[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

Substituted Chromones

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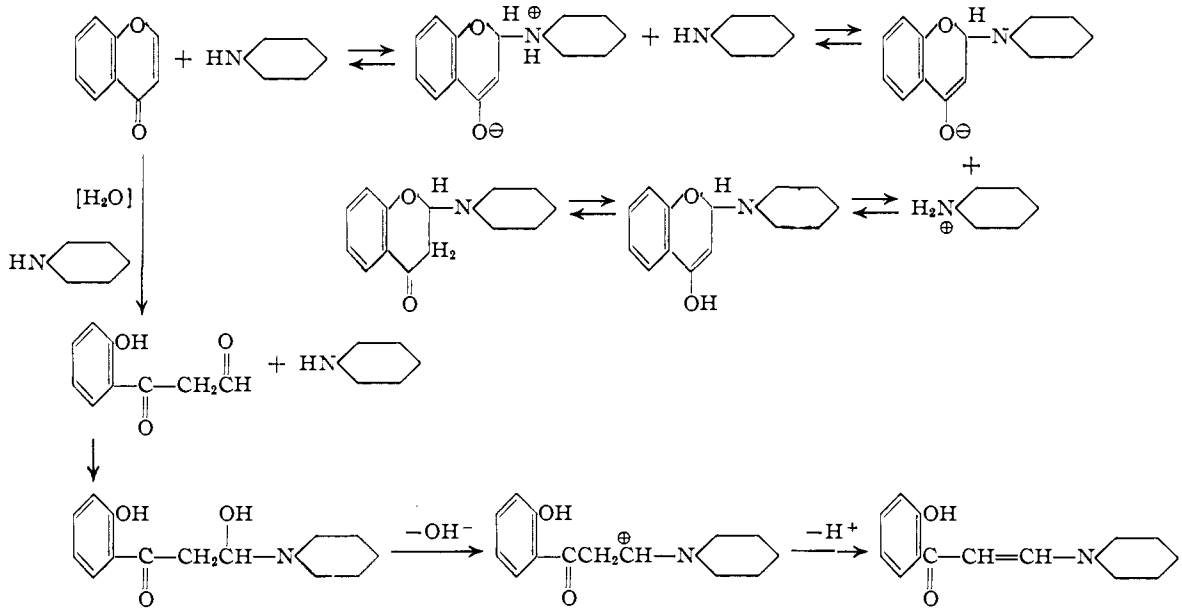
The structure of the compound formed by the bromination of 2-methylchromone has been determined. Piperidine reacts with 3-bromo-2-methylchromone to form 2-methyl-3-piperidinochromone. 3-Cyclohexylamino- and 3-piperidinochromone have been prepared from the corresponding amine and 3-bromochromone. Chromone reacts with amines to form β-amino-2-hydroxyacrylophenones. Absorption spectrum measurements between 220 and 600 mμ are reported.

During a study of some reactions of chromones, the bromination of 2-methylchromone was reinvestigated. Earlier Simonis, *et al.*,[2,3] reported that bromine adds to 2,3-dimethylchromone in the cold to form an unstable dibromo addition product which readily loses the bromine when dried. He also stated that when the reaction mixture is heated in benzene several substitution products are formed, one of which is 2,3-dibromodimethylchromone. Offe[4] investigated the reaction of bromine and manganese dioxide with 2-methylchromone in glacial acetic acid and obtained what he claimed was 2-bromomethylchromone. In this study, the procedure of Offe was repeated and a compound having an identical melting point with that reported by him was obtained. Evidence gathered in this Laboratory, however, indicates that the compound is 3-bromo-2-methylchromone rather than the 2-bromomethyl derivative. An iodine release study gave the characteristic negative result of α-bromo-α,β-unsaturated ketones when a technique described by Cromwell and Wankel[5] was employed. It was found also that when 6-chloro-2-methylchromone is treated with hydrochloric acid and manganese dioxide the resulting compound is identical with the known 3,6-dichloro-2-methylchromone[6] synthesized by the direct reaction of acetic anhydride and sodium acetate with α,5-dichloro-2-hydroxyacetophenone. 3-Bromo-2-methylchromone was also produced by the reaction of bromine or of N-bromosuccinimide with 2-methylchromone.



2-Methyl-3-N-piperidinochromone was formed by warming 3-bromo-2-methylchromone with piperidine. Apparently this reaction is not a direct replacement of bromine by the amine group because silver bromide was not readily obtained by heating 3-bromo-2-methylchromone with alcoholic silver nitrate. The failure of 3-bromo-2-methylchromone to react with a sodium alkoxide is additional evidence against direct substitution. The reaction may be satisfactorily explained by 1,4-addition[7] with the amine first adding to the β-carbon atom causing the separation of charges. The positively charged amino group may then lose a proton to a second molecule of the amine followed by a transfer of the proton to the negatively charged oxygen. Ketonization would then give a saturated α-bromo-β-aminochromanone, which could rearrange to an α-amino α,β-unsaturated ketone by a mechanism proposed for open chain aminoketones by Cromwell and Cram.[8]

(1) Parke, Davis and Company Fellow. Polychemicals Department, E. I. du Pont de Nemours and Co., Wilmington, Del.

(2) E. Petochek and H. Simonis, *Ber.*, **46**, 2014 (1913).

(3) H. Simonis and L. Herovici, *ibid.*, **50**, 646 (1917).

(4) H. A. Offe, *ibid.*, **71**, 1837 (1938).

(5) N. H. Cromwell and R. A. Wankel, THIS JOURNAL, **70**, 1320 (1948).

(6) G. Wittig, *Ann.*, **446**, 155 (1925).

(7) (a) N. H. Cromwell, D. B. Capps and E. S. Palmer, THIS JOURNAL, **73**, 1226 (1951); (b) N. H. Cromwell, H. H. Eby and D. B. Capps, *ibid.*, **73**, 1230 (1951).

(8) N. H. Cromwell and D. J. Cram, *ibid.*, **65**, 301 (1943).

TABLE I

Name	M.p., °C. (uncor.)	Cryst. structure	Yield, %	Reaction time, min.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3-Bromo-2-methylchromone (I)	117–118	White needles	67	30	$C_{10}H_7O_2N$	50.24	50.23	2.95	2.94		
2-Methyl-3-piperidinochromone (II)	90–91	White needles	80	360	$C_{15}H_{17}O_2N$	74.05	73.93	7.04	7.03	5.76	5.86
2-Methyl-3-piperidinochromone hydrogen sulfate (V)	203–204	White needles	100								
3-Piperidinochromone (VI)	137–138	White needles	60	15	$C_{14}H_{15}O_2N$	73.34	73.64	6.60	6.80	6.11	6.12
3-Piperidinochromone hydrogen sulfate (IX)	181–182	White needles	100								
3-Cyclohexylaminochromone (X)	157–157.5	Yellow needles	55	15	$C_{15}H_{17}O_2N$	74.04	73.80	7.04	7.21	5.74	5.82
2-Hydroxy-β-piperidinoacrylophenone (XI)	123–124	Yellow plates	89	15	$C_{14}H_{17}O_2N$	72.70	72.45	7.41	7.48	6.06	6.28
β-Anilino-2-hydroxyacrylophenone (XII)	144–145	Yellow plates	92	15	$C_{15}H_{13}O_2N$	75.29	75.34	5.48	5.65	5.85	5.85
β-Cyclohexylamino-2-hydroxyacrylophenone (XIII)	117–118	Yellow green plates	90	15	$C_{15}H_{19}O_2N$	73.44	73.30	7.81	7.76	5.71	5.92
β-[p-Dimethylaminoanilino]-2-hydroxyacrylophenone (XIV)	178–179	Red plates	90	15	$C_{17}H_{18}O_2N_2$	72.32	72.04	6.43	6.53	9.92	10.04

It was expected that the hydrolysis of 2-methyl-3-piperidinochromone with mineral acids might yield 3-hydroxy-2-methylchromone. However, only the acid salt was obtained, and neutralization of the reaction mixture regenerated the original amine. This study proved that the pyrone ring was not opened during the reaction of 3-bromo-2-methylchromone with piperidine. Similar results were obtained with investigations of 3-N-piperidinochromone and 3-N-cyclohexylaminochromone.

The reaction of chromone with several amines was also studied. In the reaction of chromone with piperidine, a yellow product giving a positive phenol or enol test with ferric chloride was obtained. The pyrone ring was opened[9] by piperidine with the subsequent production of the corresponding β-N-piperidinoacrylophenone. The identical product was obtained by the reaction of α-formyl-2-hydroxyacetophenone with piperidine. Since the ring was not opened when piperidine reacted with 3-bromochromone, it would seem that the cleavage of chromone with piperidine is possible because the 1,4-addition of the amine to chromone is reversible. Since chromone is unstable in base, prolonged reaction with piperidine would open the pyrone ring. Once the ring is opened, piperidine reacts with the 1,3-dicarbonyl compound to form 2-hydroxy-β-N-piperidinoacrylophenone.

Experimental

Absorption Spectrum Measurements.—Absorption spectrum measurements between the range of 220 to 600 mμ were made using a Beckman photoelectric spectrophotometer, model DU. They were taken at 1 to 5 mμ intervals in 1-cm. quartz cells using redistilled heptane as the solvent.

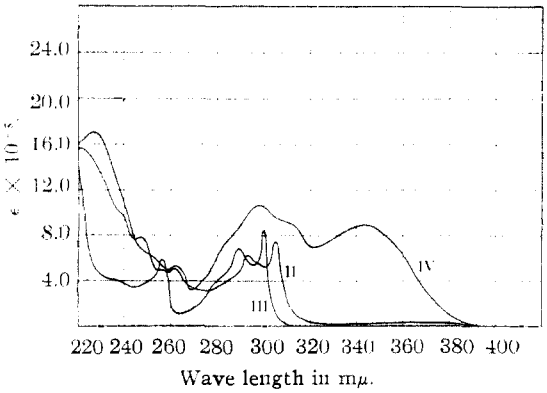


Fig. 1.—Ultraviolet absorption spectra of II, II and IV.

In Fig. 1 a comparison of 2-methyl-3-piperidinochromone (II) is made with 2-methylchromone (III), and 2-hydroxyacetylacetophenone (IV). The weak broad-banded absorption of the 3-amino derivatives between 320 and 380 mμ is characteristic of α-amino α,β-unsaturated ketones and is not present in the parent α,β-unsaturated ketones.[10] In Fig. 2 the spectra of 2-hydroxy-β-N-piperidinoacrylophenone (XI) and of β-N-cyclohexylamino-2-hydroxyacrylophenone (XIII) show strong maxima near 355 mμ which is characteristic of β-amino-α,β-unsaturated ketones.[10]

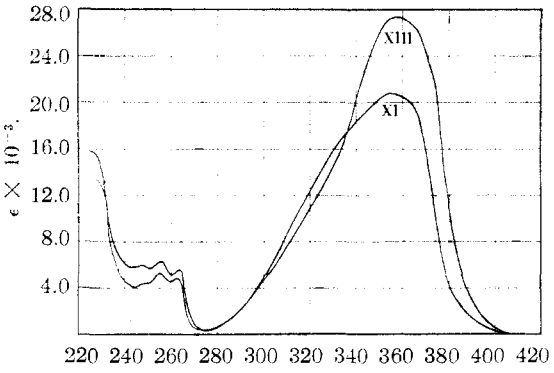


Fig. 2.—Ultraviolet spectra of XI and XIII.

3-Bromo-2-methylchromone.—3-Bromo-2-methylchromone was prepared according to the procedure of Offe.[4] The identical compound was prepared also by standard procedures using N-bromosuccinimide in carbon tetrachloride or bromine in carbon disulfide.

General Method for the Preparation of 3-Aminochromones.—A mixture of 1 mole of 3-bromo-2-methylchromone and 2.1 moles of the primary or secondary amine was heated on a steam-bath for 3 hours. Enough dry ether was added to precipitate completely the amine hydrobromide, which was removed by filtration. Evaporation of the ether gave a residue which was recrystallized from a 70% ethanol–water solution.

The amines were soluble in 25% sulfuric acid and formed only the acid salt when heated for 1.5 hours on a steam-bath. 2-Methyl-2-piperidinochromone hydrogen sulfate, for example, was prepared in a quantitative yield by adding an equivalent amount of concentrated sulfuric acid to an ether solution of the amine. Titration with standard sodium hydroxide showed that one mole of sulfuric acid had reacted with one mole of 2-methyl-3-piperidinochromone.

General Method for the Preparation of β-Amino-2-hydroxyacrylophenones.—A mixture of 1 mole of chromone and 1.2 moles of the amine was warmed on a steam-bath for 15 minutes. The crude product was removed by filtration, and recrystallized from ethanol. Identical products were obtained in very good yields by heating equimolar amounts

(9) G. Wittig and H. Blumenthal, *Ber.*, **60**, 1085 (1927), found that the pyrone ring is opened and β-amino-2-hydroxy-3-methylcrotonophenone is formed when 3-acetyl-2,8-dimethylchromone is permitted to stand with ammonium hydroxide.

(10) N. H. Cromwell and W. R. Watson, *J. Org. Chem.*, **14**, 411 (1949).

of the amine and α-formyl-2-hydroxyacetophenone for 1 hour on a steam-bath.

Reaction of β-Anilino-2-hydroxyacrylophenone with Piperidine.—One gram of β-anilino-2-hydroxyacrylophenone was heated on a steam-bath for 2 hours with 5.2 g. of piperidine. Trituration with water resulted in a quantitative yield of 2-hydroxy-β-piperidinoacrylophenone; m.p. 123–124°. The reaction was reversed by heating 2-hydroxy-β-piperidinoacrylophenone with excess aniline.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Preparation of Substituted 3-Piperidones[1]

BY F. F. BLICKE AND JOHN KRAPCHO[2,3]

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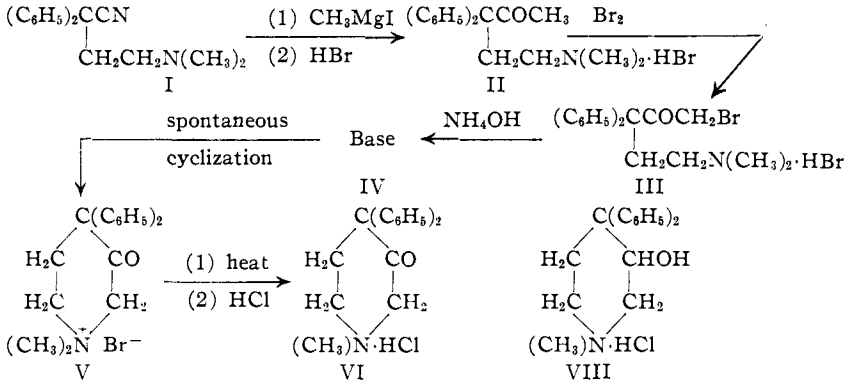
The bromination of basic ketone hydrobromides, analogous to Amidone in structure, produced bromo derivatives which, in the form of their free bases, cyclized spontaneously to methobromides of substituted 3-piperidones. The latter compounds when heated, lost methyl bromide with the formation of substituted 3-piperidones which were isolated as hydrochlorides.

Substituted 3-piperidones have been obtained from a diester by a Dieckmann condensation[4] and from a basic γ-bromo ketone by cyclization.[5]

In this paper we have described a synthesis for substituted 1-methyl-3-piperidones which, in the last step, consists of a cyclization of an α-bromo ketone. The procedure is especially adaptable for the preparation of a wide variety of substituted 1-alkyl-3-piperidones.

The synthesis is illustrated below in the case of 1-methyl-4,4-diphenyl-3-piperidone.[6] The yield of each compound (I–VI) was at least 80%. When



the free base of VI was treated with methyl bromide, the methobromide V was obtained.[6] This experiment proved that there was no ring contraction during the conversion of V into VI. By the use of the proper disubstituted acetonitrile, basic alkyl chloride and Grignard reagent, various 2-, 4-, 5- and 6-substituted 1-methyl-3-piperidones were obtained.

It was found that the nitrile I could be hydrolyzed to 2,2-diphenyl-4-dimethylaminobutyric acid hydrobromide in 84.5% yield by refluxing it with 48% hydrobromic acid. The corresponding diethylamino nitrile, by the same process, yielded the corresponding diethylaminobutyric acid hydrobromide in 85% yield.[7]

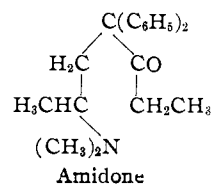
Bromination of II with two molecular equivalents of bromine yielded a dibromo derivative.

The ketone V was reduced to the corresponding alcohol VII. When the latter was heated under reduced pressure, methyl bromide was evolved with the formation of the same alcohol, VIII, which was obtained by reduction of ketone VI. Alcohol VIII was converted into its acetyl, *p*-nitrobenzoyl and *p*-aminobenzoyl derivative.

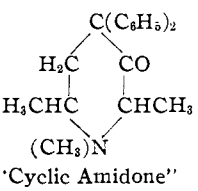
1-Methyl-4-phenyl-4-cyclohexyl-, 1,2,5-trimethyl-4,4-diphenyl- and 1,2,6-trimethyl-4,4-diphenyl-3-piperidinol hydrochlorides were obtained by catalytic reduction of the corresponding 3-piperidone hydrochlorides. The first-mentioned piperidinol was converted into its acetyl derivative.

When the ketone V was treated with zinc and hydrochloric acid, compound II, in the form of its hydrochloride, was produced in 79% yield. Compound V probably was first reduced to the corresponding alcohol which underwent a "hydramine fission" similar to that observed in the case of other β-hydroxyamines.[8]

Amidone and isoamidone hydrobromides were



Amidone



"Cyclic Amidone"

(1) Abstracts of Papers, 113th Meeting of the American Chemical Society, Chicago, Ill., April 19–23, 1948, p. 3K.

(2) This paper represents part of a dissertation submitted by John Krapcho in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, August, 1949.

(3) Parke, Davis and Company Fellow.

(4) S. M. McElvain, *et al.*, THIS JOURNAL, **55**, 1233 (1933); **71**, 896 (1949); **73**, 448 (1951); A. W. D. Avison and A. L. Morrison, *J. Chem. Soc.*, 1471 (1950).

(5) T. S. Work, *ibid.*, 194 (1946).

(6) In contrast to the smooth conversion of the quaternary compound V into the tertiary amine VI, it is interesting to note that Mannich and Gollasen (*Ber.*, **61**, 263 (1928)) obtained only a tar when they heated 1-methyl-3-pyrrolidone methobromide in an attempt to convert it into 1-methyl-3-pyrrolidone. However, they were successful in the elimination of methyl bromide after the quaternary ketone had been reduced to the secondary alcohol.

(7) D. J. Dupré, *et al.*, (*J. Chem. Soc.*, 500 (1949)) hydrolyzed these two nitriles by heating them with hydrochloric acid in sealed tubes at 150–160°.

(8) Paul Karrer, "Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1950, pp. 839, 867, 869 and 881; P. Rabe and W. Schneider, *Ann.*, **365**, 377 (1909).