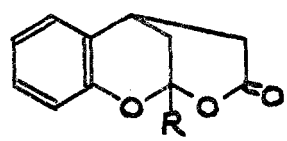


VI, $n=3$

VII, $n=4$



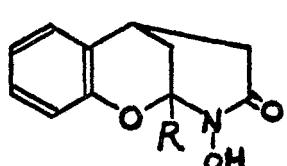
VIII



IX, $R=C_2H_5$

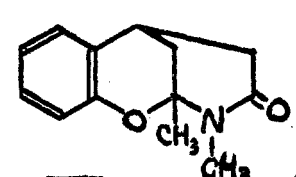
X, $R=CH_3$

It was previously reported (1) that the oxy-oxo-acid corresponding to X gave an oxime. The same product was obtained in the present work directly from X with hydroxylamine hydrochloride in pyridine, but it appeared to be a hydroxamic acid (XI). It was soluble in alkali, gave a red color with ferric chloride, and was not soluble in aqueous carbonate. Similarly IX formed a hydroxamic acid (XII).



XI, $R=CH_3$

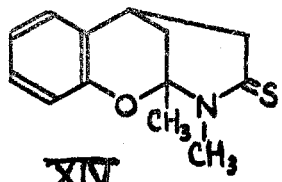
XII, $R=C_2H_5$



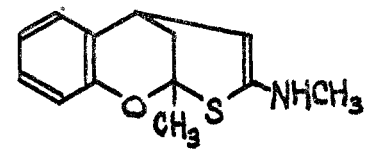
XIII

Some attempts were made to convert lactam XIII (from III by decarboxylation) into an amine. Hydrogenation with Raney nickel below 125° caused no change; and at higher temperature, part of the starting material was recovered and part was converted into a neutral sirup. Electrolytic reduction with lead electrodes in alcoholic hydrochloric acid caused no change; treatment with sodium in butyl alcohol gave an inhomogeneous amphoteric product which furnished no crystalline derivatives. Lithium aluminum hydride was not available when the work was being done, but XIII was recovered unchanged after it had been treated with methylmagnesium iodide.

With phosphorus pentasulfide, XIII gave the corresponding thiolactam, XIV. This substance was not affected by amalgamated aluminum and gave an unworkably small yield of a basic sulfur-free product (m.p. 170°) when treated with Raney nickel. Electrolytic reduction of the thiolactam was also unsuccessful;



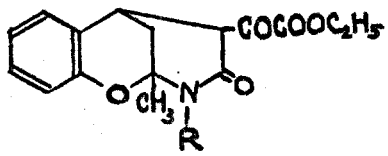
XIV



XV

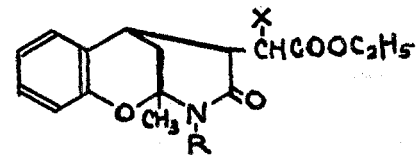
part of the material was recovered unchanged, and part was recovered in an isomerized form. The isomerization led to a secondary amine, XV, and was brought about best by the controlled action of hydrochloric acid on XIV. Prolonged action of hydrochloric acid caused elimination of hydrogen sulfide and methylamine, with formation of X.

To secure model compounds for the morphine synthesis referred to above, it was of interest to examine the possibility of attaching a side chain to position 3 of lactam XIII. Ethyl oxalate condensed with the lactam forming XVI, and this substance was hydrogenated with amalgamated aluminum or with hydrogen and Raney nickel to a mixture of diastereoisomeric hydroxy compounds, XVIII.



XVI, R = CH_3

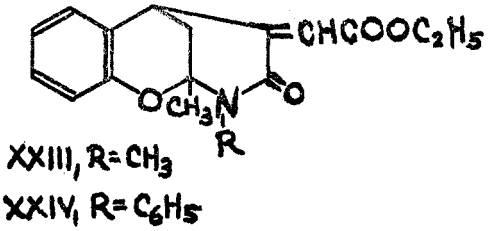
XVII, R = C_6H_5



XVIII, R = CH_3, X = OH

XIX	CH_3	$OCOCH_3$
XX	CH_3	$OSO_2C_7H_7$
XXI	C_6H_5	OH
XXII	C_6H_5	$OCOCH_3$

Acetylation of this mixture gave the mixed acetyl derivatives (XIX), from which only one form was isolated in a pure state. However, two forms of the corresponding *p*-toluenesulfonyl derivative (XX) were isolated. The acyl derivatives were unchanged by hot collidine, but with sodium acetate at 200° they gave the unsaturated compound XXIII. In no case, however, was the yield satisfactory.



XXIII, R = CH_3

XXIV, R = C_6H_5

Introduction of a side chain into lactam II was also studied. Condensation of this lactam with ethyl oxalate furnished XVII. Reduction of the oxalo-derivative with amalgamated aluminum gave two diastereoisomers (XXI), whereas hydrogen and Raney nickel gave only one in poor yield. Acetylation of the mixture (XXI) gave a mixture of acetates (XXII), and pyrolysis of this with sodium acetate furnished the unsaturated ester XXIV.

EXPERIMENTAL

The lactam carboxylic acids. A mixture of 10 g. of coumarin-3-carboxylic acid, 45 ml. of a ketone, and 12 ml. of 25% aqueous methylamine was treated with enough alcohol to bring about formation of one liquid phase (some solid was not dissolved). After it had been kept at room temperature for three days, the mixture was heated for one hour on a steam-bath and then evaporated to a sirup. This was stirred with 10 ml. of concentrated hydrochloric acid and then with 50 ml. of water, and finally allowed to stand for several hours. The product was removed, dissolved in sodium carbonate solution, washed with ether, reprecipitated with dilute hydrochloric acid, and crystallized from dilute alcohol. All of the acids formed colorless needles that melted with gas evolution at 150°.

2-Methyl-2-methylaminochroman-4-malonic acid lactam (III) was formed from acetone in a yield of 69%.

Anal. Calc'd for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8.
Found: C, 64.5; H, 6.0.

This lactam formed a white microcrystalline insoluble silver salt; treatment of the dried salt with excess methyl iodide in benzene gave a 75% yield of the corresponding *lactam methyl ester*, prisms from dilute methanol, m.p. 140°.

Anal. Calc'd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2.
Found: C, 65.4; H, 6.4.

2-Ethyl-2-methylaminochroman-4-malonic acid lactam (VIII) was formed from methyl ethyl ketone in 81.5% yield.

Anal. Calc'd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2.
Found: C, 65.4; H, 6.2.

2-Methylamino-2-phenylchroman-4-malonic acid lactam (IV) was formed from acetophenone in a yield of 47%.

Anal. Calc'd for $C_{19}H_{17}NO_4$: C, 67.7; H, 6.4.
Found: C, 67.9; H, 6.4.

2-Ethyl-3-methyl-2-methylaminochroman-4-malonic acid lactam (V) was formed from diethyl ketone in 26% yield. The relatively poor yield was caused, at least in part, by not adding alcohol to the reaction mixture. Whenever two liquid phases were present, much of the coumarin carboxylic acid was degraded to salicylaldehyde, 3 g. of which was isolated in this preparation.

Anal. Calc'd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6.
Found: C, 66.6; H, 6.6.

2-Methylamino-2,3-cyclopentachroman-4-malonic acid lactam (VI) was formed from cyclopentanone in 86% yield.

Anal. Calc'd for $C_{16}H_{17}NO_4$: C, 66.9; H, 6.0.
Found: C, 66.8; H, 6.0.

2-Methylamino-2,3-cyclohexachroman-4-malonic acid lactam (VII) was formed from cyclohexanone in 78% yield.

Anal. Calc'd for $C_{17}H_{19}NO_4$: C, 67.8; H, 6.4.
Found: C, 67.9; H, 6.4.

Decarboxylations. When the preceding acids were heated at 150°, they lost carbon dioxide. The products were crystallized from ether-ligroin or dilute alcohol, forming colorless prisms.

2-Methyl-2-methylaminochroman-4-acetic acid lactam (XIV), from III in 86% yield, had m.p. 110°.

Anal. Calc'd for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0.
Found: C, 71.7; H, 7.2.

2-Ethyl-2-methylaminochroman-4-acetic acid lactam, from VIII in 53% yield, had m.p. 89–90°.

Anal. Calc'd for $C_{14}H_{17}NO_2$: C, 72.7; H, 7.4.
Found: C, 72.7; H, 7.4.

2-Methylamino-2-phenylchroman-4-acetic acid lactam, from IV in 53% yield, had m.p. 162–163°.

Anal. Calc'd for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.1.
Found: C, 77.4; H, 6.4.

2-Ethyl-3-methyl-2-methylaminochroman-4-acetic acid lactam, from V in 31% yield, had m.p. 122–123°.

Anal. Calc'd for $C_{15}H_{19}NO_2$: C, 73.5; H, 7.8.
Found: C, 73.6; H, 7.9.

2-Methylamino-2,3-cyclopentachroman-4-acetic acid lactam, from VI in 50% yield, had m.p. 116–118°.

Anal. Calc'd for $C_{15}H_{17}NO_2$: C, 74.0; H, 7.0.
Found: C, 73.9; H, 7.1.

2-Methylamino-2,3-cyclohexachroman-4-acetic acid lactam, from VII in 51% yield, had m.p. 113–114°.

Anal. Calc'd for $C_{16}H_{19}NO_2$: C, 74.7; H, 7.4.
Found: C, 74.8; H, 7.3.

Hydrolysis of lactam XIII, and structure proof of VIII. A mixture of 2 g. of XIII and 10 ml. of conc'd hydrochloric acid was heated under reflux for one hour and then allowed to stand for 15 hours. The solid was removed, and the mother liquor was heated for one hour more. The combined insoluble products from the two treatments were crystallized from ether giving 53% of 2-methyl-2-hydroxychroman-4-acetic acid lactone (X), colorless needles, m.p. 147–148° [reported (1) 148°]. When 50 mg. of X was dissolved in 4 ml. of dioxane containing 1.5 ml. of 10% sodium hydroxide and treated with iodine-potassium iodide, iodoform, m.p. 119–120°, was produced. A solution of 0.8 g. of X and 0.8 g. of hydroxylamine hydrochloride in 5 ml. of pyridine and 5 ml. of methanol was boiled for three hours and then evaporated at 100°. The product was washed with water and methanol and then crystallized from methanol, giving the N-hydroxylactam (XII), m.p. 197° [reported (1) 197–198°]. This substance was insoluble in bicarbonate but soluble in dilute sodium hydroxide, and gave a deep red color with ferric chloride.

A mixture of 5 g. of VIII and 10 ml. of conc'd hydrochloric acid treated in the same way as described for the methyl homolog gave 68% of 2-ethyl-2-hydroxy-chroman-4-acetic acid lactone (IX) colorless needles, m.p. 142°. The lactone gave no iodoform with sodium hypoiodite in aqueous dioxane.

Anal. Calc'd for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5.
Found: C, 71.6; H, 6.5.

With hydroxylamine hydrochloride in methanol and pyridine, IX gave *2-ethyl-N-hy-*

droxychroman-4-acetic acid lactam (XII), faintly orange prisms, m.p. 227°. The product was insoluble in aqueous sodium carbonate, but soluble in 10% sodium hydroxide. It gave a deep red color with alcoholic ferric chloride.

Anal. Calc'd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5.
Found: C, 67.0; H, 6.7.

Reaction of lactam XIII with phosphorus pentasulfide. A mixture of 9 g. of XIII with 5.4 g. of phosphorus pentasulfide in an 8-inch test tube was heated in a boiling water-bath. The mixture was stirred and heated until it had partly liquefied, and then for five minutes longer. The product was extracted with hot toluene and the extract was filtered. The toluene was removed under reduced pressure, and the residue was crystallized from alcohol. There was obtained 4.2 g. of *2-methyl-2-methylaminochroman-4-acetic acid thiolactam* (XIV), colorless needles m.p. 122–124°.

Anal. Calc'd for $C_{13}H_{15}NOS$: C, 66.9; H, 6.5.
Found: C, 67.2; H, 6.6.

When 0.7 g. of the thiolactam was boiled with 5 ml. of conc'd hydrochloric acid for one hour, there was obtained a nearly clear solution. Dilution with water and extraction with ether removed about 0.1 g. of the lactone (X); basification with 10% sodium hydroxide gave a crystalline precipitate (0.5 g.) of *2-methyl-4-methylamino-2,6-methano-1,3,6-benzoxathiocin* (XV), colorless plates from alcohol, m.p. 147°.

Anal. Calc'd for $C_{13}H_{15}NOS$: C, 66.9; H, 6.5.
Found: C, 67.1; H, 6.6.

With benzoyl chloride in pyridine, XV yielded a benzoyl derivative, colorless crystals from dilute alcohol, m.p. 157–157.5°.

Anal. Calc'd for $C_{20}H_{19}NO_2S$: C, 71.2; H, 5.7.
Found: C, 71.0; H, 5.6.

Condensation of lactam XIII with ethyl oxalate. Sodium ethoxide was prepared by adding 8 ml. of absolute alcohol to 3 g. of powdered sodium in 200 ml. of dry ether. This was treated with 18 ml. of ethyl oxalate and then with 29.5 g. of XIII. The mixture was heated and stirred for four hours, allowed to stand for 15 hours, and finally extracted with 200 ml. of water containing 0.5 g. of sodium hydroxide. The extract was acidified, and the product was taken up in ether and dried. Removal of the ether left a sirupy residue which soon crystallized. Recrystallization from dilute alcohol gave 19 g. of *α-ethoxalyl-2-methylaminochromanacetic acid lactam* (XVI), colorless needles, m.p. 103.5–104.5°. The compound gave a red color with alcoholic ferric chloride.

Anal. Calc'd for $C_{17}H_{19}NO_5$: C, 64.3; H, 6.0.
Found: C, 64.2; H, 6.1.

With acetic anhydride and potassium acetate at 100°, XVI gave an *enol acetate*, colorless prisms from ether, m.p. 171–173°. The acetate gave no color with ferric chloride and was not affected by hydrogen in presence of platinum black.

Anal. Calc'd for $C_{19}H_{21}NO_6$: C, 63.5; H, 5.9.
Found: C, 63.6; H, 5.9.

With *phenylhydrazine* in alcohol containing a little acetic acid, XVI gave a *phenylhydrazone*, colorless prisms from dilute alcohol, m.p. 176–177°.

Anal. Calc'd for $C_{23}H_{25}N_3O_4$: C, 67.8; H, 6.2.
Found: C, 68.0 H, 6.4.

When one gram of XVI was warmed to 50° for five hours with 25 ml. of 2% aqueous potassium hydroxide, it yielded 0.26 g. of XIII, and a solution from which dilute sulfuric acid precipitated 0.26 g. of *2-methyl-2-methylamino-α-oxalylchromanacetic acid lactam*, colorless prisms from ethyl acetate, m.p. 172–174° dec.

Anal. Calc'd for $C_{15}H_{15}NO_6$: C, 62.3; H, 5.2.
Found: C, 62.5; H, 5.5.

A mixture of 10 g. of XVI, 2.3 g. of Raney nickel, and 170 ml. of absolute alcohol was shaken for a short time with hydrogen at 65° and 130 atmospheres. Removal of the catalyst and solvent left a waxy white solid which gave no color with ferric chloride. Most of this

mixture was acylated without purification, but a portion extracted with boiling water furnished the lower-melting form of *α-(hydroxycarbethoxymethyl)-2-methyl-2-methylaminochroman-4-acetic acid lactam* (XVIII), colorless crystals from water, m.p. 103°.

Anal. Calc'd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6.
Found: C, 64.1; H, 6.8.

Further extraction of the residue yielded a small amount of the high-melting isomer (?), m.p. *ca.* 146° (Found: C, 62.7; H, 6.8).

A solution of 6.5 g. of the crude reduction product in 20 ml. of acetic anhydride was boiled for 30 minutes, then cooled, and treated with 100 ml. of water. Crystallization of the precipitate from 95% alcohol gave 1.5 g. of the higher-melting acetate XIX, colorless prisms, m.p. 203°.

Anal. Calc'd for $C_{19}H_{23}NO_6$: C, 63.2; H, 6.4.
Found: C, 63.3; H, 6.6.

The main product was a mixture of acetates, m.p. 110–115°, which was not purified.

A solution of 8.5 g. of the crude reduction product and 8.2 g. of *p*-toluenesulfonyl chloride in 20 ml. of pyridine was allowed to stand for 12 hours and then was treated with 100 ml. of water and 250 ml. of ether. The ether layer was separated and washed with dil. hydrochloric acid, whereupon 1.6 g. of the high-melting *p*-toluenesulfonate (XX) separated. Crystallization of this from alcohol gave colorless needles, m.p. 174.5–175°, that gave positive tests for nitrogen and sulfur.

Anal. Calc'd for $C_{24}H_{27}NO_7S$: C, 60.9; H, 5.8.
Found: C, 60.7; H, 6.0.

The ether solution was evaporated, and the remaining sirup was extracted with 15 ml. of 95% alcohol and then with 50 ml. of boiling water. The insoluble part solidified and was fractionally crystallized from dilute alcohol, giving 1.5 g. of the low-melting *p*-toluenesulfonate (XX), colorless coarse needles that gave positive tests for nitrogen and sulfur, m.p. 132–134°.

Anal. Calc'd for $C_{24}H_{27}NO_7S$: C, 60.9; H, 5.8.
Found: C, 61.0; H, 5.9.

A mixture of 0.3 g. of XX, m.p. 174°, with 1.5 g. of powdered anhydrous sodium acetate was heated at 200° and stirred for five minutes. The mixture was then cooled and stirred with one ml. of acetic acid, and water was added to turbidity. There was obtained 80 mg. of crude (m.p. 116–118°) *α-(carbethoxymethylene)-2-methyl-2-methylaminochroman-4-acetic acid lactam* (XXIII). Crystallization from dilute alcohol gave colorless prisms, m.p. 120–121°.

Anal. Calc'd for $C_{17}H_{19}NO_4$: C, 67.8; H, 6.4.
Found: C, 67.8; H, 6.4.

The same compound (XXIII) was obtained in a similar way but in poorer yield from the low-melting toluenesulfonate (XX), and from both the crude and the purified acetates (XIX).

Condensation of lactam II with ethyl oxalate. The lactam II was prepared in 45% yield over-all from salicylaldehyde by the procedures of Boehm and Themlitz. It was condensed with ethyl oxalate in the same way as described for XIII, giving 68% of *α-ethoxalyl-2-methyl-2-phenylaminochromanacetic acid lactam* (XVII), colorless needles, m.p. 132°. The product gave a red color with ferric chloride.

Anal. Calc'd for $C_{22}H_{21}NO_5$: C, 69.6; H, 5.5.
Found: C, 69.7; H, 5.7.

A solution of 13.5 g. of XVII in 200 ml. of ether was added to 15 g. of amalgamated aluminum foil covered with 150 ml. of ether, and 10 ml. of water was added dropwise during 4½ hours. The ethereal solution was then removed, washed with 10% sodium carbonate, and concentrated. The crystalline product (8 g.) was a mixture of diastereoisomers of *α-(hydroxycarbethoxymethyl)-2-methyl-2-phenylaminochroman-4-acetic acid lactam* (XXI). A

portion was fractionally crystallized from ether and from alcohol, to obtain two pure forms, mainly (a) m.p. 213°, and a little (b) m.p. 157°.

Anal. Calc'd for $C_{22}H_{23}NO_5$: C, 69.3; H, 6.0.
Found: (a) C, 69.3; H, 6.1.
(b) C, 69.8; H, 6.4.

When 4 g. of XVII in 125 ml. of absolute alcohol was treated with hydrogen at 100 atmospheres and 95° in the presence of Raney nickel, there was obtained an oil, from which only the lower-melting form of XXI (1 g.) could be isolated.

Acetylation of 4.4 g. of the mixed forms of XXI by boiling 30 minutes with 24 g. of acetic anhydride, and crystallization of the product from acetic acid gave 3.7 g. of mixed acetates (XXII), prisms, m.p. 165–200°. A small amount of one form was isolated in a pure state, m.p. 217°.

Anal. Calc'd for $C_{24}H_{25}NO_6$: C, 68.1; H, 6.0.
Found: (165–200°) C, 68.3; H, 6.3.
(217°) C, 68.0; H, 6.0.

When 1.3 g. of mixed acetates (XXII) and 2 g. of anhydrous sodium acetate were heated together in a metal bath at 200°, acetic acid was evolved. The residue was treated with ether and water, and the ether-soluble part was crystallized from alcohol. There was obtained 0.77 g. of *α-(carbethoxymethylene)-2-methyl-2-phenylaminochroman-4-acetic acid lactam* (XXIV), colorless prisms, m.p. 126°, that decolorized permanganate in acetone.

Anal. Calc'd for $C_{22}H_{21}NO_4$: C, 72.7; H, 5.8.
Found: C, 72.8; H, 6.1.

Acknowledgments. Analytical results were furnished by Messrs. Roger Amidon, J. S. Buckley, William Cummings, and William Hunter. The authors thank the Shell Development Company and the Carbide and Carbon Chemicals Corporation for fellowship grants for 1947–1948 and 1948–1949, respectively.

SUMMARY

Coumarin-3-carboxylic acid was found to react with ketones and methylamine to form lactams of 2-substituted (or 2,3-disubstituted) 2-methylaminochroman-4-malonic acid; the products underwent decarboxylation when they were heated. One of the substances obtained in this way, 2-methyl-2-methylaminochroman-4-acetic acid lactam, has been studied in detail. It reacted with phosphorus pentasulfide with formation of a thiolactam, and it condensed with ethyl oxalate. The thiolactam underwent rearrangement with acids, forming a compound with a sulfur-containing ring. Some reactions of the ethoxalyl derivative were also investigated.

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