from residues by evaporation on a water-bath, this figure is significant only as a limit, indicating the maximum amount of ethoxyl compounds which could have been formed from the metal ketyl in this experiment. If all the silver iodide resulted from cleavage of benzopinacol monoethyl ether or α-bromobenzohydryl ethyl ether to ethyl iodide, the result could account for a reduction in the yield of benzophenone from the theoretical 100 to 67.1%, but not to 19.9% as was actually observed in this experiment. By attributing the silver iodide to cleavage of benzopinacol diethyl ether, it is only possible to account for a reduction in the yield of benzophenone to 83.5%. This result proves conclusively that the reduction in the yield of benzophenone can be explained only by the fact that it is formed in a secondary reaction which was curtailed by the rapid decomposition of the ketyl with ethyl bromide.[10]

Summary

It has been shown that the reaction between metal ketyls and alkyl halides does not follow the course suggested by Schlenk. The ketone which is regenerated results from a secondary reaction between a product of the primary reaction and a second molecule of the ketyl. When the ketyl is consumed with sufficient rapidity in the primary reaction, the secondary reaction may be greatly curtailed, resulting in very reduced yields of ketone.

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[10] The referee to whom this paper was submitted inquired, "why the authors have omitted discussion of the reaction $(C_6H_5)_2CONa + C_2H_5Br = NaBr + (C_6H_5)_2CO + C_2H_5$— which is in all probability strongly exothermic. The ethyl groups formed could then react with the ketyl to give the carbinolate or if present in higher concentration might be expected also to react . . . with . . . benzophenone to give an ether."

As this thought may also occur to other readers it seems advisable to point out that the chief objection to this hypothesis is that it implies that the ketone is formed in the primary reaction, whereas the evidence in this paper shows that it results from a secondary reaction. The referee's mechanism suggests that the yield of benzophenone might be *increased* when the secondary reaction is largely eliminated (by rapid decomposition of the ketyl), but does not account for the *reduced* yield actually observed, for even if all of the ethyl radicals which were unable to combine with a ketyl radical reacted with the benzophenone to form, for instance, the ethyl ether of diphenylethylcarbinol, the yield of free benzophenone would still equal that required by Equation 1. As a matter of fact, the results of the ethoxyl determination described above show that in at least one case not more than 16.5% of the ketyl molecules were converted into ethoxyl compounds.

Finally, to the extent that the referee's mechanism may be considered to imply that the reaction between sodium benzophenone and ethyl bromide should be identical with the reaction between sodium and a mixture of benzophenone and ethyl bromide, this mechanism is essentially that of Schmidlin which has been discussed in a previous paper of this series [Wooster, THIS JOURNAL, **51**, 1856 (1929)].

PROVIDENCE, RHODE ISLAND RECEIVED JULY 25, 1934

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of Certain Methoxychalcones and Methoxybenzal-β-coumaranones from Methoxyacetophenones and Nitrobenzaldehydes[1]

BY DONALD PRICE[2] AND MARSTON TAYLOR BOGERT

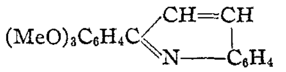
In continuance of our studies of the connection between chemical constitution and tinctorial properties in various groups of dyes,[3] we have carried out some experimental work in the field of the chalcones and structurally related benzal-β-coumaranones (1-benzal-2(1)-benzofuranones). The present paper records the synthesis of the compounds required and incidental observations. A subsequent paper will report the tinctorial properties of these products and discuss the apparent influence of chemical constitution upon these properties.

2,3,4-Trimethoxyacetophenone was condensed with *o*-, *m*- and *p*-nitrobenzaldehyde, in the presence of alkali, and the resulting nitrochalcones were reduced with stannous chloride and hydrochloric acid in glacial acetic acid solution

(I) $(MeO)_3C_6H_2COCH_3 + OCHC_6H_4NO_2 \longrightarrow$

(II) $(MeO)_3C_6H_2COCH{=}CHC_6H_4NO_2 \xrightarrow{+H_2}$

(III) $(MeO)_3C_6H_2COCH{=}CHC_6H_4NH_2 \xrightarrow{-H_2O}$

(IV) 

$(MeO)_3C_6H_4C\begin{cases} CH{=}CH \\ \quad\quad\quad | \\ {=}N{-}{-}C_6H_4 \end{cases}$

The aminochalcones (III) were obtained readily in the case of the *m*- and *p*-derivatives. As was expected, however, reduction of the *o*-nitrochal-

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[1] Presented at the Washington Meeting of the American Chemical Society, March 27, 1933, before the Division of Dye Chemistry. Based upon the Dissertation submitted by Donald Price, 1929, in partial fulfilment of the requirements for the Ph.D. degree in the Faculty of Pure Science, Columbia University, and to which the reader is referred for further details.

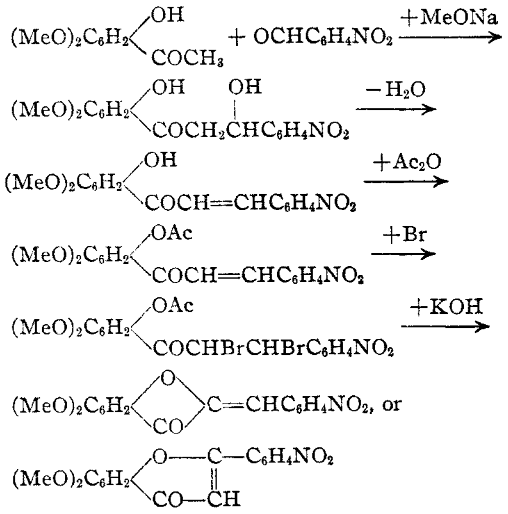
[2] Du Pont Fellow at Columbia University, 1928–1929.

[3] See Bogert and Allen, THIS JOURNAL, **49**, 1315 (1927), where references to earlier publications also are given.

cone gave only the quinoline (IV), and the intermediate *o*-aminochalcone was not secured.

For the preparation of the benzalcoumaranones needed, the 2-hydroxychalcones were essential, and these latter were obtained most satisfactorily by dissolving 2-hydroxy-3,4-dimethoxyacetophenone in absolute methanol, adding sodium methoxide and allowing the whole to stand cold for some time. This gave a mixture of the desired chalcone (VI) and the intermediate aldol (V). By the action of heat, the colorless or pale yellow aldols readily lost water with formation of the darker colored chalcones.

When the chalcone, the aldol, or the mixture of the two was digested with acetic anhydride and sodium acetate, there resulted the acetyl derivative (VII) of the chalcone, which was brominated, and the dibromide (VIII) converted into the coumaranone (IX) by the action of alkali. The nitrobenzal derivative so prepared was then reduced to the corresponding aminobenzalcoumaranone.



$$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{OH}\\ \text{COCH}_3\end{matrix}\right. + \text{OCHC}_6\text{H}_4\text{NO}_2 \xrightarrow{+\text{MeONa}}$$

(V) $$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{OH} \quad \text{OH}\\ \text{COCH}_2\text{CHC}_6\text{H}_4\text{NO}_2\end{matrix}\right. \xrightarrow{-\text{H}_2\text{O}}$$

(VI) $$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{OH}\\ \text{COCH=CHC}_6\text{H}_4\text{NO}_2\end{matrix}\right. \xrightarrow{+\text{Ac}_2\text{O}}$$

(VII) $$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{OAc}\\ \text{COCH=CHC}_6\text{H}_4\text{NO}_2\end{matrix}\right. \xrightarrow{+\text{Br}}$$

(VIII) $$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{OAc}\\ \text{COCHBrCHBrC}_6\text{H}_4\text{NO}_2\end{matrix}\right. \xrightarrow{+\text{KOH}}$$

(IX) $$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{O}\\ \text{CO}\end{matrix}\right\rangle\text{C=CHC}_6\text{H}_4\text{NO}_2\text{, or}$$

(X) $$\text{(MeO)}_2\text{C}_6\text{H}_2\left\langle\begin{matrix}\text{O—C—C}_6\text{H}_4\text{NO}_2\\ \text{CO—CH}\end{matrix}\right.$$

This was the process used by Von Kostanecki and his co-workers,[4] for the production of flavones (X), although in many cases the isomeric benzalcoumaranones (IX) were formed instead. Von Kostanecki[4h] regarded the ring closure as proceeding in three steps—(a) saponification of the acetoxy group, (b) cyclization and (c) elimination of hydrobromic acid, and that the nature of the product was determined by the relative velocities of the two competing reactions (a) and (c). If (a) occurred first, a flavone resulted; if (c), a benzalcoumaranone.

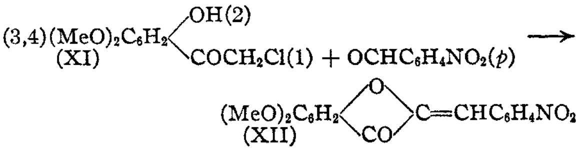
Auwers and Anschütz,[5] however, as the outcome of their investigations in this field, concluded that the course of the reaction was independent of the velocity of saponification of the acetoxy group. It was their belief that the determining factor was the temperature at which the reaction was carried out, for they observed that certain chalcone dibromides gave flavones when suspended in cold alcohol and shaken with alkali, but if treated with alkali in hot alcohol, gave benzalcoumaranones.

The researches of Von Kostanecki's laboratory,[4a,b,c,d,e,f,g,i] and of Auwers and Anschütz,[6] have shown that the character of the substituents present on the aromatic nuclei is also of influence in determining the course of the reaction.

As nitro derivatives of type (VIII), so far as we are aware, have not previously been subjected to this reaction, it was impossible to predict *a priori* whether the products would be flavones (X), or benzalcoumaranones (IX). Our evidence indicates that they were the latter.

Woker, Von Kostanecki and Tambor[7] found that benzalcoumaranones dissolved in concentrated sulfuric acid to orange, red or violet solutions; whereas the flavones gave colorless or pale yellow solutions, which often exhibited a violet, green or blue fluorescence. Our products gave non-fluorescent orange-red solutions in concentrated sulfuric acid.

As a further proof of the correctness of our assumption concerning the structure of these products, the *p*-nitrobenzal derivative (IX) was synthesized by the method of Friedländer and co-workers,[4b,d,7,8,9] a method which has been shown to yield exclusively benzalcoumaranones:



$$\underset{\text{(XI)}}{(3,4)\text{(MeO)}_2\text{C}_6\text{H}_2}\left\langle\begin{matrix}\text{OH(2)}\\ \text{COCH}_2\text{Cl(1)}\end{matrix}\right. + \text{OCHC}_6\text{H}_4\text{NO}_2(p) \longrightarrow \underset{\text{(XII)}}{\text{(MeO)}_2\text{C}_6\text{H}_2}\left\langle\begin{matrix}\text{O}\\ \text{CO}\end{matrix}\right\rangle\text{C=CHC}_6\text{H}_4\text{NO}_2$$

The product so synthesized was identical with

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[4] (a) Klobski and Von Kostanecki, *Ber.*, **31**, 725 (1898); (b) Feuerstein and Von Kostanecki, *ibid.*, **31**, 1758 (1898); (c) Emilewicz and Von Kostanecki, *ibid.*, **32**, 310 (1899); (d) Feuerstein and Von Kostanecki, *ibid.*, **32**, 316 (1899); (e) Herstein and Von Kostanecki, *ibid.*, **32**, 319 (1899); (f) Von Kostanecki and Rozycki, *ibid.*, **32**, 2258 (1899); (g) Von Kostanecki and Tambor, *ibid.*, **32**, 2264 (1899); (h) **32**, 2268 (1899); (i) Von Kostanecki, *Bull. soc. chim.*, [3] **30**, XIX (1903).

[5] Auwers and Anschütz, *Ber.*, **54**, 1543 (1921).

[6] Auwers and Anschütz, *ibid.*, **54**, 1544 (1921).

[7] Woker, Von Kostanecki and Tambor, *ibid.*, **36**, 4235 (1903).

[8] (a) Friedländer and Rudt, *ibid.*, **29**, 879 (1896); (b) Friedländer and Löwy, *ibid.*, **29**, 2432 (1896); (c) Friedländer and Neudorfer, *ibid.*, **30**, 1077 (1897); (d) Friedländer and Schnell, *ibid.*, **30**, 2154 (1897).

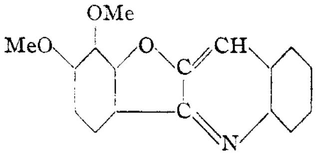
[9] Kesselkaul and Von Kostanecki, *ibid.*, **29**, 1888 (1896).

that which we obtained by the Von Kostanecki method.

Contrary to the experience of Auwers and Anschütz,[5] temperature was without effect upon the course of the Von Kostanecki reactions carried out by us.

The action of caustic alkali upon the acetylated *o*-nitrochalcone dibromide (VIII) gave not only the expected coumaranone (IX), but also another crystalline product (m. p. 133°), containing bromine, which has not yet been identified.

Reduction of the *o*-nitrobenzalcoumaranone (IX) with stannous chloride and hydrochloric acid, yielded two different products, according to the conditions of the reaction. Carried out at room temperature, the product was the aminobenzalcoumaranone; but at 100° only a small amount of this was formed, the main product being a compound apparently identical with the dimethoxycoumarinoline of Feist and Siebenlist,[10] prepared in another way, and to which they assigned the constitution



(XIII)

Experimental

Pyrogallol trimethyl ether was prepared by the method of Ullmann,[11] with a number of modifications which we found advantageous when working with the large quantities of material required. The process was as follows.

To 300 g. of pyrogallol in a 5-liter flask, there was added all at once 900 g. of a 40% aqueous sodium hydroxide solution heated to 100°. Dimethyl sulfate was immediately added, in small portions (not over 50 cc.) at a time, with thorough agitation of the flask contents before each addition. The violent reaction which ensued was thus kept under control, care being taken also to maintain the alkalinity of the solution toward the end of the operation by the use of more sodium hydroxide if necessary. In all, 848 cc. of commercial dimethyl sulfate was added, for a larger excess was found to improve the yield.

As the solution cooled, most of the trimethyl ether crystallized. After standing cold for twelve hours or more, two to three volumes of ice water was added, the mixture stirred thoroughly, filtered, the precipitate washed with cold water and dried. It was dissolved in ether (2–3 liters), the ether solution filtered, dried over calcium chloride and the ether distilled off. There remained a yellow, or reddish-yellow, oil which crystallized upon standing, and then melted 2 or 3° below the m. p. of 47° recorded by Ullmann for the pure compound; yield, 70–80%. This product, without further purification, proved to be entirely suitable for our experiments.

Gallacetophenone trimethyl ether (2,3,4-trimethoxyacetophenone) (I) was prepared as described by Blumberg and Von Kostanecki,[12] by the action of dimethyl sulfate upon gallacetophenone, was a transparent highly refractive pale yellow oil, b. p. 175–176° at 20 mm. (Blumberg and Von Kostanecki give the b. p. as 174° at 19 mm.); yield, 50%. In one of the experiments the dimethyl ether formed in the reaction was also recovered and amounted to 20%.

Gallacetophenone-3,4-dimethyl Ether (2-Hydroxy-3,4-dimethoxyacetophenone).—The Perkin and Weizmann[13] procedure was followed in the production of this compound, by condensing pyrogallol trimethyl ether with acetyl chloride, in the presence of aluminum chloride. After a single crystallization from methanol, the product formed colorless needles, which melted at 77° (corr.); yield over 50%. Perkin and Weizmann recorded the m. p. also as 77°.

The demethylation of a methoxyl ortho to an entering acetyl group in such reactions is not uncommon, for it has been observed also by others.[14]

This method proved much more satisfactory than that of David and Von Kostanecki,[15] because the latter yielded a considerable amount of the trimethyl ether and the desired dimethyl ether was always badly contaminated with tarry by-products.

2-Hydroxy-3,4-dimethoxy-ω-chloroacetophenone (XI).—To a solution of 7 g. of chloroacetyl chloride in 35 cc. of carbon disulfide, there was added, in small portions, 8 g. of finely pulverized aluminum chloride, dissolving completely each portion before the next one was added. An addition compound of chloroacetyl chloride and aluminum chloride gradually separated as a yellow oil. If the mixture was allowed to cool much below ordinary room temperature, this oil crystallized. If this occurred, the flask was immersed in warm water until the solid liquefied again.

When all the aluminum chloride had dissolved, a solution of 10 g. of pyrogallol trimethyl ether in 30 cc. of carbon disulfide was added all at once and the flask placed in ice water. After the abatement of the initial vigorous reaction, the mixture was warmed at 100° for about fifteen minutes, cooled to room temperature and the carbon disulfide decanted from the red tarry precipitate. Treatment of this tarry addition product with cracked ice and dilute hydrochloric acid, slowly decomposed it with separation of a coffee-colored oil. When the mass was filtered with suction, a dark brown oil ran through into the filtrate and there remained a colorless solid. Crystallized from alcohol, this solid weighed 2.2 g. (16% yield). Recrystallized from the same solvent, it formed fine colorless needles, m. p. 161.5° (corr.).

Anal. Calcd. for $C_{10}H_{11}O_4Cl$: C, 52.05; H, 4.81; Cl, 15.38. Found: C, 52.33; H, 5.05; Cl, 15.63.

3-Methoxy-1,5-di-(chloroacetyl)-pyrogallol (1,5) $(ClCH_2CO)_2C_6H(OH)_2(2,4)OMe(3)$.—When the foregoing

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[10] Feist and Siebenlist, *Arch. Pharm.*, **265**, 196 (1927). See also Stoermer and Barthelmes, *Ber.*, **48**, 62 (1915).

[11] Ullmann, *Ann.*, **327**, 116 (1903).

[12] Blumberg and Von Kostanecki, *Ber.*, **36**, 2191 (1903); see also Bülow and Schmidt, *ibid.*, **39**, 217 (1906).

[13] Perkin and Weizmann, *J. Chem. Soc.*, **89**, 1654 (1906).

[14] Friedländer and Schnell, *Ber.*, **30**, 2153 (1897).

[15] David and Von Kostanecki, *ibid.*, **36**, 127 (1903).

reaction was conducted under somewhat different conditions, a different product was obtained.

Pulverized aluminum chloride (53 g.) was added in small portions to a solution of pyrogallol trimethyl ether (50 g.) and chloroacetyl chloride (35 g.) in carbon disulfide (175 cc.). A dark red oil separated. The mixture, protected by a calcium chloride tube, was refluxed gently until the evolution of hydrochloric acid had considerably abated (five to six hours). The solution was then cooled, the carbon disulfide decanted, and the residual dark solid decomposed as before. The muddy precipitate was separated by decantation and washed with a small quantity of cold alcohol. The residual colorless solid, crystallized from methanol, weighed 6.2 g. Recrystallized from the same solvent colorless needles were obtained, m. p. 154.5° (corr.), which melting point was not changed by further crystallizations.

Anal. Calcd. for $C_{11}H_{10}O_5Cl_2$: C, 45.05; H, 3.44; Cl, 24.20. Found: C, 45.47; H, 3.66; Cl, 24.65.

The compound was very slightly soluble in water, alcohol, ether, acetone, chloroform or carbon tetrachloride, cold; rather more so in cold benzene; and dissolved in alcohol, acetone, chloroform or benzene, hot.

In both this and the foregoing reaction, it should be remembered that the initial materials, products and by-products, are toxic, irritating and lachrymatory.

Condensation of Gallacetophenone Trimethyl Ether with Nitrobenzaldehydes

An equimolar mixture of the trimethyl ether and aldehyde was dissolved in alcohol with warming and when the solution was cold, a 10% aqueous sodium hydroxide solution was stirred in gradually (about 10 cc. for 10–30 g. of the ether). The mixture changed to deep red or brown and crystals separated generally very soon. These crystals were washed with cold alcohol, decolorized if necessary, and crystallized to constant melting point from the same solvent. The products were mostly very slightly soluble in water, ether, alcohol, benzene, glacial acetic acid, acetone, chloroform, carbon tetrachloride or petroleum ether, cold; more freely, hot. Their other physical properties are summarized in Table I.

TABLE I

TRIMETHOXYNITROCHALCONES

HOC-$C_6H_4NO_2$	Yield, %	M. p. (corr.), °C.	Product
Ortho	50	125	Pale yellow micro needles or plates
Meta	95	135	Glistg. pale yellow needles
Para	90 (crude)	160.5	Glistg. yellow leaflets

ANALYSES

	C	H
Calcd. for $C_{18}H_{17}O_6N$	62.95	4.99
Found for *o*-nitro	62.91	4.98
Found for *m*-nitro	62.79	5.13
Found for *p*-nitro	62.99	5.06

Reduction of the Trimethoxynitrochalcones

For the reduction of the *m*- and *p*-nitrochalcones, the procedure varied only in details.

Crystalline stannous chloride was dissolved in glacial acetic acid by saturating the mixture with dry hydrochloric acid and the gain in weight was noted. To this solution, the nitrochalcone was added in small portions, cooling if necessary. Upon standing cold for some time (up to forty-eight hours), the double tin salt of the amine crystallized out (scarlet in the case of the meta derivative, yellow for the para). These crystals were collected, washed with a small quantity of glacial acetic acid, dissolved in water, excess of 10% aqueous sodium hydroxide solution added and the mixture left at room temperature for three to five hours. The crude free amine separated in crystals, which were washed with water, dried and crystallized from alcohol (by dilution, if necessary), occasionally with a decolorizing carbon, until the melting point remained constant. The yield of crude product depended considerably upon the length of time allowed for the separation of the double tin salt.

These two amines were more or less difficultly soluble in water, ether, benzene or cold alcohol; but dissolved in glacial acetic acid, acetone, ethyl acetate, chloroform or hot alcohol.

Preparative details are given in Table II.

TABLE II

TRIMETHOXYAMINOCHALCONES

Derivative	Meta	Para
Nitrochalcone, g.	10	5
$SnCl_2 \cdot 2H_2O$, g.	23	15
Glacial AcOH, cc.	75	75
Dry HCl, g.	9.5	6
Yield (crude), %	75	70
M. p. (corr.), °C.	98	104
Product	Bright greenish-yellow crystals	Lustrous deep golden-yellow leaflets
C found	69.30	69.16
H found	6.23	6.36
N found	4.52	4.50

Calcd. for $C_{18}H_{19}O_4N$: C, 68.98; H, 6.12; N, 4.47.

2-[2′,3′,4′-Trimethoxyphenyl]-quinoline (IV).—Reduction of the *o*-nitrochalcone resulted in the immediate condensation of the aminochalcone to the methoxylated 2-phenylquinoline (IV), which was the only product isolated.

A mixture of 10 g. of crystalline stannous chloride with 50 cc. of glacial acetic acid was brought into solution by saturation with dry hydrochloric acid, and this solution was cooled to a temperature just above the congealing point of the acetic acid. To it there was added, in small lots, 5 g. of the nitrochalcone and, when all had dissolved, the mixture was left at room temperature for twelve to twenty-four hours, with occasional shaking. The yellow crystals which separated were dissolved in alcohol, the solution filtered and the filtrate precipitated by careful dilution with water; yield, 64% (crude). The crystalline precipitate so obtained was purified by repetition of this solution and precipitation, until the product formed colorless glistening needles, m. p. 105° (corr.).

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 73.19; H, 5.81; N, 4.75. Found: C, 73.46; H, 6.16; N, 4.63.

Subjected to an attempted diazotization and coupling with β-naphthol, no color reaction was observed. Primary aromatic amines, therefore, were absent.

Production of 2′-Hydroxy- and 2′-Acetoxychalcones from 2-Hydroxy-3,4-dimethoxyacetophenone and Nitrobenzaldehydes

By the condensation of gallacetophenone-3,4-dimethyl ether (2-hydroxy-3,4-dimethoxyacetophenone) with *o*- *m*- and *p*-nitrobenzaldehydes, in the presence of sodium methoxide and in absolute methanol solution, there were formed both nitrochalcones (VI) and intermediate aldols (V). When *o*-nitrobenzaldehyde was used, only the aldol was isolated; but with the *m*- or *p*-nitrobenzaldehyde, a mixture of aldol and chalcone resulted.

Instead of sodium methoxide, other chemicals were tested as condensing agents in this reaction, *e. g.*, sodium hydroxide in various concentrations, sodium ethylate or dry hydrochloric acid in absolute alcohol solution, and acetic anhydride, but all proved much less satisfactory.

The sodium methoxide condensation was carried out as follows. A mixture of 100 g. of the dimethyl ether with 77 g. of the aldehyde (equimolar proportions) was dissolved in 600–750 cc. of hot absolute methanol, the solution cooled to room temperature and treated with 2.5 g. of pulverized sodium methoxide. The mixture was allowed to stand in a cool place, with occasional shaking, for twelve to forty-eight hours and the separated crystals were then removed, washed with ice-cold absolute methanol and purified by recrystallization to constant melting point.

2′,β - Dihydroxy - 3′,4′ - dimethoxy - 2 - nitro - dihydrochalcone (V), as noted above, was the only product isolated when *o*-nitrobenzaldehyde was subjected to this condensation. The yield of crude product, washed and dried was about 43%. By repeated crystallization from 95% ethyl alcohol, it was obtained in small colorless needles, which melted at 132° (corr.), with slight softening a few degrees below this. It was unchanged by prolonged refluxing in absolute ethyl alcohol solution, and did not go over into a flavanone, which latter transition might have been expected from the work of Von Kostanecki, Levi and Tambor.[16] On exposure to light, the compound rapidly turned yellow. It was practically insoluble in water, methyl or ethyl alcohol, ether or benzene, cold; but dissolved in methyl or ethyl alcohol, or benzene, hot. It was more or less soluble also in acetone, chloroform or glacial acetic acid.

2′,β - Dihydroxy - 3′,4′ - dimethoxy - 3 - nitro - dihydrochalcone (V).—In the condensation with *m*-nitrobenzaldehyde, the crude product, after washing with absolute methanol, was yellow and crystalline, and appeared to be a mixture of aldol and chalcone. The yield was about 64%, calculating the mixture as composed of equal weights of the two. No attempt was made to separate the mixture, as it could be conveniently converted directly into the acetoxy derivative, as explained beyond.

2′,β - Dihydroxy - 3′,4′ - dimethoxy - 4 - nitro - dihydrochalcone (V).—With *p*-nitrobenzaldehyde, the crude product, washed and dried (70% yield), consisted chiefly of cream-colored aldol, mixed with some of the bright orange-red chalcone crystals. By crystallization, first from benzene and then repeatedly from alcohol, it was obtained in fine pale yellow needles, m. p. 156° (corr.), which melting point varied slightly depending upon the rate at which it was dehydrated to the chalcone. It was insoluble in water, methyl or ethyl alcohol, glacial acetic acid or benzene, cold; but was soluble in all of these, except water, when hot, and dissolved also in acetone.

When the foregoing aldols were heated above their melting point, or were refluxed for a few minutes with acetic anhydride, water was split out and the chalcone produced. Longer heating with acetic anhydride, especially in the presence of fused sodium acetate, then acetylated the free hydroxyl group. The acetyl derivatives could thus be prepared directly from either the aldol, the chalcone, or a mixture of the two.

2′-Hydroxy-3′,4′-dimethoxy-2-nitrochalcone (VI).—The aldol was fused for a short time above its melting point and the crude product purified by crystallization from alcohol; yellow crystals, m. p. 163.5° (corr.); yield, 20–25%. In alcohol, acetone, glacial acetic acid or acetone, the compound dissolved but slightly cold, more freely hot. It was practically insoluble in water or in ether.

2′-Hydroxy-3′,4′-dimethoxy-3-nitrochalcone.—This was obtained in the earlier experiments, in which sodium hydroxide was used as the condensing agent.

To a solution of 50 g. of gallacetophenone-3,4-dimethyl ether and 38.5 g. of *m*-nitrobenzaldehyde in 200 cc. of 95% ethyl alcohol, there was added 100 g. of 30% aqueous sodium hydroxide solution, and the mixture was left for some time at room temperature, with frequent shaking. A brilliant scarlet precipitate gradually separated. It was removed and washed with a little absolute alcohol, and was probably the sodium salt of the nitrochalcone for, when dissolved in about 2 liters of water, the color changed immediately to the yellow of the free chalcone. The solution was acidified with 3 *M* hydrochloric acid and stirred until all of the sodium salt was hydrolyzed, when the yellow precipitate was collected, washed, dried and crystallized from glacial acetic acid; yield, 20–30%. By repeated crystallization from the same solvent, a constant m. p. of 190.5° (corr.) was obtained. It formed orange-yellow leaflets, but slightly soluble in water, methyl or ethyl alcohol, ether, acetone, glacial acetic acid, toluene and xylene, cold; but dissolved in the latter three hot.

2′-Hydroxy-3′,4′-dimethoxy-4-nitrochalcone was prepared from the mixture of aldol and chalcone, described under the former as constituting the first crude product. This mixture was refluxed for ten to fifteen minutes with acetic anhydride. Hot water was then added and the mixture boiled for a short time, cooled, diluted, the precipitate filtered out, washed and dried. By repeated crystallization from xylene, it was obtained in bright orange-red flakes or rosets, m. p. 188.5° (corr.); yield, over 80%. In cold methyl or ethyl alcohol, ether, acetone, glacial acetic acid or benzene, it dissolved with difficulty, but was soluble in glacial acetic acid or benzene, hot, and slightly in acetone.

2′-Acetoxy-3′,4′-dimethoxy-2,3, and 4-Nitrochalcones (VII).—Either the aldol, the chalcone or a mixture of the two, was refluxed with acetic anhydride and fused sodium acetate, and the solution was poured into a large volume of ice water. The crude product separated either as a

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(16) Von Kostanecki, Levi and Tambor, *Ber.*, **32**, 330 (1899).

solid, or as an oil which solidified on standing. It was collected, washed, dried and crystallized to constant m. p. from suitable solvents. Experimental details are given in Table III.

TABLE III

2'-ACETOXY-3',4'-DIMETHOXYNITROCHALCONES

	2-Nitro	3-Nitro	4-Nitro
Initial material	Aldol	Chalcone	Mixture of aldol and chalcone
Initial material, amt., g.	36.5	10	50
Acetic anhydride, cc.	80	50	125
Fused sodium acetate, g.	12	4	16
Time of refluxing, min.	5	60	30
Yield, %	95	70	95[a]
Solvent for crystn.	EtOH	Toluene then EtOH	C_6H_6
M. p. (corr.), °C.	115	99	173.5
Appearance of crystals	Lustrous pale yellow needles or blades	Pale yellow microscopic crystals	Pale yellow microscopic needles

[a] Assuming that the initial material was 50% aldol and 50% chalcone.

These acetoxy derivatives were insoluble in water or ether; generally difficultly soluble in methyl alcohol, ethyl alcohol, glacial acetic acid, benzene or toluene, cold; more freely hot; and more or less soluble in acetone or chloroform.

TABLE IV

ANALYSES OF NITROCHALCONES, THEIR ACETOXY DERIVATIVES AND ANTECEDENT ALDOLS

	C	H	N
Calcd. for $C_{17}H_{17}O_7N$ (aldols)	58.78	4.94	4.04
Found for *o*-nitroaldol	58.70	5.29	4.14
Found for *p*-nitroaldol	58.85	4.99	4.01
Calcd. for $C_{17}H_{15}O_6N$ (chalcones)	61.98	4.59	4.26
Found for *o*-nitrochalcone	62.03	4.88	4.34
Found for *m*-nitrochalcone	61.91	4.64	4.27
Found for *p*-nitrochalcone	61.68	4.59	4.50
Calcd. for $C_{19}H_{17}O_7N$ (acetoxychalcones)	61.43	4.62	
Found for *o*-nitroacetoxychalcone	61.31	4.68	
Found for *m*-nitroacetoxychalcone	61.37	4.70	
Found for *p*-nitroacetoxychalcone	61.63	4.64	

Conversion of the 2-Acetoxychalcones into the Aminobenzalcoumaranones

2'-Acetoxy-3',4'-dimethoxy-2,3 and 4-nitrochalcone Dibromides (VIII).—A solution of the acetoxychalcone (VII) in carefully dried chloroform was treated with a solution of bromine in the same solvent, adding the bromine solution in small portions and agitating until the color disappeared before adding another lot, so as to avoid excess of bromine at the end. A solution of one volume of bromine in nine of chloroform was found satisfactory. After the chalcone had taken up as much bromine as it would, the chloroform was distilled off, the residual yellow crystalline meal was washed with a small quantity of ice-cold alcohol, and purified by repeated crystallization from the same solvent.

The 2- and 4-nitro derivatives were thus obtained in colorless prisms, m. p. 143.5° (corr.) and 148° (corr.), respectively, whereas the 3-nitro derivative separated as a heavy oil which we were unable to crystallize. The yields were as follows: for the crude 3-nitro derivative, washed with cold alcohol, 86%; for the crude (m. p. 143–145°) 4-nitro derivative, 89–92%.

These dibromides were generally insoluble in water, methyl or ethyl alcohol, ether, glacial acetic acid or benzene, cold; soluble in methyl or ethyl alcohol, glacial acetic acid or benzene, hot; and also soluble in chloroform or acetone.

5,6-Dimethoxy-2'-nitrobenzalcoumaranone (IX).—To a hot solution of 50 g. of the crude 2'-nitro dibromide (VIII) in about 1 liter of alcohol, there was added gradually 30 cc. of a 40% aqueous potassium hydroxide solution. The yellow solution changed to orange as the alkali was added. At first this orange color disappeared upon shaking the solution, but finally persisted. When the above amount of alkali had been added, a yellow flocculent precipitate separated. After cooling the mixture well, it was filtered and the precipitate (A) washed with cold alcohol. It formed a brilliant canary-yellow crystalline cake, of the quite pure coumaranone. From the filtrate, a further crop of these crystals (A) was precipitated by the addition of a little more of the potassium hydroxide solution. The combined weight of the two lots was 6.12 g. and the m. p. 196–196.5° (corr.).

The filtrate, which was now alkaline, on standing deposited 9.22 g. of another yellow crystalline solid (B), which melted at 127–130°. The filtrate from (B), when acidified with acetic acid, precipitated a mixture of (A) and (B), from which 2.57 g. of (A) was recovered by crystallization from glacial acetic acid.

The total yield of the coumaranone (A) (IX) was therefore 8.69 g., or approximately 28%. For analysis it was further purified by repeated crystallization from glacial acetic acid, when it formed bulky brilliant canary-yellow flakes or rosets, m. p. 197.5° (corr.); insoluble in water, alcohol, acetone, glacial acetic acid or benzene, cold; slightly soluble in hot alcohol; more so in acetone, glacial acetic acid or benzene, hot; and soluble in chloroform.

When the finely divided dibromide (VIII) was suspended in a small volume of alcohol and shaken with dilute alkali cold, according to the procedure of Auwers and Anschütz,[17] the product was again the coumaranone, m. p. 197.5° (corr.), identical with (A) above.

The other product (B) crystallized from alcohol in long bright greenish-yellow needles, m. p. 133° (corr.). Its analysis gave the following figures: C, 52.05; H, 4.19; Br, 18.72. It has not been identified as yet.

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(17) Auwers and Anschütz, *Ber.*, **54**, 1545 (1921).

5,6-Dimethoxy-3′-nitrobenzalcoumaranone.—The oily dibromide (VIII) obtained from the 3′-nitrochalcone was dissolved in alcohol and treated gradually with a 10% aqueous potassium hydroxide solution, until the addition of alkali caused no further separation of a yellow precipitate. The reaction was exothermic, and the alkali at first caused a transient bright red color which finally became permanent. The precipitate was collected, washed with cold alcohol and dried at 100°. Crystallized from glacial acetic acid, it formed long silky yellow needles, apparently containing solvent of crystallization, which was easily removed by drying at 100°; yield, about 37%, calculated to the initial unbrominated acetoxy derivative (VII).

For analysis, the original crude precipitate was purified by repeated crystallization from alcohol until it appeared in pale yellowish microscopic needles, m. p. 220° (corr.); insoluble in water, alcohol, ether, acetone, glacial acetic acid, benzene or toluene, cold; soluble in alcohol, benzene or toluene, hot; more easily in hot glacial acetic acid, and soluble also in chloroform. Its solution in concentrated sulfuric acid was orange-red.

5,6-Dimethoxy-4′-nitrobenzalcoumaranone was prepared from the appropriate dibromide (VIII) in much the same way as the 2′- and 3′-nitro isomers, using an alcoholic solution of the dibromide and an 8% aqueous potassium hydroxide solution. After the alkali had precipitated as much of the coumaranone as it would, a further crop was secured by acidifying the alkaline filtrate with acetic acid. The precipitates were combined and crystallized from glacial acetic acid; yield, 39%; silky brilliant orange needles, m. p. 265.5° (corr.). The product was insoluble in ligroin, alcohol, ether, acetone, glacial acetic acid, carbon disulfide or benzene, cold. Boiled with these solvents, it dissolved freely only in glacial acetic acid, and slightly in chloroform.

From the mother liquor of the first crystallization of the crude product, there was isolated a small quantity (1.5 g. from 10 g. of dibromide) of fine pale yellow needles, m. p. about 127°, which was not further investigated.

Like the 2′-nitro isomer, when the finely divided 4′-nitrodibromide was suspended in alcohol and treated with dilute alkali cold, according to the method of Auwers and Anschütz,[17] the product was the same as the coumaranone described above.

This same nitrobenzalcoumaranone was obtained by condensing 2-hydroxy-3,4-dimethoxy-γ-chloroacetophenone (XI) with *p*-nitrobenzaldehyde, in the presence of alkali. Crystallized from glacial acetic acid, it melted at 265.5° (corr.) and no change in melting point occurred when mixed with the nitrobenzalcoumaranone produced by the other method. In other respects, the two were likewise identical.

The dimethoxyaminobenzalcoumaranones were obtained by reducing the corresponding nitro compounds with stannous chloride and hydrochloric acid in glacial acetic acid solution. The reduction proceeded exothermically, with solution of the nitro derivative and separation of a complex tin salt of the amine. If necessary, it was completed by warming. The precipitate was collected, dissolved or suspended in water and decomposed by the addition of 10% sodium hydroxide solution. The precipitate which separated was removed, washed, dried and crystallized from alcohol.

5,6-Dimethoxy-2′-aminobenzalcoumaranone.—Unless this reduction was conducted with efficient cooling, the main product was not the coumaranone but the quinoline derivative (XIII) described beyond.

The pure coumaranone formed bright orange-red needles, m. p. 211–212° (corr.); yield, about 45%; insoluble in water, alcohol, ether, acetone, glacial acetic acid or benzene, cold; soluble in alcohol or glacial acetic acid, hot.

Feist and Siebenlist[10] claim to have prepared this compound, but give no description of the method used or any properties of the product.

When the reduction of the 2-nitrocoumaranone was carried out at 100°, the crude product crystallized from alcohol, on careful dilution, in cream-colored silky needles; yield, about 42%. Purified by repeated crystallization from alcohol, it formed fine colorless needles, m. p. 179° (corr.), apparently identical with the dimethoxycoumarinoline which Feist and Siebenlist[10] seem to have prepared by condensing 5,6-dimethoxycoumaranone with *o*-aminobenzaldehyde, and for which they recorded a melting point of 176°. Dilute solutions in alcohol exhibited a pale blue fluorescence, in benzene a bright green one.

A small amount of the aminocoumaranone was also isolated from the products of this reduction.

5,6-Dimethoxy-3′-aminobenzalcoumaranone.—Microscopic pale lemon yellow needles, m. p. 205.5° (corr.); yield, about 77%. In the cold, the compound was either insoluble or very slightly soluble in water, methyl or ethyl alcohol, ether or benzene; rather more soluble in chloroform or acetone, and still more so in glacial acetic acid. On boiling, it dissolved in chloroform, acetone or ethyl alcohol, but only slightly in methanol.

5,6-Dimethoxy-4′-aminobenzalcoumaranone.—This reduction was carried out at 100° and was incomplete after eight hours of heating, for considerable unchanged nitrocoumaranone was recovered in the purification of the crude product. The pure compound crystallized from alcohol in deep orange or orange-red needles, much the same in color as the 2′-amino isomer, and melted at 174° (corr.); yield, about 70%. It was practically insoluble in ether or benzene, cold, but dissolved in the latter hot, and was soluble also in acetone or glacial acetic acid.

TABLE V

ANALYSES OF ACETOXYCHALCONE DIBROMIDES, NITRO- AND AMINO-BENZALCOUMARANONES

	C	H	N	Br
Calcd. for $C_{19}H_{17}O_7NBr_2$ (dibromides)	42.94	3.23		30.10
Found for 2′-nitro deriv.	42.90	3.56		32.26[a]
Found for 4′-nitro deriv.	42.85	3.45		30.88
Calcd. for $C_{17}H_{13}O_6N$ (nitrobenzal-coum.)	62.36	4.01	4.28	
Found for 2′-nitro derivative	62.42	4.22	4.27	
Found for 3′-nitro derivative	62.57	3.89	4.27	
Found for 4′-nitro derivative	62.63	4.25	4.55	
Calcd. for $C_{17}H_{15}O_4N$ (aminobenzal-coum.)	68.65	5.09	4.71	
Found for 2′-amino derivative	68.93	5.24	4.80	
Found for 3′-amino derivative	68.61	5.13	4.55 4.61	
Found for 4′-amino derivative	68.60	5.40	4.62	
Calcd. for $C_{17}H_{13}O_3N$ (XIII)	73.09	4.70	5.21	
Found for Compound (XIII)	73.16	4.62	5.11	

[a] Great difficulty was experienced with these Br determinations, and the figures are not satisfactory.

Summary

1. 2,3,4-Trimethoxyacetophenone has been condensed with *o*-, *m*- and *p*-nitrobenzaldehydes to the corresponding nitrochalcones.

2. Reduction of the *m*- and *p*-nitro derivatives gives the corresponding amino derivatives, whereas the *o*-nitro gives a trimethoxyphenylquinoline.

3. A similar condensation of 2-hydroxy-3,4-dimethoxyacetophenone with the nitrobenzaldehydes, gives first the aldols and then the chalcones.

4. When these hydroxynitrochalcones are acetylated, the acetyl derivatives converted into dibromides, and the latter subjected to the action of caustic alkali, the products are benzalcoumaranones and not flavones.

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[Contribution from the Laboratories of the Rockefeller Institute for Medical Research, New York]

Reactions of Carbohydrates in Liquid Ammonia. II. Apparatus and Methods. Alkyl, Acyl and Certain Metallic and Non-metallic Derivatives of Diacetoneglucose

By Irving E. Muskat[1]

Since the publication of the preliminary paper on the reactions of carbohydrates in liquid ammonia,[2] the author has endeavored to develop and standardize the *modus operandi* of this process so that the method can be of general use. The apparatus used and the procedure followed have been modified and in the present paper these will be described.

At the time the preliminary paper was published, some previous work by L. Schmid[3] had been overlooked. Schmid and his collaborators tried liquid ammonia as a medium for the methylation of sugars and starch but failed. It is obvious from the work reported in the preliminary paper and here that the results differ markedly from those reported by Schmid and his co-workers.

Apparatus

The apparatus now used is shown in Fig. 1. It is so designed that it is easy to introduce either gaseous or liquid ammonia, solids or liquids, and carry on further reactions with the alkali metal salts of the carbohydrates without transferring them to other vessels. The tank used for the liquid ammonia is fully described by Johnson and Fernelius[4] and will not be described here. It is possible to obtain both gaseous and liquid ammonia from this tank. A is the reaction vessel, B is a ground glass top through which all materials are added, C is the inlet tube for gaseous ammonia and D is the outlet tube for the ammonia vapors or any gases which may be liberated during the reaction. E is a ground glass opening into which any one of three different parts—F, H or I—may be fitted. Attachment F is used to introduce the alkali metals or any solids used in the reaction (G is a glass rod used to push the substance down in case it sticks or cakes); attachment H to introduce liquids; and attachment I, shown in place, to introduce liquid ammonia or liquid ammonia solutions of the reagents. At the tip of I is attached a small test-tube J with a perforated bottom. In this test-tube the alkali metal is placed and the liquid ammonia allowed to drop over it, thus dissolving the metal to form a solution which drops down into the reaction vessel A.

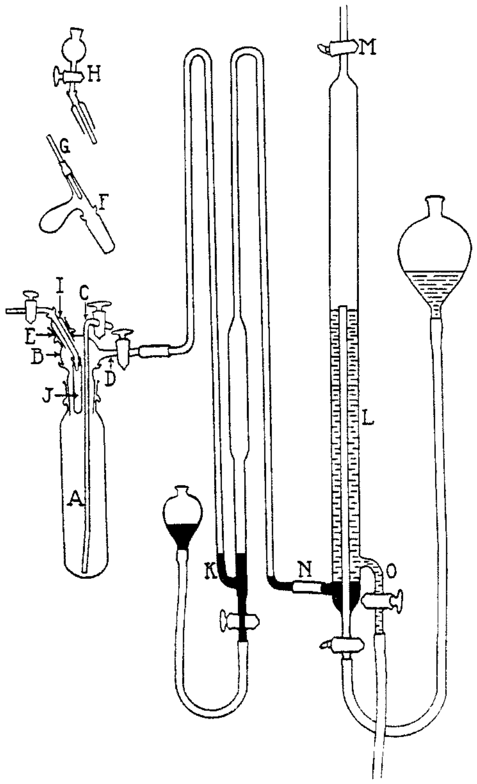

Fig. 1.

The rest of the apparatus and the general methods concerning the technique of working with liquid ammonia as

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[1] National Research Fellow in Chemistry.

[2] Muskat, This Journal, **56**, 693 (1934).

[3] L. Schmid and B. Becker, *Ber.*, **58**, 1966 (1925); Schmid Waschkau and Ludwig, *Monatsh.*, **49**, 107 (1928).

[4] Johnson and Fernelius, *J. Chem. Ed.*, **6**, 441 (1929).