[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

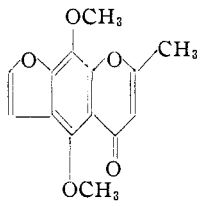
Chromones and Related Compounds as Bronchodilators

BY PAUL F. WILEY

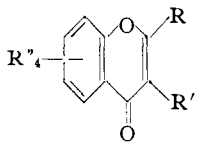
RECEIVED MARCH 3, 1952

Several chromones somewhat similar to khellin have been synthesized and found to have bronchodilator activity. Some methoxyacetophenones and some 1-(methoxyphenyl)-1,3-butanediones, both of which could be considered chromone analogs having open pyrone rings, were also found to be quite active bronchodilators.

It has been shown recently that khellin (I) is capable of very effective relaxation of the bronchi.[1,2] Khellin is a complex compound and is difficult to synthesize or to isolate from natural sources. In view of this it was thought that more readily accessible chromones having bronchodilator activity equal to or greater than that of khellin would be desirable. Accordingly, several chromones (II) lacking the furan ring of khellin were synthesized and tested. In the synthetic work leading to the chromones several substituted acetophenones (III) and 1-aryl-1,3-butanediones (IV) were prepared as intermediates. These could also be considered

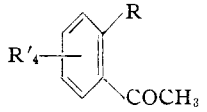


I



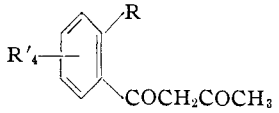
II

R = H, CH_3 or CH_2Br
R′ = H or $(CH_3)_2NCH_2 \cdot HCl$
R″$_4$ = combinations of hydrogen and methoxyl groups



III

R = H, OH or CH_3O
R′$_4$ = combinations of hydrogen and methoxyl groups



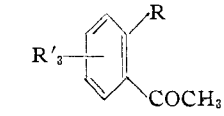
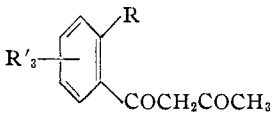
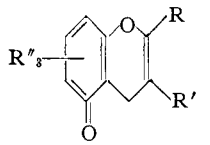
IV

R = OH or CH_3O
R′$_4$ = combinations of hydrogen and methoxyl groups

khellin analogs in which the furan ring is absent and the γ-pyrone ring has been opened by hydrolysis, and they too were studied for bronchodilator action. The formulas and activities of the compounds tested are listed in Table I. The activity of khellin on the same test is also shown for purposes of comparison.

The acetophenones were synthesized by well known methods. These methods were (1) methylation of an hydroxy group or groups in an acetophenone using methyl sulfate and an inorganic base,[3-5] (2) introduction of an acetyl group into phenolic compounds or phenol ethers by the Friedel-Crafts or Hoesch reactions[6-10] and (3) combinations of these two procedures. The butanediones were prepared by the reaction of ethyl acetate with an acetophenone in the presence of

TABLE I

No.	Substituents	Activity γ epinephrine/mg.
	Section A, 	
1	2-Methoxy	< 1
2	3-Methoxy	< 1
3	2-Hydroxy-5-methoxy	< 3
4	2,5-Dimethoxy	4
5	2-Hydroxy-4-methoxy	3
6	2,4-Dimethoxy	3
7	3,4-Dimethoxy	10
8	2-Hydroxy-4,6-dimethoxy	2.5
9	2-Hydroxy-4,5-dimethoxy	4
10	2,3,4-Trimethoxy	< 3
11	2-Hydroxy-3,4,6-trimethoxy	2.5
12	2,3,4,6-Tetramethoxy	< 3
	Section B, 	
13	2-Hydroxy-5-methoxy	< 1
14	2,5-Dimethoxy	< 3
15	2,4-Dimethoxy	< 3
16	2-Hydroxy-3,4-dimethoxy	3
17	2,3,4-Trimethoxy	3
18	2-Hydroxy-4,6-dimethoxy	< 0.5
19	2,4,6-Trimethoxy	< 1
20	2-Hydroxy-3,4,6-trimethoxy	2
21	2,3,4,6-Tetramethoxy	< 0.1
	Section C, 	
22	6-Methoxy	0
23	7-Methoxy	0.6
24	2-Dimethylaminomethyl-7-methoxy hydrochloride	0.2
25	2-Methyl-6-methoxy	4
26	2-Methyl-7-methoxy	5
27	2-Bromomethyl-7-methoxy	1
28	2-Methyl-5,7-dimethoxy	< 1
29	2-Methyl-7,8-dimethoxy	3
30	2-Methyl-5,7,8-trimethoxy	< 3
Khellin		30

(1) E. E. Swanson, private communication.
(2) G. V. Anrey, G. S. Barsoum and M. R. Kenaway, *J. Pharm. Pharmacol.*, **1**, 164 (1949).
(3) R. Adams, THIS JOURNAL, **41**, 247 (1919).
(4) M. Blumberg and St. v. Kostanecki, *Ber.*, **36**, 2191 (1903).
(5) V. D. N. Sastri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **23A**, 262 (1946) [*C. A.*, **41**, 449 (1947)].
(6) G. H. Jones, J. B. D. Mackenzie, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 562 (1949).
(7) W. M. Lauer and E. E. Renfrew, THIS JOURNAL, **67**, 808 (1945).
(8) P. F. Wiley, *ibid.*, **73**, 4205 (1951).
(9) C. R. Noller and R. Adams, *ibid.*, **46**, 1889 (1924).
(10) W. Baker, *J. Chem. Soc.*, 662 (1941).

TABLE II

Substituents	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Section A, 1-Aryl-1,3-butanediones							
2-Hydroxy-5-methoxy	29	102–104	$C_{11}H_{12}O_4$	63.46	64.17	5.78	5.80
2,5-Dimethoxy	28	[a]	$C_{12}H_{14}O_4$	64.86	65.07	6.32	6.63
2-Hydroxy-3,4-dimethoxy	20	104–107	$C_{12}H_{14}O_5$	60.51	60.46	5.88	6.28
2-Hydroxy-4,6-dimethoxy	37	83–85	$C_{12}H_{14}O_5$	60.51	60.77	5.88	6.26
2-Hydroxy-3,4,6-trimethoxy	72	117–119	$C_{13}H_{16}O_6$	58.21	58.48	5.97	6.42
2,3,4,6-Tetramethoxy	41	76–78	$C_{13}H_{18}O_6$	59.57	59.75	6.38	6.32
Section B, Chromones							
2-Bromomethyl-7-methoxy	10	161–163	$C_{11}H_9BrO_3$[b]	49.07	48.81	3.34	3.24
2-Methyl-5,7-dimethoxy	..	121–123	$C_{12}H_{12}O_4$[c]	65.45	65.60	5.46	5.86
2-Methyl-5,7,8-trimethoxy	85	167–169	$C_{13}H_{14}O_5$	62.40	62.20	5.60	5.76

[a] This compound was a liquid, b.p. 97° under 0.1 mm. pressure; $n^{25}D$ 1.5893. [b] *Anal.* Calcd. for $C_{11}H_9BrO_3$: Br, 29.74. Found: Br, 29.74. [c] This compound forms a hydrate melting at 68–70°.

sodium sand or sodium hydride.[4,8] It was found to be advisable to use three equivalents of sodium for each mole of acetophenone when the acetophenones had three or more methoxyl substituents, and an additional equivalent of sodium was needed if an hydroxyl group were present.

The 2-methylchromones were prepared by acid-catalyzed cyclization of the proper 1-(2-hydroxyphenyl)-1,3-butanediones. In these syntheses the intermediate diones were not isolated but were recyclized with little purification. 6-Methoxy- and 7-methoxychromone were synthesized as described previously.[11] 3-Dimethylaminomethyl-7-methoxychromone hydrochloride was prepared by the reaction of 7-methoxychromone with dimethylamine hydrochloride and formaldehyde.[11] Bromination of 2-methyl-7-methoxychromone using N-bromosuccinimide, as described for the 6-methoxy isomer,[11] gave 2-bromomethyl-7-methoxychromone.

The new compounds synthesized in this work are listed with melting points and analytical data in Table II.

The tests for bronchodilator activity were run on the isolated guinea pig tracheal chain. The activity of the compound being tested was compared to the activity of epinephrine. Results are expressed (Table I) in the number of micrograms of epinephrine required to equal the activity of 1 mg. of the compound tested. Very little correlation of structure with activity was observed. All of the three types of compounds tested showed about equal activity. Some relatively simple compounds (No. 4, 7 and 9, Table I) had considerable activity. Those chromones having no 2-methyl substituent (No. 22, 23 and 24, Table I) showed negligible activity.

Acknowledgment.—I wish to thank Mr. E. E. Swanson for the pharmacological work. Thanks are also due to Mr. W. L. Brown, Mr. H. L. Hunter and Mr. W. J. Schenck for microanalyses.

Experimental[12]

Acetophenones.—All of the acetophenones used were known compounds and were prepared according to the literature.

1-Aryl-1,3-butanediones.—1-(2-Hydroxy-5-methoxyphenyl)-1,3-butanedione was synthesized as described previously[8] in the description of the preparation of 2-methyl-6-methoxychromone. The remainder of the butanediones were prepared as described below. The procedure used for 1-(2-hydroxyphenyl)-1,3-butanediones was somewhat different from that used when preparing 1-(2-methoxyphenyl)-1,3-butanediones. The method used for the 2-hydroxy compounds is exemplified using 1-(2-hydroxy-4,6-dimethoxyphenyl)-1,3-butanedione and for the 2-methoxy compounds using 1-(2,4,6-trimethoxyphenyl)-1,3-butanedione.

1-(2-Hydroxy-4,6-dimethoxyphenyl)-1,3-butanedione.—A few milliliters of a solution of 29.4 g. (0.15 mole) of 2-hydroxy-4,6-dimethoxyacetophenone in 79.2 g. (0.9 mole, 88 ml.) of dry ethyl acetate was added to 13.8 g. (0.6 atom) of sodium sand. The mixture was stirred until vigorous reaction began. The remainder of the acetophenone solution was added dropwise with stirring followed by two hours' heating on the steam-bath. The excess ethyl acetate was removed by evaporation, and a solution of 50 ml. of acetic acid in 200 ml. of water was added to the residue. The oil which appeared solidified after the acidified mixture was cooled strongly. The solid was filtered off and recrystallized once from alcohol to give 13.7 g. (37%) of white solid melting at 73–78°. Further recrystallization from alcohol raised the melting point to 83–85°.

The analytical data for this compound are given in Table II.

1-(2,4,6-Trimethoxyphenyl)-1,3-butanedione.—A solution of 11.1 g. (0.053 mole) of 2,4,6-trimethoxyacetophenone in 50 ml. of dry ethyl acetate was prepared, and a few milliliters of the solution was added to 3.7 g. (0.16 atom) of sodium sand. The mixture was stirred until reaction began. The remainder of the acetophenone solution was then added slowly with stirring. The reaction mixture was stirred overnight and acidified with a solution of 14 ml. of acetic acid in 240 ml. of water. The aqueous mixture was extracted with three 75-ml. portions of ether. The combined ether extracts were washed with 50 ml. of water and extracted with two 50-ml. portions of 10% sodium hydroxide solution. The combined basic extracts were acidified with concentrated hydrochloric acid, and the dione was extracted with three 50-ml. portions of ether. The ether extracts were combined and concentrated by evaporation. The residue was distilled *in vacuo*. The higher boiling fraction was retained and purified by three recrystallizations from alcohol. The melting point of the product was 96–97° (lit. 97–98°).

Chromones.—6-Methoxy- and 7-methoxychromone were prepared from the corresponding acetophenones by treatment with diethyl oxalate and sodium followed by acid hydrolysis and thermal decarboxylation.[11] 2-Bromomethyl-7-methoxychromone was prepared by N-bromosuccinimide bromination of 2-methyl-7-methoxychromone in the manner previously described[11] for 2-bromomethyl-6-methoxychromone. The reaction of 7-methoxychromone with paraformaldehyde and dimethylamine hydrochloride gave 3-dimethylaminomethyl-7-methoxychromone hydrochloride.[11] 2-Methyl-6-methoxychromone and 2-methyl-7-methoxychromone were synthesized by the reaction of ethyl acetate and sodium hydride with the proper acetophenone followed by cyclization with acid. This was described in a previous publication.[8] The remainder of the chromones were prepared as was 2-methyl-5,7,8-trimethoxychromone.

2-Methyl-5,7,8-trimethoxychromone.—A solution of 2.5 g. (0.0093 mole) of 1-(2-hydroxy-3,4,6-trimethoxyphenyl)-

(11) P. F. Wiley, THIS JOURNAL, **74**, 4326 (1952).

(12) Melting points are not corrected.

1,3-butanedione in 12.5 ml. of acetic acid containing 0.5 ml. of concentrated hydrochloric acid was refluxed for 15 minutes. Volatile material was removed from the reaction mixture by evaporation under reduced pressure on the steam-bath. The residue was triturated with ether and the mixture was filtered. The solid product weighed 1.9 g. (yield 81%) and melted at 157–162°. Four recrystallizations from 50% alcohol gave a yellow crystalline compound, m.p. 167–169°. The analytical data for this compound are given in Table II.

INDIANAPOLIS, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Dinitrophenylhydrazones of α-Halo Ketones

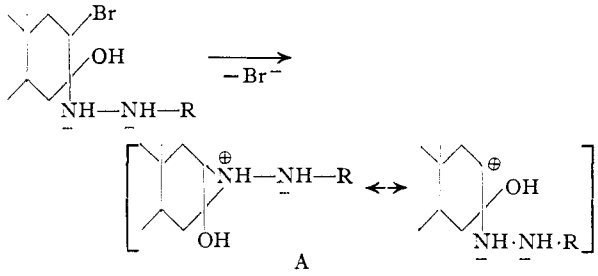
BY FAUSTO RAMIREZ AND ARTHUR F. KIRBY[1]

RECEIVED MARCH 10, 1952

In a study of the behavior of α-halo ketones toward the usual carbonyl reagents the following dinitrophenylhydrazones (DNPH) were prepared. DNPH of: 2-chlorocyclohexanone (Ia), 2-bromocyclohexanone (IIa), 6,6-dimethyl-2-bromocyclohexanone (IIIa), 2-bromo-1-tetralone (IVa) and 2-bromo-1-keto-1,2,3,4-tetrahydrophenanthrene (Va). When solutions of the halo hydrazones Ia, IIa or IIIa in acetic acid were kept at their boiling points for five minutes, smooth dehydrohalogenation took place with formation of the corresponding α,β-unsaturated hydrazone. Loss of hydrogen halide occurred on similar treatment of the halo ketones with 1 mole of dinitrophenylhydrazine in acetic acid solution. No elimination from the halo hydrazone or the halo ketone was observed in those cases (IVa and Va) in which an aromatic ring was conjugated to the phenylhydrazone group. The methoxyhydrazones were easily obtained from the halo hydrazones on short warming in methanol. From Ia, IIa and IIIa osazones were obtained on treatment with excess dinitrophenylhydrazine. These observations suggest the formation of an intermediate halo hydrazone in the Mattox–Kendall reaction used to introduce the Δ^4-3-keto system in some steroids and are consistent with a recently stated picture of the reaction involving a solvolysis of the halogen facilitated by the electron-donor character of the nitrogen atom α to the phenyl in the phenylhydrazone.

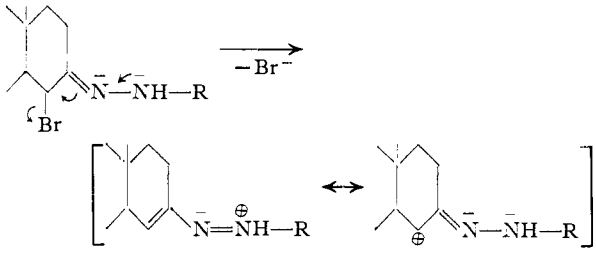
The behavior of α-halo ketones toward the usual carbonyl reagents presents some interesting features. Hantzsch[2] described the formation of osazones and 1,2-dioximes from compounds of the type R_1–CHX–CO–R_2 using 1–3 moles of phenylhydrazine and hydroxylamine, respectively. Curtin and Tristram[3] established the formula $C_{28}H_{24}N_4$ for the product of the reaction between α-haloacetophenones and phenylhydrazine and furnished evidence in favor of a tetrahydropyridazine structure for that product. With hydroxylamine, α-bromoacetophenone is reported to form the dioxime of phenylglyoxal.[4] An unsuccessful attempt to prepare the (*p*-carboxyphenyl)-hydrazone of 2-chlorocyclohexanone has been recorded[5] and this is in agreement with the isolation of a dinitrophenylosazone[6] and of a 1,2-dioxime[7] on treatment of 2-chlorocyclohexanone with the corresponding carbonyl reagent.

A recent communication by Mattox and Kendall[8] reporting the formation of α,β-unsaturated dinitrophenylhydrazones from steroidal α-bromo ketones by means of dinitrophenylhydrazine in acetic acid solution, has prompted further studies on the course of this smooth and useful dehydrohalogenation.[9,10] Djerassi[9a] pictures the reaction as proceeding *via* a cyclic immonium intermediate A, without initial formation of a hydrazone of the bromo ketone.



A

On the other hand, Mattox and Kendall[9b] favor the formation of an α-bromo hydrazone in which the reactivity of the halogen atom is explained as



In one case,[9b] bromination of the dinitrophenylhydrazone of the parent ketone in chloroform solution led to a rather unstable α-bromo hydrazone which eliminated hydrogen bromide in acetic acid solution. The α-bromo hydrazones were not isolated from the reaction between the corresponding α-halo ketone and the carbonyl reagent.

The present communication deals with the preparation of the dinitrophenylhydrazones of several simple α-halo ketones of varied structure and re-

(1) From the Ph.D. thesis of Arthur F. Kirby. Presented at the 121st National Meeting of the American Chemical Society, Buffalo, N. Y., March, 1952.

(2) A. Hantzsch and W. Wild, *Ann.*, **289**, 285 (1896).

(3) D. Y. Curtin and E. W. Tristram, THIS JOURNAL, **72**, 5238 (1950).

(4) R. Scholl and G. Matthaiopoulos, *Ber.*, **29**, 1550 (1896). The 2,4-dinitrophenylhydrazone of α-bromoacetophenone has just been described (G. D. Johnson, THIS JOURNAL, **73**, 5888 (1951)).

(5) H. W. Murphy and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **32**, 83 (1943).

(6) R. B. Loftfield, THIS JOURNAL, **73**, 4707 (1951).

(7) N. Tokura and R. Oda, *Bull. Inst. Phys. Chem. Research (Tokyo)*, **22**, 844 (1943); *cf.* A. F. Childs, L. J. Goldsworthy, G. F. Hardings, S. G. P. Plant and G. A. Weeks, *J. Chem. Soc.*, 2320 (1948).

(8) V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948).

(9) (a) C. Djerassi, *ibid.*, **71**, 1003 (1949); (b) V. R. Mattox and E. C. Kendall, *ibid.*, **72**, 2290 (1950).

(10) These studies have been carried out in the steroid field. Recently, W. W. Rinne, *et al.* (*ibid.*, **72**, 5759 (1950)) prepared 2-methyl-2-cyclohexen-1-one dinitrophenylhydrazone from an unidentified mixture of bromo ketones obtained by bromination of 2-methylcyclohexanone. For a recent application in the morphine series see M. Gates and G. Tschudi, *ibid.*, **74**, 1110 (1952).