with the fact that the direction of addition of hydrogen chloride to olefinic double bonds is not usually reversed by peroxides and in fact was not reversed in the case of allyl chloride under conditions leading to the simultaneous formation of telomers. The generally accepted mechanism for the peroxide-reversed addition of hydrogen bromide to unsymmetrical olefins[8] involves reaction of a free radical with the hydrogen of the hydrogen bromide, leaving the bromine atom to propagate the chain. The bromine atom then attacks the olefin double bond at the point of highest electron density. If hydrogen chloride reacts in the opposite way so that the chlorine is combined with the free radical, leaving the hydrogen atom to propagate the chain, the hydrogen atom should attack the point of highest electron density, and the same isomer should be formed by the free-radical chain reaction as by the ionic addition.

Reversal of the direction of hydrogen chloride addition to double bonds by free radicals has seldom been noted. Raley, Rust and Vaughan,[9] have reported that infrared analyses indicated the presence of small amounts of both *n*-propyl chloride and isopropyl chloride in the products of vapor-phase reactions of propylene with hydrogen chloride in the presence of di-(*t*-butyl) peroxide. From the reaction of 3,3-dimethyl-1-butene with hydrogen chloride in the presence of benzoyl peroxide, Ecke, *et al.*,[10] found some of the "abnormal" primary alkyl chloride along with the secondary alkyl chloride corresponding to "normal" addition. In both instances anhydrous systems were used. In the latter case it should be noted also that the experimental data show formation of some "abnormal" product even in the absence of added peroxide, and addition of a free-radical-forming initiator caused a large increase in the quantity of the "normal" adduct formed.

In order to reach a firm conclusion as to the manner in which hydrogen chloride is attacked by free radicals, it would be necessary to establish the structure of one of the 2:1 or higher telomers that are formed only in the presence of a free-radical initiator.

Acknowledgment.—The authors wish to acknowledge the assistance of Mr. H. S. Young and the staff of the Pressure Research Laboratory, who designed and operated the pressure equipment.

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[8] F. R. Mayo and C. Walling, *Chem. Revs.*, **27**, 351(1940).

[9] J. H. Raley, F. F. Rust and W. E. Vaughan, THIS JOURNAL, **70**, 2767 (1948).

[10] G. G. Ecke, N. C. Cook and F. C. Whitmore, *ibid.*, **72**, 1511 (1950).

WILMINGTON, DELAWARE

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Chromones in the Mannich Reaction

BY PAUL F. WILEY

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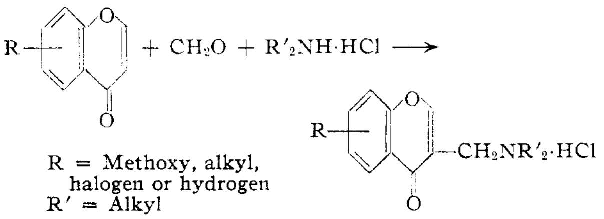
The reaction of chromones with formaldehyde and secondary amine hydrochlorides has been studied. Chromones unsubstituted in the 2- and 3-positions react to form 3-dialkylaminomethylchromone hydrochlorides. This reaction does not occur with 2-methylchromones.

The replacement of an α-hydrogen atom in a saturated ketone by an alkyl- or dialkylaminomethyl group in the Mannich reaction is well known. However, 2-hydroxy-1,4-naphthoquinone is the only α,β-unsaturated ketone that has been reported[1,2] to undergo a similar reaction, and it is unlikely that this compound participates as an α,β-unsaturated ketone, but either as 1,2,4-triketotetralin or as a phenol. In the research reported here it has been found that a special type of α,β-unsaturated ketone does undergo α-substitution in the Mannich reaction. These ketones are chromones which are not substituted in the 2- or 3-positions. The reaction is as follows



R = Methoxy, alkyl, halogen or hydrogen
R′ = Alkyl

The chromones found to react were chromone and its 6-methoxy-, 7-methoxy-, 6-chloro- and 6-methyl- derivatives. The amine hydrochlorides used were those of dimethylamine, diethylamine, piperidine and morpholine. Yields varied from 7.5 to 60%.

The structure of the Mannich bases from chromones is shown by several lines of evidence. Analytical data agree completely with the chromone structure. Absorption spectra, both ultraviolet and infrared, indicate that the chromone nucleus is still present. The reaction must thus have occurred by attack at the 2- or 3-position in the pyrone ring (or by opening of this ring and subsequent closure giving the same net effect) or by substitution at a vacant position in the benzene ring, which can be eliminated since such substitution in non-activated benzene rings is unknown. Substitution in the 3-position is proved by the fact that the product of the reaction of 7-methoxychromone with formaldehyde and dimethylamine hydrochloride has been reduced to the known 3-dimethylaminomethyl-7-methoxychromanone hydrochloride. This proof is somewhat weakened by the 1.5% yield obtained in the reduction but is strengthened by the finding that 2-dimethylamino-

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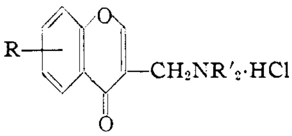
[1] M. T. Leffler and R. J. Hathaway, THIS JOURNAL, **70**, 3222 (1948).

[2] C. E. Dalgleish, *ibid.*, **71**, 1697 (1949).

TABLE I



Substituents R	Substituents R′R′	Yield, %	M.p., °C.	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
H	$(CH_3)_2$	60	238–239	$C_{12}H_{14}ClNO_2$	60.12	60.13	5.83	6.07	5.84	5.77	14.82	14.80
H	$(C_2H_5)_2$	7.5	167–168	$C_{14}H_{18}ClNO_2$	62.80	62.93	6.73	6.65	5.24	5.48	13.27	12.59
H	$-(CH_2)_5-$	14	262–263	$C_{15}H_{18}ClNO_2$	64.40	64.33	6.44	6.79	5.02	4.87	12.72	12.93
H	$-(CH_2CH_2)_2O$	20	244–246	$C_{14}H_{16}ClNO_3$	59.68	59.71	5.68	6.02	4.98	5.20	12.61	12.85
6-CH_3O	$(CH_3)_2$	22	234–236	$C_{13}H_{16}ClNO_3$	57.85	57.69	5.93	6.07	5.19	5.38	13.16	13.36
7-CH_3O	$(CH_3)_2$	47	235–236	$C_{13}H_{16}ClNO_3$	57.85	57.85	5.93	6.33	5.19	5.05	13.16	13.03
6-CH_3	$(CH_3)_2$	21	230–231	$C_{13}H_{16}ClNO_2$	61.54	61.68	6.32	6.42	5.53	5.29	14.00	13.84
6-Cl	$(CH_3)_2$	46	243–245	$C_{12}H_{13}Cl_2NO_2$	52.55	52.47	4.74	5.01	5.10	4.82	25.91	25.77

methyl-6-methoxychromone hydrochloride is different from the Mannich product of 6-methoxychromone, formaldehyde and dimethylamine hydrochloride. The 2-substituted aminochromone was obtained by the action of N-bromosuccinimide on 2-methyl-6-methoxychromone followed by treatment of the product with dimethylamine, then sodium hydroxide and finally hydrogen chloride. The only proofs of structure for 2-dimethylaminomethyl-6-methoxychromone hydrochloride are analysis and method of synthesis. Thus it is possible, but unlikely, that the synthesis gives some product other than the one postulated.

Further experiments were carried out to investigate the scope of this reaction. A series of 2-methylchromones did not react. These were 2-methyl-, 2-methyl-6-methoxy-, 2-methyl-7-methoxy-, 2-methyl-6-chloro- and 2,6-dimethylchromone. β-Ethoxyacrylophenone and β-ethoxycrotonophenone were tried and appeared to undergo some type of reaction, but no basic product could be isolated from the reactions. γ-Pyrone underwent a Mannich reaction giving a white crystalline product, the structure of which was not ascertained. Analytical data indicated that a mixture of 3-substituted and 3,5-disubstituted γ-pyrone was obtained.

It is of interest in connection with the above findings that 2-methylchromanones have been found[3] to give much poorer yields in the Mannich reaction than chromanones unsubstituted in the 2-position.

The chromones used in these experiments were synthesized by standard procedures.[4,5] Synthesis of chromones with no 2-methyl group was accomplished by reaction of 2-hydroxyacetophenones with diethyl oxalate in the presence of base followed by treatment with acid to give 2-carboxychromones. These were decarboxylated thermally to the desired compounds. The 2-methylchromones were prepared from 2-hydroxyacetophenones by Claisen condensation with ethyl acetate followed by acid cyclization of the 1,3-diketones thus obtained.

2-Bromomethyl-6-methoxychromone was synthesized by the action of N-bromosuccinimide on 2-methyl-6-methoxychromone. Direct bromination according to the method of Offe[6] gave only dibromination.

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Experimental[7]

Chromones.—All of the 2-methylchromones were known compounds. They were prepared as described previously. 7-Methoxychromone, a known compound, was synthesized in the same manner as was 6-methoxychromone.

6-Methoxychromone.—A mixture of 6.9 g. (0.3 atom) of sodium sand with a solution of 43.8 g. (0.3 mole) of diethyl oxalate in 100 ml. of dry dioxane was stirred vigorously while a solution of 16.6 g. (0.1 mole) of 2-hydroxy-5-methoxyacetophenone in 50 ml. of dry dioxane was added slowly. The reaction was very vigorous and was moderated occasionally by cooling with ice-water. After the reactants were all added, stirring of the red suspension was continued for two hours. The stirring was followed by addition of 10 ml. of alcohol and 15 ml. of acetic acid in that order. The resulting stiff paste was mixed with 900 ml. of water, and the solution was extracted continuously with ether for 24 hours. The solvent was removed from the ether extract by evaporation under reduced pressure. The residue was dissolved in 200 ml. of ether. This ether solution was extracted with 80 ml. of 10% sodium bicarbonate solution, washed with two 50-ml. portions of water and dried over magnesium sulfate. The drying agent was removed by filtration, and the ether was distilled from the filtrate. The residual liquid was dissolved in a mixture of 125 ml. of alcohol and 125 ml. of concentrated hydrochloric acid solution. This solution was refluxed for one hour, cooled and filtered, the yield of 2-carboxy-6-methoxychromone, m.p. 258–261° (dec.), was 10.4 g. (47%).

A small amount of this acid, obtained in a previous run, was recrystallized several times from alcohol. There was obtained a white crystalline solid melting at 268° with decomposition.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.00; H, 3.63. Found: C, 60.20; H, 4.00.

Ten and four-tenths grams of the acid was heated at about 350° until no more evolution of carbon dioxide occurred. The residue was then distilled under a pressure of 0.2 mm. retaining the portion boiling at 90–110°. The white crystalline distillate was recrystallized from 50% alcohol to give 5.1 g. of 6-methoxychromone, m.p. 93–95°. The overall yield was 29%.

Anal. Calcd. for $C_{10}H_8O_3$: C, 68.18; H, 4.54. Found: C, 68.23; H, 4.68.

In the case of 2-carboxy-7-methoxychromone decarboxylation occurs at about 265°.

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[3] P. F. Wiley, THIS JOURNAL, **73**, 4205 (1951).

[4] M. Bloch and St. v. Kostanecki, *Ber.*, **33**, 1998 (1900).

[5] E. David and St. v. Kostanecki, *ibid.*, **35**, 2547 (1902).

[6] H. A. Offe, *ibid.*, **71**, 1837 (1938).

[7] Melting points are not corrected.

3-Dialkylaminomethylchromone Hydrochlorides.—A mixture of 0.05 mole of chromone, 0.052 mole of dialkylamine hydrochloride, 3.0 g. (0.1 mole) of formaldehyde as paraformaldehyde and 16 ml. of absolute alcohol was refluxed for four or five hours. The reaction mixture was refrigerated until a crystalline precipitate appeared or in case a precipitate did not appear the reaction mixture was concentrated and again cooled until a precipitate formed. The white crystalline solids were filtered off and purified by recrystallization from alcohol.

Absorption Spectra of Chromones.—Three chromones were used. These were 6-methoxychromone, 3-dimethylaminomethyl-6-methoxychromone hydrochloride and 3-dimethylaminomethyl - 7 - methoxychromone hydrochloride. These compounds all had ultraviolet absorption bands at 225 to 240 mμ and 300 to 320 mμ. The intensity of absorption of 6-methoxychromone was somewhat less than that of the other two. Infrared absorption occurred at 6.10 to 6.16 μ in all three cases. The 6-methoxychromone is a known compound and so was used as a standard.

2-Methylchromones, β-Ethoxyacrylophenone and β-Ethoxycrotonophenone in the Mannich Reaction.—These reactions were run exactly as were the ones with chromones having no 2-methyl substituent. In general, attempts were made to recover starting material and to isolate basic products. Starting materials were usually recovered to the extent of 70–80% except in the cases of β-ethoxyacrylophenone and β-ethoxycrotonophenone. In these cases a gummy gelatinous non-basic material was isolated. No basic product was isolated from any of these reactions.

3-Dimethylaminomethyl-7-methoxy-4-chromanone Hydrochloride by Reduction of 3-Dimethylaminomethyl-7-methoxychromone Hydrochloride.—A mixture of 2.0 g. (0.0073 mole) of 3-dimethylaminomethyl-7-methoxychromone hydrochloride, 0.1 g. of platinum oxide and 100 ml. of 95% alcohol was shaken under hydrogen at 50 p.s.i. until the theoretical amount of hydrogen was absorbed. The solution was filtered, and the filtrate was evaporated to dryness on the steam-bath under reduced pressure. The residue was recrystallized four times from absolute alcohol. The final product (0.03 g.) was a white crystalline solid melting at 168–170°. A mixture of this compound with an authentic sample of 3-dimethylaminomethyl-7-methoxy-4-chromanone hydrochloride,[3] m.p. 170–172°, melted at 170–172°.

Anal. Calcd. for $C_{13}H_{15}ClNO_3$: Cl, 13.07. Found: Cl, 13.24.

2 - Bromomethyl - 6 - methoxychromone. — Five grams (0.028 mole) of 2-methyl-6-methoxychromone and 5 g. (0.028 mole) of N-bromosuccinimide were dissolved in 50 ml. of carbon tetrachloride. The solution was stirred and refluxed for three hours. At the end of this time the potassium iodide–starch test for positive bromine was negative. The cooled reaction mixture was filtered to remove a solid, presumably succinimide. The solvent was removed from the filtrate by evaporation under reduced pressure. The residue resulting was recrystallized five times from alcohol. The yield of slightly tan needle-like crystals, m.p. 122–123°, was 1.3 g. (17%).

Recrystallization of a small sample three more times from alcohol raised the melting point to 124–126°.

Anal. Calcd. for $C_{11}H_9BrO_3$: C, 49.07; H, 3.35; Br, 29.74. Found: C, 49.10; H, 3.11; Br, 29.73.

2-Dimethylaminomethyl-6-methoxychromone Hydrochloride.—A mixture of 5.9 g. (0.022 mole) of bromomethyl-6-methoxychromone, 2.0 g. (0.044 mole) of dimethylamine and 100 ml. of alcohol was shaken and heated at 95–105° for six hours in a hydrogenation bomb. The cooled reaction mixture was poured out, and the alcohol was removed by evaporation. One hundred ml. of water and 200 ml. of ether were added to the residue. This mixture was filtered, and the ether layer was separated and dried over magnesium sulfate. The drying agent was removed, and dry hydrogen chloride was bubbled into the ether solution until no more precipitate formed. The mixture was refrigerated for three days and filtered. Four recrystallizations of the product from absolute alcohol gave 0.05 g. of light tan solid melting with decomposition at 223°.

Anal. Calcd. for $C_{13}H_{16}ClNO_3$: Cl, 13.15. Found: Cl, 13.02.

2-Dibromomethyl-6-methoxychromone.—This procedure is that by which Offe[6] reported monobromination of 2-methylchromone.

A boiling solution of 12.5 g. (0.05 mole) of 2-methyl-6-methoxychromone in 600 ml. of acetic acid was stirred while 2.35 g. (0.027 mole) of manganese dioxide and 4.32 g. (0.027 mole) of bromine was added at once. The mixture was refluxed for 15 minutes, but decolorization did not occur. The cooled solution was decanted from the unreacted manganese dioxide. The acetic acid was removed by evaporation under reduced pressure. Seven recrystallizations of the residue from alcohol gave a silvery crystalline solid melting at 158.5–160°.

Anal. Calcd. for $C_{11}H_8Br_2O_3$: C, 37.93; H, 2.31; Br, 45.90. Found: C, 37.61; H, 2.02; Br, 45.81.

Mannich Reaction on γ-Pyrone.—A mixture of 5.0 g. (0.052 mole) of γ-pyrone, 4.4 g. (0.054 mole) of dimethylamine hydrochloride, 1.6 g. (0.052 mole) of formaldehyde as paraformaldehyde and 16 ml. of absolute alcohol was refluxed for five hours. The refrigerated reaction mixture was filtered, and the precipitate was recrystallized four times from absolute alcohol. There was obtained 2.0 g. of white crystalline solid, m.p. 206°.

Anal. Calcd. for $C_8H_{12}ClNO_2$: C, 50.65; H, 6.34; N, 7.38; Cl, 18.95. Calcd. for $C_{11}H_{20}Cl_2N_2O_2$: C, 46.38; H, 7.07; N, 9.92; Cl, 25.05. Found: C, 48.30; H, 6.79; N, 8.33; Cl, 21.97.

Indianapolis Indiana