

Nitration of Substituted Chromans

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The nitration of substituted chromans has been studied and the structure of the nitro compounds has been confirmed by chemical and spectral data.

The nitration of substituted chromans has been the subject of a very limited number of investigations. Chroman on nitration has been reported to give the 6-nitro- (1) or the 6,8-dinitro derivative (2) according to the concentration of the employed nitric acid. Recently (3) a series of new substituted chromans has been synthesized

and the nitro derivatives have been prepared for their characterization; however, no mention as to the structure of formed nitro compounds has been made.

Due to our interest in substituted aminochromans, easily prepared *via* the corresponding nitro derivatives, we felt it necessary to establish unequivocally the structure

Scheme 1

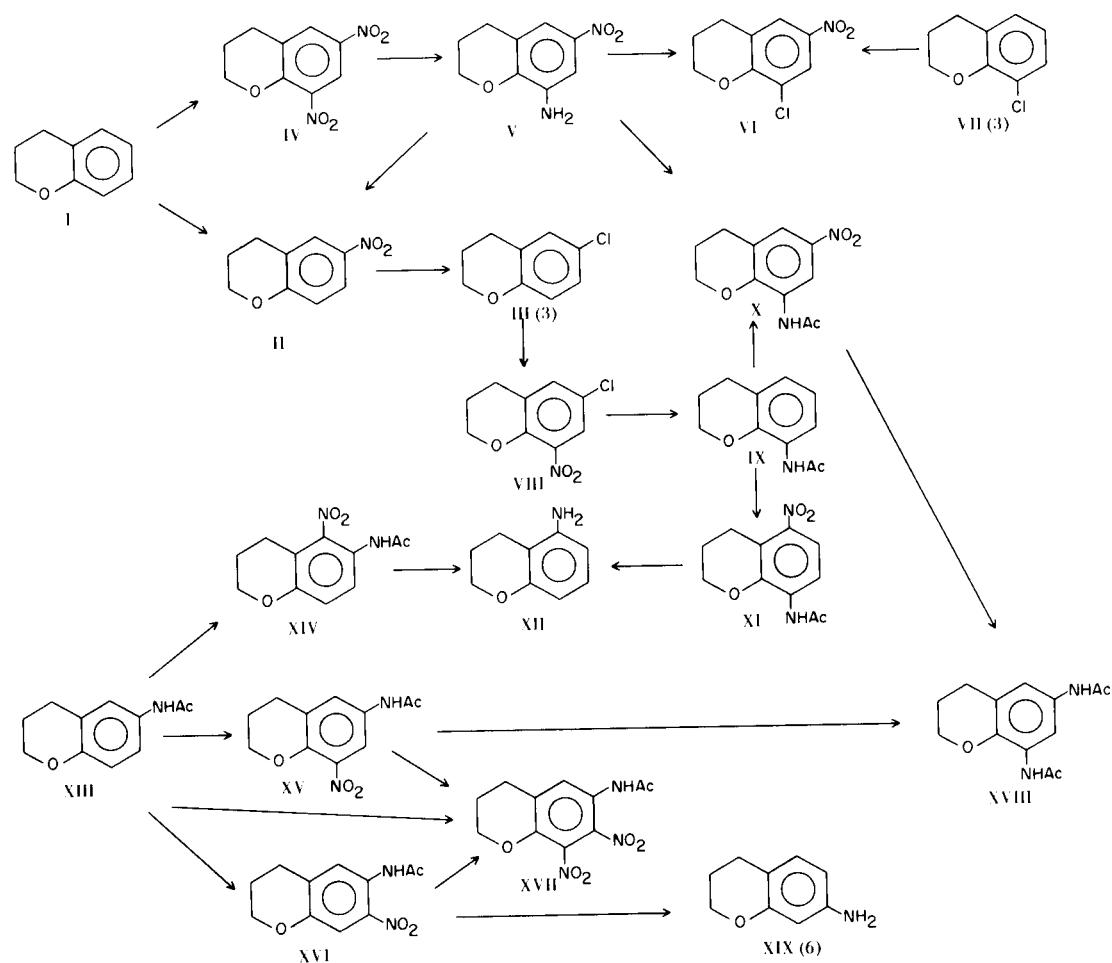


TABLE I
Reaction Products Obtained in the Nitration of Substituted Chromans

Chromanyl Reactants Rn	Nitric Acid conc. %	Reaction Temperature °C	Rn	Isolated Reaction Products		NMR Data
				Yield %		
H	60	15-20	6-NO ₂ (II)	45	δ CDCl ₃ ; H ₄ 2.83 (t); H ₅ , H ₇ 7.96 (m); H ₈ 6.86 (d)	
H	99	25-30	6,8-bis-NO ₂ (IV)	55	δ CDCl ₃ ; H ₄ 2.80 (t); H ₅ 8.08 (m); H ₇ 8.44 (d); J _{H_{5,7}} = 2.7 cps	
6-Cl	60	25-30	6-Cl; 8-NO ₂ (VIII)	65	^a	
6-NHCOCH ₃	99	10	5-NO ₂ ; 6-NHCOCH ₃ (XIV)	20	δ(CDCl ₃ + 20% DMSO): H ₄ 2.72 (t); H ₇ 6.91 (d); H ₈ 7.30 (d); J _{H_{7,8}} = 9 cps	
			6-NHCOCH ₃ ; 7-NO ₂ (XVI)	25	δ CDCl ₃ ; H ₄ 2.87 (t); H ₅ 7.56 (s); H ₈ 8.38 (s)	
			6-NHCOCH ₃ ; 8-NO ₂ (XV)	4	δ (CDCl ₃ + 20% DMSO): H ₄ 2.84 (t); H ₅ 7.59 (d); H ₇ 7.95 (d); J _{H_{5,7}} = 2.5 cps	
6-NHCOCH ₃	65	20-25	6-NHCOCH ₃ ; 7,8-bis-NO ₂ (XVII)	35	δ CDCl ₃ ; H ₄ 2.86 (t); H ₅ 7.20 (s)	
8-CH ₃	60	5-10	6-NO ₂ ; 8-CH ₃ (XX)	70	δ CCl ₄ ; H ₄ 2.81 (t); H _{5,7} 7.70 (s)	
8-Cl	60	25-30	6-NO ₂ ; 8-Cl (VI)	35	δ CDCl ₃ ; H ₄ 2.86 (t); H ₅ 7.87 (m); H ₇ 8.07 (d); J _{H_{5,7}} = 2.6 cps	
8-NHCOCH ₃	99	10-15	5-NO ₂ ; 8-NHCOCH ₃ (XI)	25	δ CDCl ₃ ; H ₄ 3.08 (t); H ₆ 8.30 (d); H ₇ 7.60 (d); J _{H_{6,7}} = 9 cps	
			6-NO ₂ ; 8-NHCOCH ₃ (X)	10		
6-NHCOCH ₃ ; 8-CH ₃	99	5	6-NHCOCH ₃ ; 7-NO ₂ ; 8-CH ₃ (XXIII)	70	δ CDCl ₃ ; H ₄ 2.80 (t); H ₅ 7.69 (s)	
6-COOH; 8-CH ₃	99	10	XX	30		
5-NO ₂ ; 6-NHCOCH ₃	99	25-30	no reaction product			
6-NHCOCH ₃ ; 7-NO ₂	99	25-30	XVII	68		
6-NHCOCH ₃ ; 8-NO ₂	99	25-30	XVII	30		

(a) Nmr spectrum of 6-chloro-8-aminochroman: δ (deuteriochloroform) 2.08 (multiplet, H₃), 2.80 (triplet, H₄), 3.70 (singlet, NH₂), 4.28 (triplet, H₂), 6.56 ppm (broad singlet; H₅, H₇). (b) Nmr spectrum of 6-nitro-8-aminochroman: δ (deuteriochloroform) 2.10 (multiplet, H₃), 2.84 (triplet, H₄), 4.02 (singlet, NH₂), 4.34 (triplet, H₂), 7.42 ppm (singlet; H₅, H₇).

of these intermediates (see Table I and Scheme I).

Nitration of Chroman.

The structures of the mono and the dinitrochroman were correlated with already known 6-chloro and 8-chlorochroman (3). The mononitrochroman II was converted into 6-chlorochroman (III) by the Sandmeyer reaction of the corresponding amino derivative. The dinitrochroman IV was selectively reduced with sodium sulfide to the nitroamino derivative V (4). This could be converted into 6-nitrochroman (II) by a deamination reaction and into a chloronitrochroman (VI) identical with the compound obtained by nitration of 8-chlorochroman (VII).

Thus, it is univocally proved that the 6- and 8-positions are involved in the nitration of chroman.

A similar conclusion was reached in the nitration of coumaran (5).

Nitration of Monosubstituted Chromans.

Accordingly, 6-chloro (III) and 8-chlorochroman (VII) yielded the 8-nitro (VIII) and 6-nitro derivative (VI), respectively.

The structure of VIII was proved by the formation of 6-nitro-8-acetylaminochroman (X) on nitration of 8-acetylaminochroman (IX) prepared from VIII.

The nitration of IX yielded the 5-nitro isomer (XI), too. This was converted into 5-aminochroman (XII), also prepared from 5-nitro-6-acetylaminochroman (XIV) (see below).

The nitration of 6-acetylaminochroman (XIII) (1) gave the three possible isomers XIV, XV, and XVI. The assigned structures were supported by the conversion of XV into 6,8-bisacetylaminochroman (XVIII) and of XVI into the previously reported 7-aminochroman (XIX) (6), and by spectral data (see experimental). The yield of isomer XV under our conditions was very low; whereas the isomers XIV and XVI were formed in nearly equal amounts. Therefore, the combined orienting effects of the acetyl-amino and alkylene groups seem to prevail over the ether groups. It can be pointed out, moreover, that the nitration of 5-acetylaminocoumaran, under the same experimental conditions, was reported (7) to yield only one isomer.

Nitration of 8-methylchroman (3) yielded a mononitro derivative identified as the 6-nitro isomer (XX) on the basis of its nmr spectrum.

Nitration of Disubstituted Chromans.

6-Acetyl-amino-5 (7 and 8)-nitrochroman were submitted to further nitration. No reaction product was isolated in the reaction with the 5-nitro isomer (XIV), which was partly recovered unchanged. The 7-nitro (XVI) and 8-nitro isomer (XV) gave the same dinitro derivative (XVII), in high yield which was formed directly on nitrating XIII at 25°.

Nitration of 6-acetyl-amino-8-methylchroman (XXII) yielded the 7-nitro isomer (XXIII), identified on the basis of its nmr spectrum. Surprisingly, there was no evidence for the expected 5-nitro isomer.

The nitration of 6-carboxy-8-methylchroman resulted in the replacement (8) of the carboxy group with formation of 6-nitro-8-methylchroman (XX).

EXPERIMENTAL

Melting points were taken in capillary tubes in a heated copper block and are uncorrected. Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer in 95% ethanol and infrared spectra on a Perkin-Elmer spectrophotometer in a film (liquid) or in potassium bromide disks (solid). Nmr spectra were recorded on a Varian A-60 instrument using TMS as internal standard. All compounds were pure by tlc carried out on Silica Gel plates using chloroform, concentrated ammonia, and methanol (95:0.25:5) as the solvent system.

6-Chlorochroman (III).

A solution of 8.4 g. of 6-aminochroman (1) in 138 ml. of 6 *N* hydrochloric acid was diazotized with 4.4 g. of sodium nitrite in 11 ml. of water. The solution of diazonium salt was added dropwise to a stirred and cooled solution of cuprous chloride (from 19.3 g. of copper sulfate pentahydrate) in 39 ml. of concentrated hydrochloric acid. After 30 minutes at 0°, the reaction mixture was allowed to warm to room temperature and then was heated at 60° for 2 hours. After cooling, the oily precipitate was extracted with ether. The organic layer was washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was distilled obtaining 3.2 g. of product boiling at 123-125°/16 mm, identical (ir analysis) with an authentic sample of 6-chlorochroman (3).

Anal. Calcd. for C₉H₉ClO: C, 64.10; H, 5.38; Cl, 21.02. Found: C, 64.19; H, 5.52; Cl, 20.81.

6-Nitro-8-aminochroman (V).

A solution of 8.6 g. of sodium sulfide nonahydrate and 2.2 g. of sulfur in 40 ml. of water was added dropwise and with stirring to a boiling solution of 8 g. of 6,8-dinitrochroman (2) in a mixture of water (40 ml.) and ethanol (60 ml.). After the addition was completed, the heating was continued for an additional 30 minutes. Dilution with water precipitated a solid which was suspended in 4 *N* hydrochloric acid. The suspension was refluxed for several minutes and then filtered. The clear solution was made alkaline with sodium bicarbonate. The precipitate (3.4 g., m.p. 82-86°) was crystallized from an ethyl acetate-petroleum ether (b.p. 40-70°) mixture: 2.5 g., m.p. 84-85°; λ max 229 (ϵ , 11,500), 262 (11,100), 318 (5,350), 370 μ (3,930).

Anal. Calcd. for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.70; H, 4.98; N, 14.28.

The above compound (0.95 g.) when treated with acetic anhydride (1.2 ml.) gave 6-nitro-8-acetylaminochroman (X): m.p. 182-183°; λ max 234 (ϵ , 10,800), 259 (16,200), 310 μ (7,500).

Anal. Calcd. for C₁₁H₁₂N₂O₄: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.80; H, 5.03; N, 11.76.

Deamination Reaction: 6-Nitrochroman (II).

A solution of 1.9 g. of 6-nitro-8-aminochroman (V) in a mix-

ture of concentrated sulfuric acid (17 ml.) and water (50 ml.) was diazotized with 0.7 g. of sodium nitrite in 5 ml. of water. To the solution, after an additional 20 minutes of stirring, 2.5 ml. of 50% hypophosphorous acid was added. The reaction mixture was kept in an ice-box for 24 hours and then set aside at room temperature for 4 days. The separated solid was crystallized from 95% ethanol, m.p. 99-100°, and was identical with 6-nitrochroman by the methods of mixed melting point and ultraviolet and infrared analyses.

Sandmeyer Reaction: 6-Nitro-8-chlorochroman (VI).

A solution of 2 g. of 6-nitro-8-aminochroman (V) in 25 ml. of 6 *N* hydrochloric acid was diazotized with 0.8 g. of sodium nitrite in 2 ml. of water. The solution of diazonium salt was added dropwise to a stirred and cooled solution of cuprous chloride (from 3.5 g. of copper sulfate pentahydrate) in 7 ml. of concentrated acid. After 30 minutes at 0°, the reaction mixture was allowed to assume room temperature and then was heated at 60° for 15 minutes. The separated solid was crystallized from 95% ethanol to constant melting point, 99-101°, and was identical with the nitro compound obtained by nitration of 8-chlorochroman (VII) (3) by the methods of mixed melting point and ultraviolet and infrared analyses.

6,8-Diaminochroman (4).

To a stirred mixture of 4.4 g. of 6,8-dinitrochroman (IV) and 12 g. of tin powder 40 ml. of concentrated hydrochloric acid was carefully added, then the mixture was heated at 100° for 90 minutes. The cooled reaction mixture was mixed with a large excess of 50% sodium hydroxide and extracted several times with chloroform. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dryness. The residue (2.7 g.) was crystallized from benzene-petroleum ether (b.p. 40-70°): m.p. 62-63°; λ max 305 (ϵ , 3,600) and 240 μ (7,900).

Anal. Calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.68; H, 7.29; N, 16.84.

8-Acetylaminochroman (IX).

a) 6-Chloro-8-aminochroman.

To a stirred suspension of 31.5 g. of 6-chloro-8-nitrochroman in 80 ml. of concentrated hydrochloric acid and 25 ml. of ethanol 29 g. of tin powder were added portionwise. The mixture was refluxed for 1 hour, cooled, and mixed with a large excess of 50% sodium hydroxide and extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and concentrated. The residue was distilled, b.p. 114-118° at 0.001 mm; 16.6 g. The distillate solidified, m.p. 40-42°. An analytical sample was crystallized from petroleum ether, m.p. 47-49°; λ max 236.5 (ϵ , 6,900) and 297 μ (3,080).

Anal. Calcd. for $C_9H_{10}ClNO$: C, 58.85; H, 5.49; N, 7.62; Cl, 19.30. Found: C, 59.07; H, 5.36; N, 7.38; Cl, 19.59.

b) 8-Acetylaminochroman (IX).

A solution of 20 g. of 6-chloro-8-aminochroman and 13 g. of sodium hydroxide in 300 ml. of methanol was submitted to hydrogenation at room temperature and atmospheric pressure in the presence of 5 g. of 5% palladium on charcoal. When the uptake of hydrogen became very slow, the hydrogenation was suspended and the reaction mixture was filtered. The solution was evaporated to dryness and the residue was treated with a mixture of water and ether. The organic layer was separated, washed with water and dried over anhydrous sodium sulfate.

After removal of the solvent, the oily residue was distilled, b.p. 90-92°/0.001 mm. This compound (4.3 g.) when treated with acetic anhydride (3.5 ml.) gave 8-acetylaminochroman (IX): 4.7 g., m.p. 103-105° (ethanol); λ max 247.5 (ϵ , 10,600), 283.5 (4,350), 290 μ (4,230).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.85; H, 6.70; N, 7.11.

Nitration of 8-Acetylaminochroman (IX): 5- (and 6-) Nitro-8-acetylaminochroman.

A solution of 0.3 g. of fuming nitric acid ($d = 1.5$) in 1 ml. of acetic acid was added dropwise to a stirred solution of 1 g. of 8-acetylaminochroman (IX) in 5 ml. of acetic acid. The reaction temperature was kept between 12-15°. After an additional hour of stirring, the mixture was poured onto ice. The separated solid was collected by filtration and dried *in vacuo*, 0.9 g. It was dissolved in 20 ml. of hot benzene and upon cooling a crystalline solid separated, 0.1 g., m.p. range 150-161°. The solid when recrystallized from benzene melted at 182-184° (0.08 g.) and was identical with 6-nitro-8-acetylaminochroman (X) prepared from 6,8-dinitrochroman, by mixed melting point and ultraviolet and infrared analyses.

The benzene solution, after filtration of precipitated 6-nitro-8-acetylaminochroman, was evaporated to dryness. The residue was dissolved in 13 ml. of hot ethanol. On cooling and standing at room temperature for about 30 minutes, the crystalline precipitate was filtered, 0.3 g., m.p. 154-157°. After recrystallization from 95% ethanol, 0.12 g. of 5-nitro-8-acetylaminochroman (XI) was obtained, m.p. 159-161°; λ max 230 (ϵ , 10,400), 251 (7,780), 309 μ (7,100); ir 2.99 (NH), 5.98 (NHCOCH₃), 12.0 μ (*ortho* aromatic C-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.08; H, 5.34; N, 11.92.

Nitration of 6-Acetylaminochroman (XIII): 5- (7 and 8-) Nitro-6-acetylaminochroman.

A solution of 3 ml. of fuming nitric acid ($d = 1.5$) in 10 ml. of acetic acid was added dropwise to a stirred solution of 10 g. of 6-acetylaminochroman (I) in 50 ml. of acetic acid. The reaction temperature was kept at 10°. After the addition was completed, the stirring was continued for an additional 45 minutes. The reaction mixture was poured onto ice and the precipitate which formed was collected, 9.6 g., m.p. range 117-157°. This solid was extracted in a Soxhlet with hot petroleum ether (b.p. 40-70°) until the extraction solvent was practically colorless. The petroleum ether solution when evaporated to dryness gave a yellow solid, 4 g., m.p. 127-135°. It was crystallized from 95% ethanol, m.p. 139-142°. This nitro compound was identified (see below) as the 7-nitro isomer XVI: $uv \lambda$ max 240 (ϵ , 16,600) and 366 μ (2,170); ir 3.0 (NH); 5.95 (NHCOCH₃), 11.7 μ (*para* isolated aromatic C-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.87; H, 5.07; N, 11.60.

The petroleum ether insoluble solid was dissolved in hot 95% ethanol (150 ml.). On cooling a crystalline precipitate separated, 2.2 g., m.p. 177-180°. This nitro compound, chromatographically pure, was the 5-nitro isomer XIV: $uv \lambda$ max 233 (ϵ , 13,000) and 330 μ (1,250); ir 3.05 (NH), 5.95 (NHCOCH₃), 12.0 μ (*ortho* aromatic C-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.87; H, 5.13; N, 11.66.

The ethanol filtrate was diluted with water (70 ml.) and allowed to stand at room temperature overnight giving a further

crop of XIV (0.15 g., m.p. 176-180°). The filtrate was evaporated and the residue dissolved in 40 ml. of hot ethyl acetate. On cooling, yellow crystals separated, 0.35 g., m.p. 188-191°. This compound, chromatographically pure, was the 8-nitro isomer XV (see below): $\text{uv } \lambda \text{ max } 247$ (ϵ , 20,600) and $360 \text{ m}\mu$ (2,300); $\text{ir } 3.0$ (NH), 5.98 (NHCOC₂H₅), 11.4 μ (*meta* isolated aromatic C-H).

Anal. Calcd. for C₁₁H₁₂N₂O₄: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.91; H, 5.14; N, 11.70.

6-Acetylamino-7,8-dinitrochroman (XVII).

6-Acetylaminochroman (1 g.) was nitrated with 65% nitric acid at 20-25°. The reaction mixture was worked up in the usual way giving 0.4 g. of product melting at 218-219° (ethanol); $\lambda \text{ max } 233.5$ (ϵ , 18,200) and $353 \text{ m}\mu$ (2,600).

Anal. Calcd. for C₁₁H₁₁N₃O₆: C, 46.98; H, 3.94; N, 14.94. Found: C, 47.07; H, 3.89; N, 14.75.

5-Aminochroman (XII).

From 5-Nitro-6-acetylaminochroman (XIV).

A solution of 0.5 g. of 5-nitro-6-acetylaminochroman (XIV) and 0.3 g. of sodium hydroxide in 60 ml. of 95% ethanol was refluxed for 16 hours. The solvent was removed and the residue was treated with a mixture of water and ether. The organic layer was separated, washed with water and dried over sodium sulfate. After removal of ether the oil was converted into a solid by treatment with petroleum ether (b.p. 40-70°), 0.4 g., m.p. 40-43°. The solid was dissolved in 5 ml. of hot 95% ethanol and the solution was diluted with an equal volume of water. On cooling an oily precipitate was obtained which solidified as a yellow solid. This was filtered and pressed on a filter paper. During this operation the color of the solid changed from yellow to deep red. After drying *in vacuo*, 0.25 g. of 5-nitro-6-aminochroman, m.p. 62-64°, was obtained.

Anal. Calcd. for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.79; H, 5.35; N, 13.60.

The hydrochloride melted at 160-163° dec. (near 130° a starting alteration was evident); $\lambda \text{ max } 235.5 \text{ m}\mu$ (ϵ , 15,100) and $443 \text{ m}\mu$ (2,900).

Anal. Calcd. for C₉H₁₁ClN₂O₃: C, 46.86; H, 4.80; N, 12.15; Cl, 15.33. Found: C, 46.67; H, 4.77; N, 12.11; Cl, 15.60.

A suspension of 1.55 g. of 5-nitro-6-aminochroman in a mixture of water (36 ml.) and concentrated sulfuric acid (15 ml.) was heated until a clear solution was obtained. The solution was cooled with vigorous stirring and diazotized with 0.6 g. of sodium nitrite in 3 ml. of water. After 1 hour at 0° the reaction mixture was mixed with 3 ml. of 50% hyposphosphorous acid and stored in an ice-box (0-4°) for 24 hours and allowed to stand at room temperature for 5 days. The oily precipitate was extracted with ether and the ethereal solution was washed with water, dried (sodium sulfate) and evaporated. The oily residue (5-nitrochroman) did not solidify and was used for the next step directly.

The above oily compound in 35 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.15 g. of platinum dioxide. After the uptake of hydrogen ceased (about 4 hours), the hydrogenation was interrupted and the reaction mixture was filtered. The filtrate was evaporated and the residue was distilled, b.p. 98-103° (bath temperature) at 0.001 mm; $\lambda \text{ max } 285 \text{ m}\mu$ (ϵ , 1,750).

Anal. Calcd. for C₉H₁₁NO: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.66; H, 7.31; N, 9.54.

From 5-Nitro-8-acetylaminochroman (XI).

A suspension of 0.15 g. of 5-nitro-8-acetylaminochroman, m.p. 159-161°, in a mixture of 4 *N* hydrochloric acid (6 ml.) and 95% ethanol (1.5 ml.) was heated on a boiling water bath for 2 hours. The resulting solution was filtered and made alkaline by addition of a saturated potassium carbonate solution. The precipitated 5-nitro-8-aminochroman was crystallized from 95% ethanol-water mixture (1:1), m.p. 79-81°; $\lambda \text{ max } 266.5$ (6,350) and $392 \text{ m}\mu$ (11,300).

Anal. Calcd. for C₉H₁₀N₂O₃: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.71; H, 5.37; N, 14.64.

The compound by deamination reaction and further reduction of the corresponding oily nitro compound yielded the 5-aminochroman (XII), identical with that obtained in an analogous way from 5-nitro-6-aminochroman.

6,8-Bis(acetylamino)chroman (XVIII).

From 6-Nitro-8-acetylaminochroman (X).

A solution of 5 g. of 6-nitro-8-acetylaminochroman (X) in 200 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.4 g. of platinum dioxide. The theoretical amount of hydrogen was absorbed in about 1 hour. The reaction mixture was filtered and the filtrate was evaporated. The residue was crystallized from an ether-petroleum ether (b.p. 40-70°) mixture, m.p. 143-144°; $\lambda \text{ max } 313$ (ϵ , 4,800) and $245 \text{ m}\mu$ (11,200).

Anal. Calcd. for C₁₁H₁₄N₂O₂: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.34; H, 6.90; N, 13.59.

The above compound when treated with acetic anhydride yielded 6,8-bis(acetylamino)chroman (XVIII), m.p. 197-198°; $\lambda \text{ max } 239$ (ϵ , 22,200) and $298 \text{ m}\mu$ (4,050).

Anal. Calcd. for C₁₃H₁₆N₂O₃: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.18; H, 6.48; N, 11.41.

From 8-Nitro-6-acetylaminochroman (XV).

A suspension of 0.22 g. of 8-nitro-6-acetylaminochroman, m.p. 188-191°, and 0.1 g. of platinum dioxide was submitted to hydrogenation at room temperature and atmospheric pressure. After 1 hour the uptake of hydrogen had ceased. The reaction mixture was filtered and the filtrate was evaporated. The solid residue mixed with acetic anhydride (0.2 ml.) gave the diacetylamino derivative, m.p. 192-194°; $\lambda \text{ max } 239 \text{ m}\mu$ (ϵ , 21,850), 299 (4,100). This compound was shown to be identical with that one prepared from X, by methods of mixed melting point and ultraviolet and infrared analyses.

Using an analogous procedure, 5,6-bis(acetylamino) and 6,7-bis(acetylamino)chroman were prepared.

5,6-Bis(acetylamino)chroman.

This compound had m.p. 238-240°; $\lambda \text{ max } 295 \text{ m}\mu$ (ϵ , 2,360).

Anal. Calcd. for C₁₃H₁₆N₂O₃: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.05; H, 6.51; N, 11.23.

6,7-Bis(acetylamino)chroman.

This compound had m.p. 241-243°; $\lambda \text{ max } 292 \text{ m}\mu$ (ϵ , 3,220).

Anal. Calcd. for C₁₃H₁₆N₂O₃: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.67; H, 6.51; N, 11.19.

7-Aminochroman (XIX) (6).

a) 6-Amino-7-nitrochroman.

A suspension of 2 g. of 6-acetylamino-7-nitrochroman (XVI) m.p. 139-141°, in 20 ml. of 6 *N* hydrochloric acid was heated on a steam bath for about 1 hour. The solution, treated with charcoal, was filtered and diluted with water to a total volume of 250 ml.

After standing at room temperature for several hours, the red crystalline precipitate was collected by filtration and dried, 1.25 g., m.p. 139-141°; λ max 236 (ϵ , 19,100), 268.5 (6,700), 292 (5,900), 450 m μ (4,950).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.47; H, 5.05; N, 14.47.

b) 7-Nitrochroman.

A solution of 1.3 g. of 6-amino-7-nitrochroman in a mixture of water (30 ml.) and concentrated sulfuric acid (12 ml.) was diazotized by a solution of 0.5 g. of sodium nitrite in 2 ml. of water. By the procedure already described for the deamination of 6-nitro-8-aminochroman, 0.8 g. of substance, m.p. 90-93°, was obtained. An analytical sample was crystallized from 95% ethanol, m.p. 90-92°; λ max 237 (10,900), 279 (6,700), 332 m μ (2,700).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; N, 5.06; H, 7.82. Found: C, 60.13; H, 4.95; N, 7.69.

c) 7-Aminochroman.

A solution of 0.8 g. of 7-nitrochroman in 40 ml. of ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.1 g. of platinum dioxide. When the theoretical amount of hydrogen was absorbed (1.5 hours) the reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was divided in two parts, used to prepare the benzenesulphamyl and picrate derivatives.

7-Benzenesulphamylchroman.

This compound had m.p. 141-143° (lit. (6) 148-148.5°).

Anal. Calcd. for $C_{15}H_{15}NO_3S$: C, 62.27; H, 5.23. Found: C, 62.07; H, 5.17.

Picrate derivative m.p. 179-180° dec. (lit. (6) 182-183°).

Nitration of 7- and 8-Nitro-6-acetylaminochromans: 7,8-Dinitro-6-acetylaminochroman (XVII).

To a stirred solution of 0.25 g. of 6-acetyl-amino-7-nitrochroman (XVI) in 3 ml. of acetic acid 0.25 ml. of fuming nitric acid ($d = 1.5$) was added dropwise. After the addition was completed, the reaction mixture was stirred for 30 minutes, then it was poured into a mixture of water and ice. The separated solid was crystallized from 95% ethanol: 0.20 g., m.p. 218-219°.

The nitration of 6-acetyl-amino-8-nitrochroman (XV) led analogously to 7,8-dinitro-6-acetylaminochroman (XVII) (mixed melting point and ultraviolet and infrared analyses).

6-Acetyl-amino-8-methylchroman (XXII).

6-Nitro-8-methylchroman (XX) was reduced in the usual way with tin/hydrochloric acid and gave the corresponding amino compound (XXI) in 69% yield, b.p. 100-105° at 0.001 mm.

Anal. Calcd. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.44; H, 8.03; N, 8.54.

The above amino compound (XXI) with acetic anhydride yielded the acetyl-amino derivative (XXII) in 95% yield. An analytical sample crystallized from benzene melted at 139-140°; λ max 254.5 m μ (ϵ , 13,350).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.34; H, 7.26; N, 6.99.

6-Acetyl-amino-7-nitro-8-methylchroman (XXIII).

A solution of 6 ml. of fuming nitric acid ($d = 1.5$) in 3 ml. of acetic acid was added dropwise to a stirred solution of 16 g. of 6-acetyl-amino-8-methylchroman (XXII) in 60 ml. of acetic acid. The reaction temperature was maintained at 5°. After further

stirring for 20 minutes, the mixture was poured into cooled water. The separated precipitate crystallized from 95% ethanol, 14 g., m.p. 152-153°; $uv \lambda$ max 236 (ϵ , 12,150) and 338 m μ (1,420); ir 3.05 μ (NH), 5.98 (NHCOCH₃), 11.4 μ (isolated aromatic C-H).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.63; H, 5.76; N, 11.10.

6-Carboxy-8-methylchroman.

a) 6-Acetyl-8-methylchroman.

To a stirred solution of 4.5 g. of 8-methylchroman and 2.5 ml. of acetyl chloride in 40 ml. of carbon disulfide were added portionwise 4.5 g. of anhydrous aluminum chloride. The reaction temperature was kept between -5-0°. After the addition was completed the reaction mixture was allowed to stand at the above temperature for 30 minutes, and at room temperature for an additional 15 minutes. Then, it was poured onto a mixture of concentrated hydrochloric acid and crushed ice. The organic layer was separated, washed with water until neutral and dried (sodium sulfate). After removal of the solvent the residue was dissolved in hot petroleum ether (b.p. 40-70°). On cooling, a crystalline solid separated, 4 g., m.p. 58-59°. An analytical sample was recrystallized from the same solvent, m.p. 60.5-62.5°; λ max 229 (ϵ , 13,350) and 285 m μ (14,700); nmr δ (carbon tetrachloride): 1.95 (multiplet, H₃), 2.10 (singlet, CH₃), 2.31 (singlet, COCH₃), 2.72 (triplet, H₄), 4.17 (triplet, H₂), 7.40 ppm (broad singlet, H₅, H₇).

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.64; H, 7.17.

b) 6-Carboxy-8-methylchroman.

A stirred solution of 44 g. of sodium hydroxide in 180 ml. of water was cooled at 0° and 14 ml. of bromine was added. Then, at 7°, 10 g. of 6-acetyl-8-methylchroman was added at once. The mixture was stirred at room temperature for 1 hour; then, it was heated at 50° for 7 hours. After standing at room temperature overnight the reaction mixture was diluted with water and shaken with ether. The aqueous solution was cooled and acidified by addition of concentrated hydrochloric acid. The separated solid was filtered, washed with a small amount of water and crystallized from ethanol-water mixture (1:1), 3.4 g., m.p. 185-187°; λ max 262 m μ (ϵ , 13,550).

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.29. Found: C, 68.75; H, 6.18.

Nitration of 6-Carboxy-8-methylchroman: 6-Nitro-8-methylchroman (XX).

A solution of 1 ml. of fuming nitric acid ($d = 1.5$) in 1 ml. of acetic acid was added slowly to a solution of 0.5 g. of 6-carboxy-8-methylchroman in 5 ml. of acetic acid with external cooling by a water bath. After 2 hours at room temperature, the reaction mixture was poured onto cooled water. The separated precipitate was filtered, washed with water until neutral and crystallized from 95% ethanol, m.p. 63-64°. The compound was shown to be identical with 6-nitro-8-methylchroman (XX), prepared by nitration of 8-methylchroman, by methods of mixed melting point and ultraviolet and infrared analyses.

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